Development of multiple-unit pellet systems by employing the SeDeM expert diagram system

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List of Abbreviations

%RSD	Percentage relative standard deviation
API	Active pharmaceutical ingredient
BP	British Pharmacopoeia
CP	% w/w of corrective excipient
Da	Bulk density
Dc	Tapped density
d_m	Mean diameter of the particles in the majority fraction
d_{m+1}	Mean diameter of the particles in the fraction of the range immediately above the majority range
d_{m-1}	Mean diameter of the particles in the fraction of the range immediately below the majority range
F	Reliability factor
F_m	Percentage of particles in the majority range
F_{m+1}	Percentage of particles in the range immediately above the majority range
F_{m-1}	Percentage of particles in the range immediately below the majority range
GCI	Good compression index
HEC	Hydroxyethyl cellulose
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxypropyl methyl-cellulose
IC	Carr index
Icd	Cohesion index
Ie	Inter-particle porosity
IH	Hausner ratio
IP	Parameter Index
IPP	Parameter Profile Index
IΘ	Homogeneity index
MCC	Microcrystalline cellulose
MUPS	Multiple-unit pellet system

n	Order number of the fraction under study, within a series, with respect to the majority fraction
PEO	Polyethylene oxide
PVP	Polyvinylpyrrolidone
R	Mean incidence value to be obtained in the blend
r^2	Regression value of
RE	Mean incidence value of the corrective excipient
RP	Mean incidence value of the API to be corrected
SeDeM EDS	SeDeM Expert Diagram System
std dev	Standard deviation
t”	Flowability
USP	United States Pharmacopeia
UV	Ultraviolet
α	Angle of repose

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Jeremiah 29:11 "For I know the plans I have for you, declares the LORD,
plans to prosper you and not to harm you,
plans to give you hope and a future."

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Abstract

Conventional tablets and capsules are considered the most common and acceptable drug delivery systems, however, in recent years multiple unit pellet systems (MUPS) have become more popular and are considered to be an interesting alternative for oral drug administration.

MUPS provide several therapeutic advantages over other solid oral single-unit dosage forms such as conventional tablets and capsules. MUPS exhibit a reduced risk of local irritation and toxicity, predictable bioavailability, reduced likelihood of dose dumping and minimised fluctuations in the plasma concentration of the drug. MUPS comprises of a number of small uncoated or coated, spherical or semi-spherical particles (referred to as pellets or beads) which are prepared by different methods including drug layering, cryopelletisation, freeze pelletisation, spray drying, spray congealing, compression, balling and extrusion-spheronisation. The pellets are then compressed into tablets (MUPS tablets) or filled into capsules (MUPS capsules) using the same principles and equipment that are used in the manufacturing of conventional tablets and capsules. The technology used in MUPS formulations combine the advantages of conventional single unit dosage forms with that of small spherical or semi-spherical solid units into one multiple-unit dosage form.

The production of MUPS tablets present various challenges including damage or deformation of the pellets during the compression process as well as variations in tablet weight and content uniformity due to segregation of the pellets and added powder excipients. These challenges can however be resolved by using specialised tablet compression machines and/or optimised tablet formulations. Application of MUPS technology has led to the successful formulation of various marketed MUPS products with increased bioavailability and improved pharmacological response. Several sustained drug release MUPS products are available on the market today.

Formulation studies of tablets are often done by trial and error. The SeDeM Expert Diagram System (SeDeM EDS), however, provides information about the selection of the most appropriate excipient and the optimal amount thereof which is required in direct compression tablet formulations. This system provides an indication of the degree to which powder substances can be successfully compressed and also predicts which properties of the end product formulations needs to be adjusted to yield the optimal formulation for direct compression.

The aim of this study was to apply the SeDeM EDS to different size pellets (i.e. 0.5, 1.0, 1.5, 2.0 and 2.5 mm) containing different APIs (i.e. doxylamine, ibuprofen or paracetamol) to determine which properties should be corrected to yield MUPS tablet formulations. The SeDeM parameter tests were

conducted on the pellets, selected excipients, intermediate blends and final blends. The study showed that the properties of the pellets depended on the active ingredient and pellet size. The SeDeM compressibility indices indicated that the final pellet blends should be suitable for compression into MUPS tablets. MUPS tablets were prepared from the final blends and evaluated in terms of physico-chemical properties and dissolution profiles. Only three of the MUPS tablet formulations containing ibuprofen and one MUPS tablet formulation containing paracetamol failed content uniformity. All the other MUPS tablet formulation showed acceptable results for friability, hardness, and mass variation. The water solubility of the APIs as well as the pellet size (surface area exposed to the dissolution medium) attributed to the difference in drug dissolution rate. The study concluded that compression of the pellets into MUPS tablets could be achieved and the SeDeM EDS could be applied with success in the formulation of MUPS tablets.

Key words: beads; compression; extrusion-spheronisation; formulation; multiple unit pellet systems (MUPS); SeDeM EDS

Uittreksel

Konvensionele tablette en kapsules word beskou as die mees algemene en gewildste doseervorms. In die afgelope paar jaar het meervoudige eenheid-korrelsisteme (MEKS) egter meer gewildheid begin verwerf en dit word as 'n interessante alternatief vir die orale toediening van geneesmiddels beskou.

MEKS bied verskeie terapeutiese voordele bo ander soliede orale enkeleenheid doseervorms soos konvensionele tablette en kapsules. MEKS toon 'n verminderde of verlaagde risiko van lokale irritasie en toksisiteit, beskik oor ’n meer voorspelbare biobeskikbaarheid, verminder die waarskynlikheid van dosisstorting en minimale fluktuasies in die bloedplasma-geneesmiddelkonsentrasie. MEKS bestaan uit 'n aantal klein onbedekte of bedekte, sferiese of semi-sferiese deeltjies (ook genoem korrels of krale) wat vervaardig word deur verskeie metodes, insluitend geneesmiddellaag-neerlegging, krioseringskorrelvorming, vrieskorrelvorming, sproeidroging, sproeistolling, samepersing, balvorming en ekstrudering-sferonisering. Die krale word dan saamgepers in tablette (MEKS-tablette) of in kapsules (MUPS-kapsules) gevul deur gebruik te maak van dieselfde beginsels en toerusting wat van toepassing is of gebruik word in die vervaardiging van konvensionele tablette en kapsules. Die tegnologie wat gebruik word in MEKS-formulerings kombineer die voordele van konvensionele enkeleenheid doseervorms met dié van klein sferiese of semi-sferiese soliede eenhede in 'n meervoudige eenheid-doseervorm.

Die vervaardiging van MEKS-tablette bied egter verskeie uitdagings insluitende beskadiging of vervorming van die krale tydens die samepersingsproses asook variasie in tablet massa en inhoudseenvormigheid as gevolg van segregasie van die krale en hulpstowwe met ’n kleiner deeltjiegrootte. Hierdie uitdagings kan egter oorkom word deur gebruik te maak van gespesialiseerde tabletperse en/of geoptimaliseerde tabletformulerings. Die toepassing van MEKS-tegnologie het gelei tot die suksesvolle formulering en bemarking van verskeie MEKS-produkte met 'n verbeterde biobeskikbaarheid en farmakologiese respons. Verskeie MEKS-gebaseerde volgehoue geneesmiddelvrystellingsprodukte is tans kommersieel beskikbaar.

Formuleringstudies van tablette word dikwels lukraak gedoen. Die SeDeM-Deskundige-Diagram-Sisteem (SeDeM DDS) verskaf egter inligting rakende die keuse van die mees geskikte hulpstowwe asook die optimale hoeveelheid daarvan wat benodig word in die formulering van direk saampersbare tabletformulerings. Hierdie stelsel gee 'n aanduiding van die mate waarin poeiers suksesvol saamgepers kan word en voorspel watter eienskappe van die eindproduk aangepas moet word om die optimale direk saampersbare formule te lewer.

Die doel van hierdie studie was om die SeDeM DDS op krale van verskillende groottes toe te pas (nl. 0.5, 1.0, 1.5, 2.0 en 2.5 mm) wat verskillende aktiewe bestanddele bevat (nl. doksielamien, ibuprofeen en parasetamol) om te bepaal watter eienskappe aangepas moet word om MEKS-tablette te lewer. Die SeDeM DDS parameter toetse is op verskeie krale, hulpstowwe, intermediêre mengsels en finale mengsels toegepas. Die studie het getoon dat die eienskappe van die krale afhang van die aktiewe bestanddeel asook korrelgrootte. Die SeDeM-samepersingsindekse het aangedui dat die finale kraalmengsels geskik behoort te wees vir samepersing in MEKS-tablette. MEKS-tablette is uit die finale mengsels vervaardig en is geëvalueer in terme van fisies-chemiese eienskappe en dissolusieprofiele. Slegs drie van die MEKS-tablet formulerings wat ibuprofeen bevat en een MEKS-tablet formulering wat parasetamol bevat het nie die inhoudseenvormigheidstoets geslaag nie. Die ander MEKS-tablet formulerings het aanvaarbare resultate opgelewer vir tabletbrosheid, -hardheid en massavariasie. Die wateroplosbaarheid van die aktiewe bestanddele sowel as die korrelgrootte (oppervlakte wat aan die dissolusievloeistof blootgestel word) het bygedra tot die verskille in die geneesmiddelvrystellings-tempo. Die studie het bevind dat samepersing van krale om MEKS-tablette te produseer haalbaar is en dat die SeDeM DDS met sukses in die formulering van MEKS-tablette toegepas kan word.

Sleutelwoorde: ekstrudering-sferonisering; formulering; krale; meervoudige eenheid-korrelsisteme (MEKS); samepersing; SeDeM DDS

Preface

The aim of this study was to investigate the applicability of the SeDeM Expert Diagram System (SeDeM EDS) to the formulation of multiple-unit pellet system (MUPS) tablets containing different pellet sizes (i.e. 0.5; 1.0, 1.5; 2.0 and 2.5 mm) and different active pharmaceutical ingredients (API's) (i.e. doxylamine, ibuprofen and paracetamol).

This thesis is presented in article format as prescribed by the guidelines of the North-West University. It contains an introductory and conclusion chapter, two review articles published in the peer-reviewed journals *"Current Pharmaceutical Design"* (DOI: 10.2174/138161282166615082010052 4) and *"Drug Delivery Letters"* (DOI: 10.2174/2210303107666170927161351) and two full length research article published in the peer-reviewed journal *"Pharmaceutical Development and Technology"* (DOI: 10.1080/10837450.2017.1342657) and (DOI: 10.1080/10837450.2018.1435691). The guides for authors for the applicable journals are included in Appendices D–F. In addition to these articles, detailed experimental methods and data are given in Appendices A–C of this thesis.

The student is the main author of all four of the articles and was responsible for the first draft of each of the four articles. All the research was conducted by the student. The co-authors of the articles are acknowledged for their guidance, input and proofreading of the articles. The co-authors gave their consent that the articles may be submitted for this PhD degree purposes and the fulfilment thereof.

Chapter 1: Introduction and problem statement

1 Introduction

The SeDeM Expert Diagram System (SeDeM EDS) is normally applied to powders to provide information about their properties and suitability for direct compression into tablets. The SeDeM EDS also indicates the properties of the ingredients of the end product that need to be adjusted to yield the best possible tablet formulation for direct compression (Suné-Negre *et al*., 2008). The SeDeM EDS has not yet been applied in the formulation of any other tablet compression method than direct compression of powders.

Multiple-unit pellet systems (MUPS) are dosage forms consisting of uncoated or coated pellets, which are formulated into tablets or capsules. MUPS tablets and capsules provide several pharmacokinetic and pharmacodynamic advantages over single-unit dosage forms (e.g. conventional tablets and capsules) (Reddy *et al*., 2011). The parameters that are required to be characterised on powders by the SeDeM EDS can also be characterised on multi-particulate dosage forms such as pellets. The question arises whether the SeDeM EDS can be applied to pellets in order to provide information about the suitability of pellet formulations for compression into MUPS tablets and whether the impact of different pellet sizes and active pharmaceutical ingredients (APIs) would be reflected/detected by the SeDeM EDS.

2 Pellets for pharmaceutical applications

Pellets are spherical or semi-spherical free flowing solid units with a narrow size distribution which are often used as drug delivery systems. Pellets manufactured for pharmaceutical applications are generally sized between 0.5 and 1.5 mm in diameter. Pellets as drug delivery systems offer various therapeutic as well as technological advantages over conventional dosage forms. Therapeutic advantages include even distribution of drugs in the gastrointestinal tract, improved safety and efficiency of the active ingredient as well as increased and less variable bioavailability of drugs. Some of the technological advantages include a narrow particle size distribution, strong spheres with low friability, a smooth surface and improved flow properties (Vervaet *et al*., 1995 and Bhaskaran & Lakshmi, 2010).

Pellets can be prepared by various production methods such as drug layering, cryopelletisation, freeze-pelletisation, globulation/spray drying and spray congealing, compression, balling/spherical

agglomeration or extrusion-spheronisation (Dash *et al*., 2012 and Supriya *et al*., 2012). Regardless of the manufacturing method employed, pellets for pharmaceutical applications should meet the following criteria (Manivannan *et al*., 2010):

- A spherical shape and smooth surface, especially for uniform film coating;
- The particle size of the pellets should preferably be in the range of 600–1000 µm; and
- A large quantity of the active ingredient should be contained in the pellets.

3 Extrusion-spheronisation

Extrusion-spheronisation is the most widely used pelletisation method because it is a simple, fast and versatile technique for producing pellets (Supriya *et al*., 2012). This method is a multi-step process, which consists of dry mixing the ingredients, wet mass preparation, shaping the wet mass into spaghetti-like cylinders (extrusion), breaking up the extrudate and rounding off the particles into spheres (spheronisation) and lastly drying of the pellets (Dash *et al*., 2012 and Supriya *et al*., 2012). The formation of the extrudate into spheres is schematically illustrated in Figure 1. The different steps will be briefly discussed.

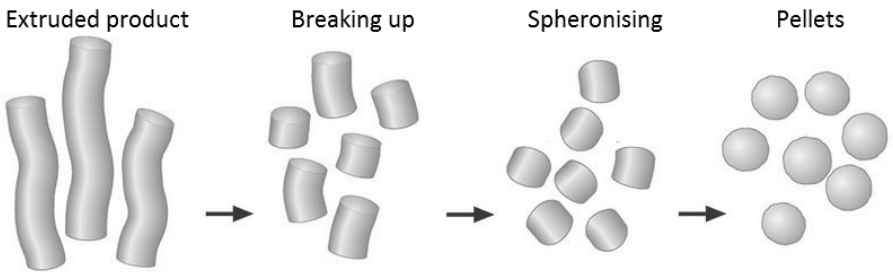

Figure 1: Schematic presentation of the steps involved in the formation of pellets by means of the extrusion-spheronisation production method (Manivannan *et al.*, 2010)

Extrusion-spheronisation offers advantages over other pelletisation methods in terms of efficiency and product quality, which include (Supriya *et al.*, 2012):

- Relatively small particles with a high loading capacity of active ingredient are produced;
- Spherical particles with a narrow size distribution and good flow properties are produced;
- Spherical pellets with a low surface area to volume ratio allows for successful coating of the spheres;
- Multiple-unit pellet system (MUPS) dosage forms (e.g. hard gelatine capsules or tablets) with more than one drug can be formulated, which can facilitate delivery of chemically incompatible or compatible drugs to the same or different sites in the gastrointestinal tract;

- Pellets facilitate even distribution of drugs in the gastrointestinal tract and are frequently used in controlled release delivery systems;
- The safety and efficiency of the active ingredient can be improved; and
- Pellets can help to increase the bioavailability of drugs by controlling or modifying the release rate of the drugs.

Excipients should have certain properties that will make them ideal for the production of pellets via the extrusion-spheronisation method. They should have the following properties (Dukić-Ott *et al*., 2009):

- Poor water solubility;
- A large water absorption and retention capacity;
- Good binding properties;
- A large enough surface area for interaction with water and other ingredients in the powder mixture; and
- Be able to enhance drug release from the pellets.

Microcrystalline cellulose (MCC) is often used as the major excipient in pellet formulation by means of extrusion-spheronisation. Other excipients that have been evaluated for their usefulness in the extrusion-spheronisation method include lactose, powdered cellulose, starch, chitosan, kappa-carrageenan, pectinic acid, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, polyethylene oxide, cross-linked polyvinyl pyrrolidone and glycerol monostearate (Tripurasundari & Prabhakar, 2012). The excipients listed in Table 1 have been used in combination with MCC to improve pellet disintegration and/or drug release from MCC-based pellets (Dukić-Ott *et al.*, 2009).

Table 1: Excipients used in combination with microcrystalline cellulose to improve the drug delivery properties of pellets (Dukić-Ott *et al.*, 2009)

Fillers	***Disintegrants***	***Surface active agents***
Lactose Dicalcium diphosphate Mannitol Starch and derivatives Glucose β-Cyclodextrin	Sodium starch glycolate Croscarmellose sodium	Glycerol monostearate Polyethylene glycol Polysorbate 80, glyceryl and sorbitan mono-oleate, sorbitan mono-palmitate Sodium lauryl sulphate

Several excipients have been suggested and researched as an alternative major constituent other than MCC in pellets produced by extrusion-spheronisation. The excipients listed in Table 2 have been

reviewed for their suitability and capability of producing good quality pellets using extrusion-spheronisation (Dukić-Ott *et al*., 2009 and Otero-Espinar *et al*., 2010). Co-processed excipients such as co-processed lactose-microcrystalline cellulose (MicroceLac® 200) have yet to be researched and reviewed.

Table 2: Excipients suggested as alternatives for microcrystalline cellulose (Dukić-Ott *et al*., 2009 and Otero-Espinar *et al*., 2010)

Celluloses	Saccharides and oligosaccharides	Polysaccharides	Synthetic polymers
Powdered cellulose Hydroxypropyl methyl cellulose (HPMC) Hydroxyethyl cellulose (HEC) Polyethylene oxide (PEO)	Lactose	Starch Alginates Chitosan Pectinic acid Carrageenans	Polyacrylates Polyvinylpyrrolidone (PVP) Cross-linked polyvinylpyrrolidone

3.1 Steps in the extrusion-spheronisation process

3.1.1 Dry mixing step

The dry ingredients in powder form, which include the active pharmaceutical ingredient(s) and the excipients, are mixed to obtain a homogeneous powder blend. Various types of mixers can be used such as the twin shell or V-blender, tumble mixer, high shear mixer or planetary mixer (Dash *et al*., 2012).

3.1.2 Wet massing step

The wetting of the powder mixture is necessary to produce a sufficient wet mass for extrusion. Ideally, the liquid phase should be homogeneously distributed throughout the powder mass. The evaporation of the fluid phase should be minimised during the wet massing step. Different types of granulators can be used for mixing of the powder blend and the wet massing fluid such as a planetary mixer, high shear mixer or a continuous granulator (Baert *et al*., 1991).

3.1.3 Extruding step

The third step of the extrusion-spheronisation method is the shaping of the wet powder mass into long rods through extrusion. Extruders are broadly classified into three classes namely screw, gravity and ram/piston type extruders, based on their feeding mechanism (Baert *et al*., 1991 and Manivannan *et al.*, 2010). The extrusion process can be performed by using an extruder from any one of these classes (Dash *et al*., 2012).

3.1.4 Spheronising step

During the spheronising step, the extrudate is dropped onto the spinning/friction plate of the spheroniser. The extrudate is broken up into smaller cylinders with a length similar to their diameter. These smaller cylinders are then rounded or spheronised due to friction forces that remove the sharp edges. In the spheronisation process, different stages can be distinguished based on the shape of the particles, i.e. starting from a cylinder, a cylinder with rounded edges, dumbbells and elliptical particles to eventually perfect spheres. It is also possible that another pellet-forming mechanism exists. In this mechanism, a twisting of the extruded cylinder occurs after the formation of smaller cylinders with rounded edges, finally resulting in the breaking of the cylinder into two distinct parts. Both parts have a round and a flat side. Due to the rotational and the frictional forces involved in the spheronisation process, the edges of the flat side fold together like a flower forming the cavity observed in certain pellets (Vervaet *et al*., 1995).

3.1.5 Drying step

During the drying step, the pellets are dried in order to obtain a final product with the desired moisture content. The pellets can be dried at room temperature or at elevated temperatures in a fluidised bed, in an oven or microwave oven or freeze drier (Vervaet *et al*., 1995, Bashaiwoldu *et al*., 2004 and Dash *et al*., 2012).

3.1.6 Screening step

During the final step, the pellets are screened through a series of sieves to obtain the desired size distribution of the pellets (Dash *et al*., 2012).

4 SeDeM Expert Diagram System

The SeDeM EDS is applied during formulation to predict the best formulation of solid oral dosage forms. The method normally provides information about the suitability of active ingredients or

excipients in powder form for direct compression. The powdered substances are characterised in terms of physico-chemical properties by the SeDeM EDS, which then facilitates the identification of the characteristics that must be improved in order to obtain direct compressible tablets. This method thus provides information that will ensure the robust design of the formulation into the final product. The SeDeM EDS is based on the selection and application of a number of selected parameters, which are used to determine whether a powder is suitable for direct compression. Pharmacopeial methods are used to determine these parameters. Suñé-Negre *et al*. (2008) identified 12 parameters to be evaluated for the SeDeM EDS. These parameters include the following (Suñé-Negre *et al*., 2008):

- Bulk density;
- Tapped density;
- Inter-particle porosity;
- Carr's index;
- Cohesion index;
- Hausner ratio;
- Angle of repose;
- Flowability;
- Loss on drying;
- Hygroscopicity;
- Particle size; and
- Homogeneity index.

These parameters are then processed into five incidence factors (i.e. dimension, compressibility, flowability/powder flow, lubricity/stability and lubricity/dosage) as shown in Table 3. After determining the values of the parameters, a specific factor value (shown in Table 3) is used to calculate diagram (i.e. a polygon) radii values ranging between 0 and 10 (Pérez *et al.*, 2006, Suné-Negre *et al.*, 2008, Suné-Negre *et al.*, 2011, Aguilar-Diaz *et al.*, 2014 and Suné-Negre *et al.*, 2014). The graphical expression (Figure 2) of the radii values indicate the characteristics of the material under investigation in terms of suitability for direct compression and indicates which incidence factor needs to be improved in order to yield a formulation that would be suitable for compression of the powders into tablets. The SeDeM EDS can also suggest the most appropriate excipient and the smallest amount thereof that is required to correct the inadequate incidence factors, thus providing a formulation suitable for direct compression (Pérez *et al*., 2006, Suñé-Negre *et al*., 2008, Suñé-Negre *et al*., 2008, Aguilar-Diaz *et al*., 2009 and Aguilar-Diaz *et al*., 2014).

Table 3: Incidence factors, parameters, symbols and equations used to calculate the SeDeM radii values (Pérez *et al*., 2006, Suné-Negre *et al*., 2008 and Suné-Negre *et al*., 2011)

Incidence factor	Parameter	Symbol	Unit	Equation	Factor applied to the parameter value (v)
Dimension	Bulk density	Da	g/ml	Da = P/Va	10v
	Tapped density	Dc	g/ml	Dc = P/Vc	10v
Compressi-bility	Inter-particle porosity	Ie	-	Ie = (Dc - Da)/(Dc x Da)	10v/1.2
	Carr index	IC	%	IC = [(Dc - Da)/Dc] x 100	v/5
	Cohesion index	Icd	N	Hardness of MUPS at maximum compression force	v/20
Flowability/ Powder flow	Hausner ratio	IH	-	IH = Dc/Da	10 - (10v/3)
	Angle of repose	(α)	º	α = tan-1 h/r	10 - (v/5)
	Powder flow	t”	s	Time taken for 100 g to flow through funnel	10 - (v/2)
Lubricity/ Stability	Loss on drying	%HR	%	%HR = (weight before drying - weight after drying)/weight before drying] x 100	10 - v
	Hygroscopicity	%H	%	%H = (weight after exposure/weight before exposure) x 100	10 - (v/2)
Lubricity/ Dosage	Particle size < 45 µm	%Pf	%	Percentage that passed through 45 µm sieve	10 - (v/5)
	Homogeneity index	(IΘ)	-	$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$	500 v

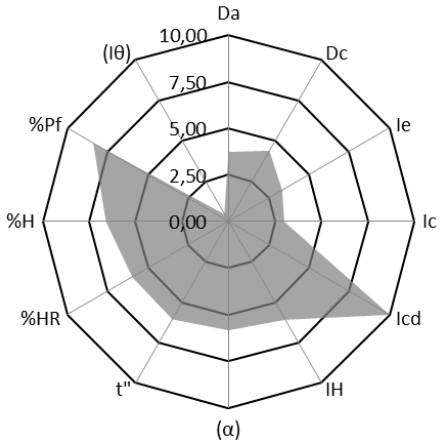

Figure 2: An example of the SeDeM diagram (graphical expression) with 12 parameters (taken from results of this study)

5 Multiple unit pellet systems (MUPS)

Multiple unit pellet systems (MUPS) comprises of a number of small uncoated or coated, spherical or semi-spherical units (referred to as pellets or beads) which are prepared by methods described above. The pellets are then compressed into tablets (MUPS tablets) or filled into capsules (MUPS capsules) using the same principles and equipment that are used in the manufacturing of conventional tablets and capsules. The technology used in MUPS formulations combine the advantages of conventional single unit dosage forms with that of small spherical or semi-spherical solid units into one multiple-unit dosage form (Reddy *et al.,* 2011, Dash *et al*., 2012 and Supriya *et al*., 2012).

6 Research aim and objectives

The aim of this study was to apply the SeDeM EDS in the formulation of MUPS tablets from pellets produced by different screen sizes and containing different APIs. This was done to determine whether the SeDeM EDS could provide information about the suitability of pellet formulations for compression into MUPS tablets and whether the impact of different pellet sizes and active pharmaceutical ingredients (APIs) would be reflected/detected by the SeDeM EDS.

The objectives of this study are:

- To prepare the following pellet formulations by means of extrusion-spheronisation each with five different extrusion screen sizes including 0.5; 1.0; 1.5; 2.0 and 2.5 mm:
    - Co-processed lactose-microcrystalline cellulose (MicroceLac® 200) alone (placebo);
    - MicroceLac® 200 with doxylamine as API;
    - MicroceLac® 200 with ibuprofen as API; and
    - MicroceLac® 200 with paracetamol as API.

- To evaluate the prepared pellet formulations in terms of the parameters required by the SeDeM EDS to calculate the incidence factors as well as constructing diagrams;

- To process the SeDeM EDS data further to predict the smallest amount of corrective excipient to be added to each of the pellet formulations (i.e. three model drugs and five pellet sizes) and to evaluate these pellet-excipient blends in terms of the parameters required by the SeDeM EDS;

- To compress the final predicted pellet formulations (for each of the three model drugs and each of the five pellet sizes) into MUPS tablets; and

- To evaluate the MUPS tablets in terms of uniformity of mass, hardness, friability, content uniformity, disintegration and dissolution.

7 References

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Chapter 2: Review Article: "*Use of natural gums and mucilages as pharmaceutical excipients*"

Chapter 2 is presented in the form of a review article entitled "*Use of natural gums and mucilages as pharmaceutical excipients*" which was published in the journal entitled *"Current Pharmaceutical Design"* in 2015 (volume 21, issue number 33, p 4775–4797; DOI: 10.2174/1381612821666150820100524). The complete guide for authors for this journal is given in Appendix D.

Pharmaceutical dosage forms comprise of API's and pharmaceutical excipients and each excipient has a specific role to fulfil in the formulation (e.g. binder, disintegrant, filler). Part of this PhD study was to investigate and apply the SeDeM EDS to different excipients and this review article gives an overview of natural excipients (i.e. gums and mucilages) and their application in the formulation of pharmaceutical dosage forms.

Use of Natural Gums and Mucilages as Pharmaceutical Excipients

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Abstract: Polysaccharide rich gums and mucilages are produced by different natural sources such as plants, animals and microbial organisms to fulfil structural and physiological functions. Their diverse structural compositions with a broad range of physicochemical properties make them useful for inclusion in dosage forms for different purposes such as to improve manufacturing processes and/or to facilitate drug delivery. A number of natural gums and mucilages have been investigated for inclusion in pharmaceutical formulations for a variety of reasons. The search for new excipients continues to be an active topic in dosage form design and drug delivery research. The aim of this review article is to give an overview of the chemical nature of natural gums and mucilages and to discuss their applications in the formulation of pharmaceutical dosage forms. Special emphasis will be placed on the use of gums and mucilages in novel drug delivery systems, such as modified release dosage forms and delivery systems that target specific sites of delivery.

Keywords: Drug delivery systems, gum, modified release dosage forms, mucilage, pharmaceutical excipients.

1. INTRODUCTION

Gums and mucilages are found in, or produced by a variety of plants, animals, fungi and microbial organisms. Both gums and mucilages are hydrocolloids and are translucent amorphous substances that consist primarily of linear or branched carbohydrate polymers that are either made up by the same repeating units of monosaccharides (i.e. homopolymer) or by mixed monosaccharides (i.e. heteropolymer or co-polymers), which are often combined with uronic acids. The hydrophilic polymeric molecules in gums form viscous solutions and mucilages form slimy masses when combined with water [1]. In general, carbohydrates perform physiological functions in plants such as providing structure or serve as a reserve energy source, while gums and mucilages specifically perform protective actions to prevent tissue desiccation [2].

Gums are pathological products, which are formed as a result of breakdown of the cell walls after injury to the plant or during droughts by means of extracellular formation [1]. Mucilages, on the other hand, are physiological products which originate in the plant either as a part of the contents of the cell or as a part of the cell wall by means of intracellular formation. Mucilages are therefore products of normal metabolism formed without injury to the plant, which are found in different parts of plants such as in the epidermal cells of leaves (e.g. senna), inside the plant roots (e.g. marshmallow), in the barks (e.g. slippery elm), in seed coats (e.g. linseed) and in the middle lamella of the plant leaves (e.g. *Aloe vera*) [1, 3].

Although advances in chemistry such as the discovery and synthesis of novel monomers make it possible to synthesize polymers with tailor made physico-chemical properties [4], natural polymers have several benefits such as being safe, biodegradable, biocompatible, stable and cost-effective [5,6]. In addition, plant biomass resources that are constantly renewed by photosynthesis provide sustainable sources of raw materials [7] that can contribute to overcoming the widespread dependency on limited fossil fuel sources [8].

Formulation of a dosage form involves mixing the drug or active ingredient with pharmacologically inactive compounds, referred to as pharmaceutical excipients, which fulfil specific roles such as improving manufacturability and facilitating drug release [9]. Pharmaceutical excipients should comply with certain general requirements such as physiological inertness and absence of toxicity, high chemical stability, compatibility with the active ingredient and commercial availability at low cost [10].

Polymers are commonly used in the formulation of dosage forms. Various natural gums and mucilages have been investigated for different pharmaceutical applications in different types of dosage forms. They have specifically been investigated for their use as binding agents, suspending agents and also mucoadhesive agents. Many of the gums and mucilages have shown potential to be used in the formulation of modified release dosage forms. In this regard, many studies have shown that the polysaccharide rich gums and mucilage materials can be used to produce matrix type tablets, gastro-retentive systems, bioadhesive systems and stimuli responsive drug delivery systems [11].

The aim of this review is to provide a comprehensive discussion on different natural gums and mucilages with specific emphasis on their potential to be employed as pharmaceutical excipients in dosage form design. Semi-synthetic and chemically modified polysaccharides fall outside the scope of this overview.

2. NATURAL GUMS

2.1. Classification of Gums

Classification of gums, as summarised in Table **1**, can be based on different characteristics or aspects, which may include the source or origin, the shape of the polysaccharide chains (e.g. linear or branched), the chemical structure, charge of the molecules and gelation behaviour.

The polysaccharides of gums and mucilages are comprised of different basic chemical units. Table **2** provides the chemical structure of these basic chemical units, while Table **3** provides information regarding the source, shape of the polysaccharide chain, chemical structure/chemical constituents and charge of different natural gums.

2.2. Pharmaceutical Applications of Natural Gums

2.2.1. Acacia Gum

Acacia gum, also known as gum arabic, is an exudate obtained from acacia trees (i.e. *Acacia arabica* and *Acacia senegal*). It consists of a mixture of the highly branched molecule, which is made

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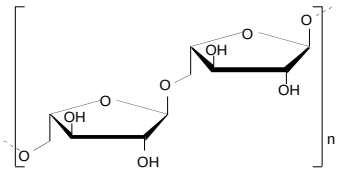
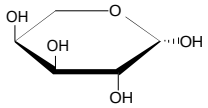
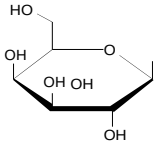
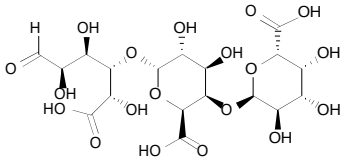
Table 1. Classification of gums (adapted from [1, 3, 12, 13]).

Basis of classification	Class	Gums
Shape of polymer chain	Linear	Alginates, carrageenans
	Short branches	Guar gum, xanthan gum, locust bean gum, konjac
	Branch-on-branch	Acacia gum, tragacanth gum
Charge	Non-ionic	Guar gum, xanthan gum, locust bean gum
	Anionic	Carrageenans, acacia gum, gellan gum
Origin / source	Plant seeds	Guar gum, karaya gum, locust bean gum
	Plant exudates	Acacia gum, karaya gum
	Plant tubers and roots	Konjac, glucomannans
	Microorganisms	Gellan gum, xanthan gum, dextran
	Marine algae and sea weed	Carrageenans, alginic acid, sodium alginate
Chemical type	Galactomannans	Guar gum, tara gum, fenugreek gum
	Glucomannans	Konjac
	Tri-heteroglycans	Gellan gum
	Tetra-heteroglycans	Acacia gum
	Penta-heteroglycans	Tragacanth gum
	Uronic acid containing gums	Xanthan gum
Gelation behaviour	Cold set gels	Gelatin, gellan gum
	Heat set gels	Konjac
	Re-entrant gels	Xyloglucan

Table 2. Chemical structures of the basic units of gums and mucilages.

Basic unit	Chemical structure
Arabinin	
Arabinose	
Galactose	
Galacturonic acid	

(Table 2) Contd….

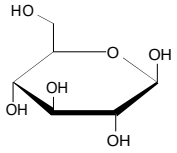
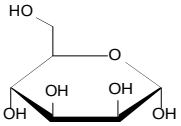
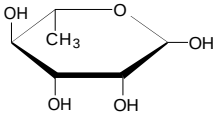
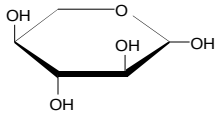
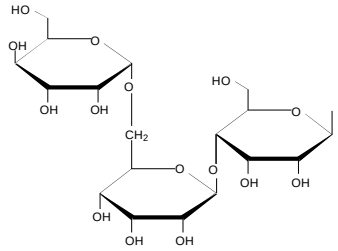
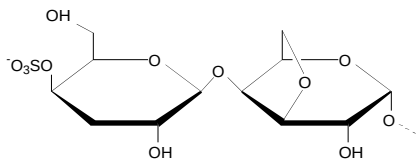
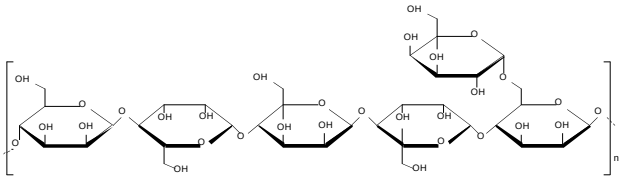
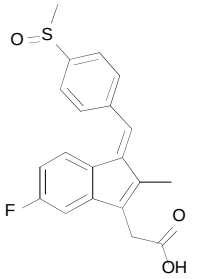
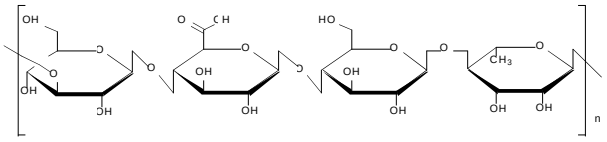
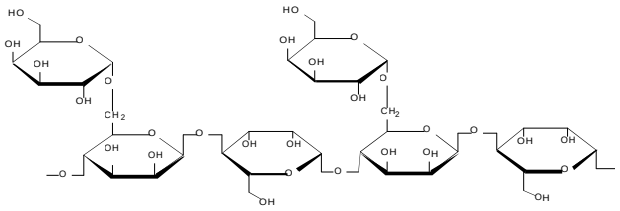
Basic unit	Chemical structure
Glucose	
Mannose	
Rhamnose	
Xylose	

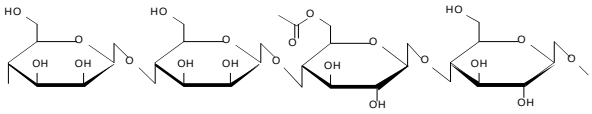
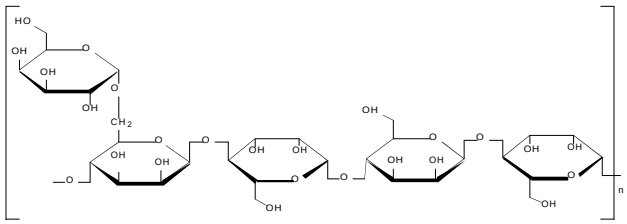
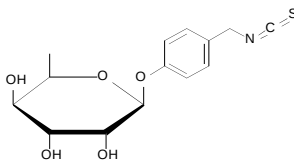
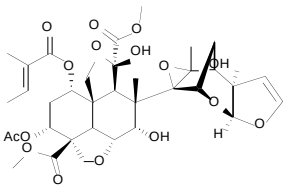
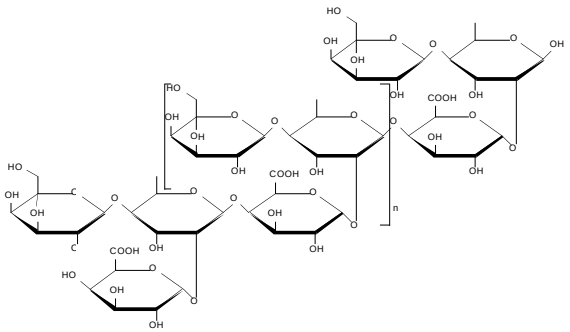
Table 3. Summary of the origin and chemical characteristics of natural gums.

Name of gum	Source/Origin	Shape of polysaccharide chain	Chemical constituent(s)/Chemical structure	Charge	Refs.
Acacia gum	*Acacia arabica* and *Acacia senegal* tree (Plant origin – exudate)	Branched, branch-on-branch		Anionic	[1, 12]
Albizia gum	*Albizia zygia* tree/shrub (Plant origin - exudate)	Highly branched	Galactose units	Ionic	[1, 14, 15]
Almond gum	*Prunus amygdalus* tree /shrub (Plant origin - exudate)	-	Galactose and arabinose with traces of xylose, rhamnose, glucose and mannose	-	[15]
Bhara gum	*Terminalia bellerica* tree (Plant origin - exudate)	-	Tannins which mainly include B-sitosterol, gallic acid, ellagic acid, ethyl gallate, galloyl glucose and chebulaginic acid	-	
Carrageenans	Red seaweed *Chondrus crispus*, *Eucheuma cottonii*, *Eucheuma spinosum*, or *Gigartina stellata* species	Liniar, unbranched	 Kappa-carrageenan	Anionic	[12, 16]

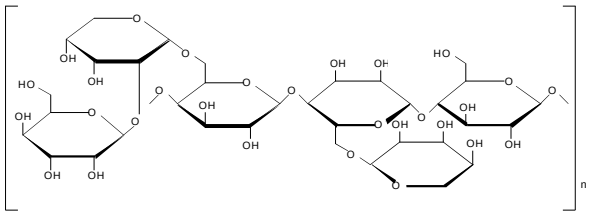
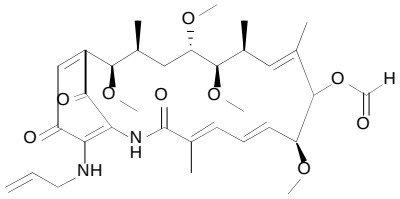
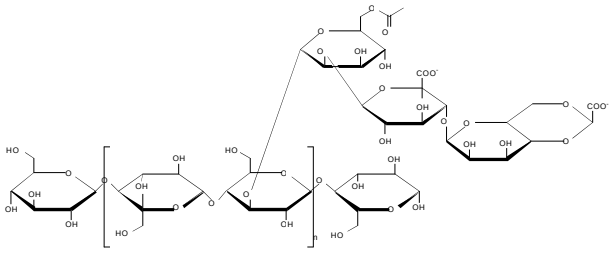
(Table 3) Contd….

Name of gum	Source/Origin	Shape of polysaccharide chain	Chemical constituent(s)/Chemical structure	Charge	Refs.
Cashew gum	*Anacardium occidentale* tree (Plant origin - exudate)	Highly branched	Polysaccharides with a main chain of galactose linked with side chains of galactose and glucose. Other monosaccharides are present as terminal units	-	[15]
Cassia gum	*Cassia fistule* or *Cassia roxburghii* tree (Plant origin - seeds)	-		-	[15]
Copal gum	*Bursera bipinnata* plant (Plant origin - exudate)	-		-	[15]
Flaxseed gum	*Linum usitatissimum* plant (Plant origin - exudate)	-	Galactose, galacturonic acid, rhamnose, and xylose	-	
Gellan gum	*Pseudomonas elodea* (Microbial origin)	Linear		Anionic	[12, 15]
Grewia gum	*Grewia mollis* plant (Plant origin - exudate)	-	Glucose and rhamnose monosaccharide units	-	[15, 17]
Guar gum	*Cyamompsis tetraganolobus* plant (Plant origin - seeds)	Linear, short branched		Non-ionic	[1, 12]
Hakea gum	*Hakea gibbosa* tree (Plant origin - exudate)	-	Arabinose, galactose, xylose and mannose	-	[15]
Honey locust gum	*Gleditsia triacanthos* L. tree (Plant origin - seeds)	Branched	Galactomannan which consists of a mannan backbone with galactose branches	Non-ionic	[1]
Karaya gum	*Sterculia urens* tree/shrub (Plant origin - exudate)	Highly branched	Galactose, rhamnose, uronic acid, some xylose residues and acetyl groups	Anionic	[1, 18]

(Table 3) Contd….

Name of gum	Source/Origin	Shape of polysaccharide chain	Chemical constituent(s)/Chemical structure	Charge	Refs.
Kondagogu gum	*Cochlospermum gossypium* tree (Plant origin - exudate)	-	Rhamnose, glucuronic acid, glucose, galactose, arabinose, mannose and fructose with sugar linkages	Anionic	[19]
Konjac glucomannan	*Amorphophallus konjac* plant (Plant origin - tubers)	Linear, short branched		-	[12]
Locust bean bum	*Ceratonia siliqua* tree (Plant origin - seeds)	Linear, short branched		Non-ionic	[1, 12]
Mango gum	*Mangifera indica* tree (Plant origin - exudate)	-	-	-	
Mimosa scabrella gum	*Mimosa scabrella* tree (Plant origin - seeds)	Branched	Mannose and galactose	Non-ionic	[15]
Moi gum	*Lannea coromandelica* tree (Plant origin – whole plant)	-	Galactose and arabinose	-	
Moringa oleifera gum	*Moringa oleifera* tree (Plant origin – exudate)	-		-	[15]
Neem gum	*Azadirachta indica* tree (Plant origin – whole plant)	-	 Azadirachtin, one of the active compounds of neem gum	-	[15]
Okra gum	*Abelmoschus esculentus* or *Hibiscus esculentus* plant (Plant origin - fruit)	Highly branched		-	[20]

(Table 3) Contd….

Name of gum	Source/Origin	Shape of polysaccharide chain	Chemical constituent(s)/Chemical structure	Charge	Refs.
Tamarind gum	*Tamarindus indica* tree (Plant origin - seeds)	Highly branched		Non-ionic	[1, 21]
Tara gum	*Caesalpinis spinosa* tree (Plant origin - seeds)	Linear, short branched	Mannose and galactose units	Non-ionic	[1, 12]
Terminalia catappa gum	*Terminalia catappa* tree (Plant origin - exudate)	-	-	-	
Tragacanth gum	*Astragalus gummifer* tree (Plant origin - exudate)	Branched, branch-on-branch		Anionic	[1]
Xanthan gum	*Xanthomonas campestris* (Microbial origin)	Linear, short branched		Anionic	[1, 12]
Xyloglucan	*Tamarindus indica* and *Hymenaea courbaril* tree (Plant origin - seeds)	-	(mannose and galactose units)	-	

up of galactose units, and other carbohydrates such as arabinose, glucuronic acid and rhamnose [16]. Acacia gum is Generally Recognized as Safe (GRAS) by the FDA [22].

Acacia gum has been used for different pharmaceutical applications such as a suspending agent, binder, emulsifying agent, matrix microencapsulating agent and as an osmotic suspending and expanding agent to prepare monolithic osmotic tablet systems [23,24]. Chopra *et al.* [25] formulated zinc oxide nanoparticles incorporated in nanohydrogel particles. The zinc oxide nanoparticles were prepared by a hydrothermal method using a zinc acetate and sodium hydroxide solution. The nanohydrogel particles were prepared by covalent cross-linking of sodium alginate/acacia gum using glutaraldehyde as a cross-linker. Zinc-loaded nanohydrogels were then prepared by adding zinc oxide nanoparticles to the sodium alginate solution. This formulation not only exhibited high encapsulation efficiency, but also showed sustained release properties.

2.2.2. Albizia Gum

Albizia gum is obtained from the trunk of the *Albizia zygia* tree and consists of polysaccharides made up of galactose units [14].

Albizia gum has been investigated as a potential substitute for acacia gum and has been used in compression coatings for colon targeted delivery of poorly water-soluble (e.g. indomethacin) and water-soluble (e.g. paracetamol) drugs. The gum was used as coating material for compressed tablets with the aim to protect the drug from being released in the stomach and small intestine. As a result of degradation of the polysaccharides in the colon, it was used as a colon targeted drug delivery system. In this study by Odeku & Fell [26] it was shown that the gum hydrates in the physiological environment of the stomach and small intestine and forms a viscous gel layer around the tablets resulting in slow diffusion of the dissolution fluid into the tablet core. The *in-vitro* drug release study was conducted by using 0.1M HCl for 2 h, then Sorensen's buffer (pH

7.4) for 3 h, followed by phosphate-buffered saline (pH 6.8) for the rest of the experiment. The results showed that albizia gum can effectively control the release of the drugs in the stomach and small intestine. Furthermore, the susceptibility of the gum to degrade in the presence of microorganisms in the colon, was investigated by dissolution studies carried out in simulated colonic fluid, containing 4% (w/v) rat fecal content. The dissolution study was conducted by using 0.1M HCl for 2 h, Sorensen's buffer (pH 7.4) for 3 h and then rat fecal content medium for the rest of the experiment. The coating was almost completely degraded leading to complete release of the drug within 24 h. These results showed that albizia gum is susceptible to enzymatic degradation in the presence of colonic microorganisms. This study concluded that albizia gum has the potential for targeted drug delivery to the colon [26].

2.2.3. Almond Gum

Almond gum is produced by almond trees and shrubs (*Prunus amygdalus*) and mainly consists of polymers made up of galactose and arabinose with traces of xylose, rhamnose, glucose and mannose [27].

Farooq *et al.* [28] extracted and studied almond gum for its suitability as pharmaceutical excipient. Almond gum exhibited excellent flow properties and was found to be soluble in warm water and insoluble in organic solvents. The results of the evaluated properties showed that almond gum has an acceptable pH and organoleptic properties which can be considered and investigated further as a pharmaceutical excipient in the formulation of solid oral dosage forms.

Sarojini *et al.* [29] investigated the use of almond gum as a tablet binder and release retardant in diclofenac sodium tablet formulations. The uncoated tablets were prepared by wet granulation with a binder solution consisting of almond gum dissolved in distilled water. Various concentrations of the binder were investigated and all the formulations exhibited good flow properties. The tablets formulated with a 2% (w/v) almond gel binder solution, yielded optimal binding properties. However, only a small retardation in drug release was observed. Almond gel can therefore be considered in future studies as a binder in solid oral dosage form formulations.

The polymer has also been investigated in the design of tablets using levofloxacin hemihydrate as a model drug. Tablets prepared by employing almond gum showed acceptable pharmaceutical properties and slow drug release (of about 90%), which extended up to 12 h. The drug release profile of various matrix type tablet formulations (F4 to F9) containing different quantities of almond gum ranging between 50 to 150 mg per tablet in different ratios to lactose is shown in Fig. **1**. Almond gum also yielded very good flow properties, better than those exhibited by other polymers such as compritol [30].

Based on these examples almond gum can be considered as a pharmaceutical excipient for its binding and sustained release properties, but the most beneficial property seems to be the positive impact that almond gum has on the flow properties of tablet formulations.

2.2.4. Bhara Gum

Bhara gum is obtained from the *Terminalia bellerica* tree in India. Its main chemical constituents are tannins which mainly include P-sitosterol, gallic acid, ellagic acid, ethyl gallate, galloyl glucose and chebulagic acid [31].

Nayak *et al.* [31] investigated the sustained release properties of bhara gum in a microcapsule formulation. Famotidine loaded microcapsules were prepared by ionic gelation yielding spherical microcapsules without aggregation and with a circularity factor close to 1.00. The mean geometric particle size ranged from 71.57 to 94.75 µm, the swelling percentage was between 80.23 and 91.53% and the wall thickness ranged between 31.01 and 38.69 µm. An *in vitro* drug release study was conducted using 0.1 N HCl. The microcapsules exhibited slow release of famotidine over a period of 10 h. The researchers concluded that bhara gum could be used for the development of oral sustained release drug delivery systems.

2.2.5. Carrageenans

Carrageenans are natural hydrophilic polymers extracted from red seaweed and are classified as anionic gums of marine origin [1; 32]. Carrageenan polymers are composed of D-galactose residues, which consist of galactopyranose units. They are classified according to the degree of the substitution that occurs on their free hydroxyl groups to iota (τ), kappa (K) and lambda (A)-carrageenans. Carrageenans are Generally Recognized as Safe (GRAS) by the FDA [22] and are one of the most used gums for different applications and have been used as gelling agents and stabilisers in emulsions and suspensions and have been found to be effective for pharmaceutical applications, especially for the preparation of controlled release formulations [32].

Karavas *et al.* [33] investigated the use of τ- and A-carrageenans as appropriate carriers for sustained release formulations of fluvastatin. From this study they found that fluvastatin can form complexes with τ- and A-carrageenan due to the sulfate groups of these carrageenans, which interact with the hydroxyl groups of fluvastatin. Their study concluded that fluvastatin-carrageenan complexes had lower dissolution rate profiles compared with physical mixtures.

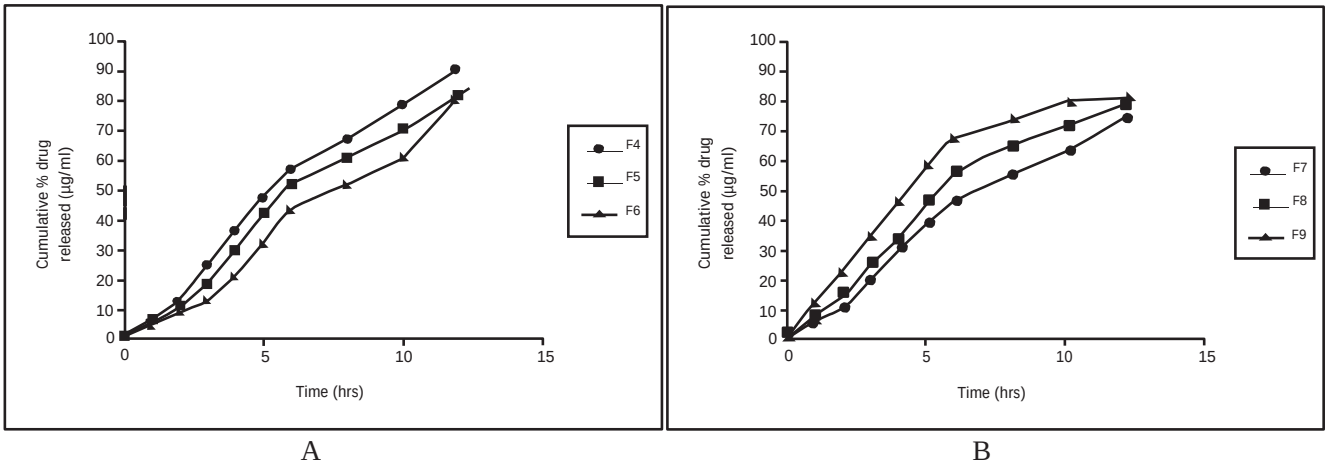


Fig. (1). Drug release profiles from various matrix formulations including **A**) F4 – F6 and **B**) F7 - F9 [with permission from 30].

A sustained release floating drug delivery system of sodium salicylate was developed using K-carrageenan as the sustained release matrix. Various concentration ratios of K-carrageenan dispersions and drug were used. The physical properties, *in vitro* buoyancy lag time, total floating time and *in vitro* drug release of the various matrices were studied in 0.1 N HCl. The results showed acceptable buoyancy lag time ranging from 50 – 55 s and total floating time of more than 12 h. Drug release varying from 47.7 – 97.0% was observed at 6 h for the various formulations. It was shown that an increase in carrageenan content resulted in an increase in drug release. Carrageenan can therefore be used as an excipient in gastro-retentive matrix formulations of sustained release floating tablets [34].

The possibility that pH-responsive carboxymethylated K-carrageenan microparticles could protect entrapped oral insulin from acidic and proteolytic degradation in the gastrointestinal tract was investigated by Leong *et al.* [35]. Insulin was entrapped in carboxymethylated K-carrageenan microparticles by using the ionotropic gelation process. The therapeutic efficiency of the microparticles was evaluated by *in vitro* and *in vivo* studies. The *in vitro* release of insulin from the microparticles was investigated by simulating the transition of microparticles from the stomach to the intestinal region after oral ingestion. The microparticles were placed in simulated gastric fluid (pH 1.2) for 2 h, after which the simulated gastric fluid was carefully removed and replaced by simulated intestinal fluid (pH 7.4) for 8 h. The release of insulin from the microparticles in the simulated gastric fluid was minimal during the first 2 h and increased gradually in the simulated intestinal fluid. Complete insulin release was observed within 10 h. *In vivo* studies were performed in diabetic induced male Sprague-Dawley rats. The microparticles were pre-packed in hard gelatin capsules and administered orally to the rats. Blood was collected from the tail vein and the blood glucose levels were measured using an Accu-Check Active blood glucose meter. The insulin-loaded microparticles showed glycemic control that lasted 12-24 h. The study concluded that insulin entrapped in carboxymethylated K-carrageenan microparticles was protected from hydrolysis and proteolysis by stomach acid and enzymes and provided sustained release up to 12-24 h [35].

2.2.6. Cashew Gum

Cashew gum is extracted from the *Anacardium occidentale* tree, widely distributed in the northeast of Brazil. Cashew gum is composed of polysaccharides with a main chain of galactose linked with side chains of galactose and glucose. Other monosaccharides are present as terminal units. Cashew gum has mainly been applied as a suspending agent [36].

Controlled drug release up to 72 h was achieved with indomethacin loaded cashew gum nanoparticles with indomethacin. *In vitro* drug release studies were conducted on the self-assembled nanoparticles by introducing the indomethacin-loaded nanoparticles into dialysis bags which were placed in phosphate buffer (pH 7.4). Samples were withdrawn periodically and the drug content was determined spectrophotometrically. The drug release profile showed an initial burst release effect in the first 2 h followed by controlled release up to 72 h. The initial burst release effect was thought to be due to the indomethacin which was absorbed onto the surfaces of the nanoparticles [37].

In another study, isoxsuprine HCl-loaded microbeads using cashew gum and sodium alginate were prepared by ionotropic-gelation. $ZnSO_4$ was used as cross-linker and the effects of the polymer-blend ratio and the cross-linker concentration on drug encapsulation efficiency and drug release were evaluated. A high drug encapsulation efficiency of 79,92% and an *in vitro* isoxsuprine HCl sustained drug release pattern over a period of 7 h was achieved. The study concluded that this type of drug delivery system could be used for the future development of sustained release systems comprising of other water soluble drugs, proteins and enzymes [38].

2.2.7. Cassia Gum

Cassia gum occurs in the seeds of *Cassia fistula* or *Cassia roxburghii* trees and comprises of mannose units with random distribution of galactose units as side chains. The ratio of mannose to galactose is about 5:1 [39, 40]. Carboxymethylation as well as carbamoylethylation of cassia gum have been reported to improve cold water-solubility, increase viscosity and increase microbial resistance as compared with native cassia gum [39]. Cassia is Generally Recognized as Safe (GRAS) by the FDA [22].

Cassia gum has been studied for its binding properties using paracetamol as a model drug. Tablets were formulated using different concentrations of aqueous binding solutions of cassia gum. These tablets yielded better mechanical properties and longer disintegration and dissolution times than tablets containing sodium carboxymethylcellulose and gelatin. The results suggest that cassia gum could be useful as a binding agent, especially when high mechanical strength and slower drug release are required [40].

Rai *et al.* [39] investigated cassia gum derivatives as superdisintegrants for fast disintegrating tablet formulations. These tablets needed to have sufficient mechanical strength as well as fast disintegration time. The study specifically investigated the use of calcium or sodium salts of carboxymethylated or carbamoylethylated cassia gum for fast disintegrating tablets containing a water-soluble drug namely metoclopramide HCl. The findings from this study indicated great potential for using these chemically modified cassia gum polysaccharides as superdisintegrants.

2.2.8. Copal Gum

Copal gum is obtained from the *Bursera bipinnata* plant and is a natural resinous material. The chemical components of copal gum include agathic acid, agathalic acid, agatholic acid, acetoxy agatholic acid, monomethyl ester of agathalic acid, ciscommunic acid, transcommunic acid, polycommunic acid and sandaracopimaric acid [41].

Oral sustained release tablets were formulated using hydrophilic Eudragit® RS PO alone and in combination with hydrophobic copal gum and damar gum. Tablets were prepared by wet granulation using metformin HCl as a model drug. The drug release revealed that Eudragit® RS PO alone was unable to sustain the drug release, however, combining Eudragit® with copal gum and damar gum sustained the drug release for more than 12 h [42].

Furthermore, copal gum-resin was investigated by Umekar & Yeole [43] for its physicochemical properties, moisture absorption and swelling properties to determine its potential as a coating material for sustained release and colon-targeted drug delivery. Films of copal gum-resin were prepared by solvent evaporation on mercury substrate and various formulations of copal gum-resin using different plasticizers were prepared and studied. The results indicated that copal gum-resin has good film-forming properties. However, further studies are needed to determine its use as matrix material for sustained, pH-dependent and colon-targeted drug delivery.

2.2.9. Flaxseed Gum

Flaxseed, also known as linseed, is produced by the flax plant (*Linum usitatissimum*) and consists of an anionic polysaccharide, which is extracted with water from the plant. The polysaccharide consists mainly of xylose, galactose, rhamnose, and galacturonic acid, with varying ratios of the acidic and neutral fractions [44].

Flaxseed gum has been investigated for its binding properties using lactose granules with different binder concentrations in an uncoated tablet formulation. Flaxseed gum was compared with regularly used binders (e.g. starch paste and polyvinylpirrolidone). Tablets containing 7% (w/v) flaxseed gum revealed good tableting properties and showed good binding properties as compared with the regular binders [45]. In another study investigating flaxseed

gum's binding properties the gum was compared with starch. The tablet formulations containing flaxseed gum showed good friability, hardness and dissolution and compared well with starch as a binder [46].

Flaxseed gum has also been investigated as an excipient in fast disintegrating tablets containing glibenclamide. The gum was compared with a synthetic superdisintegrant (e.g. crosspovidone). The tablets were prepared by direct compression and evaluated for hardness, friability, drug content uniformity, *in vitro* dispersion time, wetting time, water absorption ratio, *in vitro* drug release (in phosphate buffer, pH 6.8), stability studies (at 40°C/75% RH for 3 months) and drug-excipient interaction. The formulation containing 12% (w/w) of flaxseed yielded the best *in vitro* drug release when compared with a conventional commercial tablet formulation. The tablets containing flaxseed gum yielded acceptable disintegration results for fast disintegrating tablet formulations [47]. Another study revealed that the gum does not have good gelling properties, but has pH dependent swelling properties and can, therefore, be considered as a candidate for gastrointestinal tract drug delivery [48].

2.2.10. Gellan Gum

Gellan gum is a polysaccharide rich gum produced by *Pseudomonas elodea*. The culture fermentation process is followed by purification with isopropyl alcohol, drying and milling. The high molecular weight polysaccharides consist of repeating units of a tetrasaccharide, comprised of rhamnose, glucose, glucorunic acid and glucose. Gellan gum is mainly used as a gelling agent in oral drug delivery systems [49]. Gellan gum is Generally Recognized as Safe (GRAS) by the FDA [22].

Bhattacharya *et al.* [50] formulated gellan gum microbeads containing tranexamic acid as a model drug. The beads were prepared using a sol-gel transition induced by the ionic crosslinking method from an aqueous template containing aluminium (Al^{3+}) ions as a crosslinking agent. *In vivo* studies were performed in rabbits to determine the sustained drug release properties over a prolonged period following oral administration. The study concluded that the gellan gum microbeads could modulate drug release in an alkaline medium and minimize the release of tranexamic acid in an acidic medium. Gellan gum containing microbeads therefore provided intestinal specific controlled release of tranexamic acid.

An injectable system for the intra-bone delivery of alendronate, based on alendronate-loaded nanoparticles suspended in a gellan gum hydrogel matrix was developed by Posadowska *et al.* [51]. Alendronate-loaded nanoparticles were suspended in a gellan gum matrix and the hydrogel matrix was cross-linked with calcium ions to provide structural integrity suitable for injection. *In vitro* studies carried out by using dialysis bags showed that the system delivered controlled release up to 25 days. The system was found to be injectable and restored the elastic structure after extrusion; assured local and uniform drug delivery and inhibited osteoclast differentiation without affecting osteoblast functions [51].

Vilela *et al.* [52] prepared gellan gum microgels by atomisation followed by ionic gelation using KCl or $CaCl_2$ as hardening agent. Some of the gellan microgels were then coated with chitosan in order to improve their resistance to gastric digestion. *In vitro* digestion testing was performed on both the chitosan-coated gellan microgels and the uncoated gellan microgels. The *in vitro* testing showed that all the particles maintained their size and shape after the gastric digestion step and that the gellan microgels were resistant to the simulated gastric conditions. The enteric digestion caused disintegration of the microgels indicating that they have the potential to be used in the formulation of enteric delivery systems. The chitosan-coated gellan microgels showed a lower degree of fragmentation than the uncoated gellan microgels, indicating that the chitosan coating increased the particles' resistance to the enteric conditions [52].

2.2.11. Grewia Gum

Grewia gum is extracted from the inner stem bark of the *Grewia mollis* plant. It has been reported to consist of glucose and rhamnose monosaccharide units [17].

Grewia gum has been investigated for its bioadhesive property for sustained release. Indomethacin tablets were formulated in which the grewia gum was compared with Carbopol® 934, tragacanth and sodium carboxymethylcellulose. The tablets were prepared by wet granulation and contained 75 mg of the drug and 15-20% (w/w) of the gum. Tragacanth yielded the fastest drug release and Carbopol® 934 the slowest. Tablets containing grewia gum yielded a slower drug release when compared with that of tragacanth, but faster than that of sodium carboxymethylcellulose (sodium CMC). The drug release profiles of indomethacin tablets containing grewia gum, tragacanth gum, sodium CMC and Carbopol® 934 are shown in Fig. (**2**). The bioadhesive performance of grewia gum and the reference polymers was assessed by measuring the detachment force using a testometric machine equipped with a Newton transducer. Phosphate buffer solution (pH 7.4) and 0.1 N hydrochloric acid (HCl) were used as hydration media while pig gastric mucosa was used as substrate. The detachment force was found to be affected by the pH of the hydration medium and grewia gum can therefore be used as bioadhesive polymer for sustained release tablet formulations [53].

The binding properties of grewia gum have also been investigated by formulating paracetamol tablets. Grewia gum was treated with hydrochloric acid and compared with the untreated gum. Tablets produced with the untreated gum showed higher crushing strength, disintegration and dissolution times and lower friability than tablets produced with the treated gum. Treated grewia gum can therefore be used as a binder in the formulation of conventional tablets [54].

2.2.12. Guar Gum

Guar gum is a galactomannan produced by the seeds of *Cyamompsis tetraganolobus.* The non-ionic carbohydrate polymer consists of mannose and galactose units. The ratio of mannose to galactose in guar gum is approximately 2:1 [55]. Guar gum is Generally Recognized as Safe (GRAS) by the FDA [22] and is one of the most used gums and has various pharmaceutical uses such as a binder, thickening agent, sustained release agent, disintegrant, emulsifier and application in colon targeted drug delivery [56, 57]. A "tabs in cap" drug delivery system was developed by Gangwar *et al* [56] to investigate the biphasic, pulsed release of the model compound losartan. An erodible guar gum time spacer tablet was sandwiched between drug loaded tablets, which were then encapsulated in hard gelatin capsules. *In vivo* and *in vitro* release studies indicated that this system, which contains a guar gum spacer tablet, could produce a two pulse drug release profile involving immediate drug release followed by a delayed drug release pulse [56].

Gupta & Verma [58] produced carboxymethyl guar gum nanoparticles by using a nano-precipitation and sonication process, which resulted in nanoparticles in the range of 12-30 nm when different solvents and sonication times were used. Nanoparticles can act as potential carries for several classes of drugs such as anticancer agents, antihypertensive agents, immune-modulators, and hormones; and macromolecules such as nucleic acids, proteins, peptides and antibodies [59]. Soumya *et al.* [60] also prepared guar gum nanoparticles by using a nano-precipitation and cross-linking method, yielding spherical nanoparticles in the range of 20-50 nm. Crystal violet was chosen as the model compound in this study which indicated that the formation of nanoparticles depends upon the molecular mass of the galactomannan, solvent, surfactant, cross-linker and agitation.

Murali *et al.* [57] formulated a doxorubicin injectable hydrogel system using guar gum. A reaction between the quaternary amino groups and water molecules formed a strong gel at 37ºC resulting in

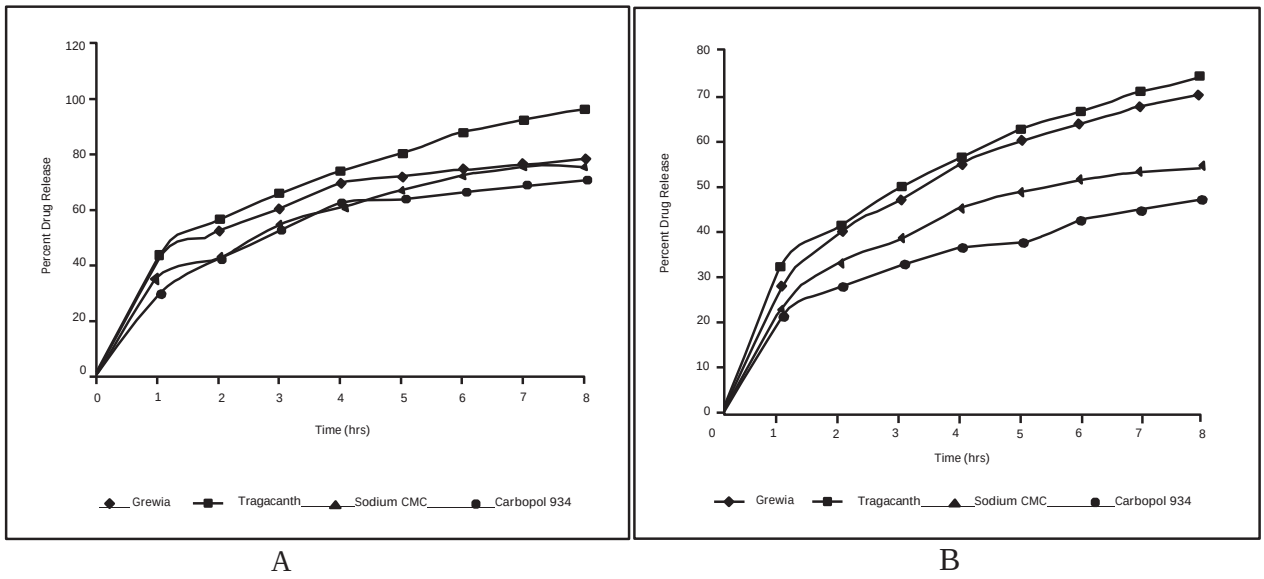


Fig. (2). Drug release profiles of indomethacin tablets containing **A**) 15% (w/w) and **B**) 20% (w/w) of the selected polymers respectively [with permission from 53].

sustained drug release. The study showed that the drug and core-shell nanoparticles can be released slowly from the hydrogel providing a delivery system for long-term drug treatment of cancer patients.

In a study investigating bi-gels, ciprofloxacin loaded bi-gels (which are semi-solid formulations prepared by mixing two gels at a high shear rate) were prepared by mixing guar gum hydrogel and a ciprofloxacin loaded organogel. The bi-gels with higher proportions of organogel were smooth and stable and showed higher viscosity and firmness than the bi-gels with lower proportions of the organogel. However, the bi-gels with lower proportions of organogel showed higher *in vitro* drug release approaching zero order kinetics which is desirable for a controlled drug release system. Although this study was only a preliminary study, the development of these bi-gels may be considered as matrices for topical drug delivery in the future [61].

2.2.13. Hakea Gum

Hakea gum is a polysaccharide containing exudate from the *Hakea gibbosa* tree. Partial acid-hydrolysis of the exudate from *H. gibbosa* yields arabinose, galactose, xylose and mannose [62].

This gum has been used to sustain the release of chlorpheniramine from a unidirectional-release buccal tablet, but it also exhibited excellent mucoadhesive properties. The mechanism, by which sustained drug release was achieved, is possibly the slow relaxation of the hydrated hakea gum polysaccharide molecules [63].

2.2.14. Honey Locust Gum

Honey locust gum is obtained from *Gleditsia triacanthos* L. found in Mediterranean counties including Turkey and Middle Europe, and in parts of America. Honey locust seeds contain the gum and the highest gum yield is obtained when the seeds and fruit are mature, from fall until the end of winter. Honey locust gum is water-soluble and forms highly viscous, stable aqueous solutions. The gum contains galactomannan which consists of a mannan backbone with galactose branches [20]. Honey locust gum is Generally Recognized as Safe (GRAS) by the FDA [22]. Honey locust gum has been used as a gel base in topical products, disintegrant, binder, thickener and stabiliser in suspensions, emulsifier in emulsions and coating material in tablet and microcapsule formulations [19].

In a study by Üner & Altinkurt [64], the properties of honey locust gum were compared with different polymers e.g. hydroxyethylcellulose (HEC) and hydroxypropyl methylcellulose (HPMC), which are conventionally used in tablet manufacturing. The release profile of the model drug (i.e. theophylline) from a matrix tablet prepared with honey locust gum was compared with a commercial sustained release tablet. The dissolution results indicated that there was no significant difference between the commercially available sustained release tablet and the matrix tablet prepared from honey locust gum in each of the three dissolution media tested. In addition, the matrix tablet formulated from honey locust gum showed zero-order release kinetics in all the dissolution media.

2.2.15. Karaya Gum

Karaya gum is a natural gum exudate of the *Sterculia urens* tree, native to India. The gum contains galactose, rhamnose, uronic acid, some xylose residues and acetyl groups [65]. Karaya gum is Generally Recognized as Safe (GRAS) by the FDA [22].

Karaya gum is widely used due to its high viscosity properties, high swelling and water retention capacity [66]. It is also used as a mucoadhesive, suspending agent, as well as sustained release agent in tablets and as an emulsifying agent [67].

Babu *et al.* [68] reported on a modified form of karaya gum with a low viscosity and better handling properties, but with comparable swelling capacity to that of natural karaya gum. The karaya gum was modified by heating the gum at 120ºC for 2 h using a sand bath and then sieving it through a 100 mesh sieve. The modified karaya gum was evaluated as a carrier for dissolution enhancement of poorly water-soluble drugs such as nimodipine. The study concluded that modified karaya gum could be used as a dissolution rate enhancer for poorly water-soluble drugs, possibly due to increased wettability, dispersibility and reduced crystallinity of nimodipine.

In another study karaya gum and nimodipine was co-grinded. The *in vitro* and *in vivo* studies on the drug release rate of co-grinded mixtures of karaya gum and nimodipine found that the drug release rate of the nimodipine from the co-grinded mixtures was significantly higher than that of the physical mixtures of pure nimodipine. The study concluded that the modified karaya gum could be used for the dissolution enhancement of nimodipine [69].

2.2.16. Kondagogu Gum

Kondagogu gum is collected from the *Cochlospermum gossypium* tree and is an anionic polysaccharide that belongs to the class of substituted rhamnogalacturonans. The gum consists of rhamnose, glucuronic acid, glucose, galactose, arabinose, mannose and fructose with sugar linkages [70].

This gum has been modified by carboxymethylation and the results of subsequent characterisation studies revealed an increase of the degree of crystallinity and surface roughness of the gum and a reduction of viscosity, leading to improved mucoadhesive properties. Ionotropically gelled beads of carboxymethyl kondagogu gum were also used in the formulation of tablets using metformin as a model drug and calcium chloride as cross-linking agent. Bioadhesion of more than 80% over a period of 24 h was achieved in *ex vivo* studies using isolated chick-ileum [71].

The emulsifying properties of kondagogu gum were investigated by preparing different concentrations of the gum in water and emulsifying it with liquid paraffin oil in a high-speed homogeniser. The emulsions showed pseudoplastic flow behaviour and it was found that the stabilisation of the emulsions was due to mutual repulsion between the electrical double layers of particles and adsorption of macromolecules on oil droplets. The study concluded that kondagogu gum is a good emulsifying agent [72].

Reddy [73] investigated the application of this gum as matrix of sustained release pellets. Gliclazide pellets were prepared by a direct layer technique using different concentrations of the gum. Sustained release properties and good bioavailability, similar to that of a commercially available extended release formulation, was achieved. Kondagogu gum therefore, has the potential to be used as a controlled release matrix polymer in the pharmaceutical industry.

2.2.17. Konjac Glucomannan

Konjac glucomannan is a polysaccharide isolated from the tubers of *Amorphophallus konjac* found in China and Japan in the mountain areas. It is a high molecular weight water-soluble natural polysaccharide and is composed of glucose and mannose units. Carboxymethyl konjac glucomannan, an anionic derivative, has been used as a biomaterial in drug delivery systems. Carboxymethyl konjac glucomannan exhibits good water-solubility, biocompatibility, bioactivity and excellent gelation ability when mixed with a polymer of opposite charge. Carboxymethyl konjac glucomannan-chitosan nanoparticles were for example shown to have potential as an advanced drug delivery system for water-soluble drugs [74].

A system capable of controlling the diffusion of small molecules was investigated by using theophylline and diltiazem HCl, with different molecular size and net charge, as model drugs. The results showed that mixtures of konjac glucomannan with xanthan gum are suitable for development of systems capable of maintaining physical integrity and drug release control for up to 8 h. The mixtures of the two gums were found to be more efficient than the individual gums. The study, however, also found that there were differences regarding the synergistic interaction between konjac glucomannan and xanthan gum depending on the origin (area where the gums were obtained) of the gums [75].

In order to decrease the release rate of drugs and to solve the burst release problems observed with hydrogels, a series of novel pH-sensitive konjac glucomannan/sodium alginate hydrogels were prepared using graphene oxide as drug-binder effector for anticancer drug (5-fluorouracil) loading and release. *In vitro* cumulative release studies as well as the effects of component ratio and pH on the swelling properties of the hydrogels were studied. The graphene oxide nanosheets significantly influenced the micromorphology, swelling ability and drug loading. The *in vitro* release studies showed that the burst phenomenon could be avoided and konjac glucomannan/sodium alginate/graphene oxide hydrogels could be a suitable carrier for site-specific drug delivery in the intestine [76].

In another study, cholesterol bearing carboxymethyl konjac glucomannan amphiphilic conjugates were synthesised. Etoposide was entrapped into the nanoparticles by a sonication method. The *in vitro* release behaviour of etoposide from the nanoparticles exhibited a sustained release property. Furthermore, these self-aggregated nanoparticles showed pH- and ionic strength-dependent properties. The study concluded that these preliminary results indicated that the synthesised nanoparticles could be a potential drug carrier for etoposide drug delivery [77].

2.2.18. Locust Bean Gum

Locust bean gum is obtained by processing the endosperm of the pods or beans of the locust bean tree (*Ceratonia siliqua*). Locust bean gum consists of a natural galactomannan polymer, which is made up of mannose and galactose units. The mannose:galactose ratio of locust bean gum is approximately 4:1 [78]. Locust bean gum is Generally Recognized as Safe (GRAS) by the FDA [22].

Locust been gum has been used as an excipient in drug products due to its thickening, gel forming and stabilising properties [79]. Prajapati *et al.* [80] prepared locust bean gum-alginate mucoadhesive macromolecules containing aceclofenac which displayed sustained drug release behaviour. This drug release profile was attributed to the diffusion, swelling and mucoadhesive properties of the locust bean gum-alginate macromolecules.

The binding efficacy of locust bean gum in spheroid formulation was investigated by comparison with a standard binder (e.g. polyvinylpirrolidone). Atorvastatin calcium spheroids were formulated by the extrusion-spheronization using a 1% (w/w) locust bean gum suspension as binder. The results of the study indicated that locust bean gum can be used as a binder to produce spheroids [81].

The application of the polysaccharide in controlled delivery formulations was also investigated using the highly water-soluble propranolol hydrochloride, as model drug. Tablets were prepared by wet granulation. *In vitro* release studies resulted in the formation of a gelatinous swollen mass which controlled the diffusion of the drug molecules. The synergistic interaction between xanthan gum and locust bean gum yielded better controlled release results than locust bean gum alone [78].

The mucoadhesive properties of locust bean gum and the bioavailability of propranolol HCl in buccal tablets were investigated by Vijayaraghavan *et al.* [82]. Propranolol HCl buccal tablets containing locust bean gum and chitosan were prepared. Tablets containing 10 mg propranolol HCl alone were also prepared. The strength of mucoadhesion of the tablets was quantified based on the tensile force required to break the adhesive bond between porcine buccal mucosa (the model membrane) and the test polymer. An *in vitro* study was conducted in phosphate buffer (pH 6.8) and the cumulative percentage drug release was determined. A bioavailability study was also conducted in 16 healthy human volunteers to determine the plasma concentration of propranolol up to 12 h. The results of the study showed that the gum and chitosan in a weight ratio of 2:3 released the drug unidirectionally from the dosage form and also yielded buccal tablets with sufficient mucoadhesive properties for clinical applications. [82].

2.2.19. Mango Gum

Mango gum is a polysaccharide rich extract obtained from the bark of the *Mangifera indica* tree [83].

Mango gum has been studied for its tablet binding, sustained release and disintegrating properties [41]. Nayak *et al.* [84] investigated mango gum's functionality as a matrix forming agent for a once-daily sustained release tablet formulation containing lornoxicam as a model drug. Sustained drug release was obtained due to the good swelling properties of the matrix type tablet.

In a study investigating the binding properties of mango gum, uncoated paracetamol tablets were prepared by wet granulation using mango gum as a binder in various concentrations. The opti-

mal binder concentration was found to be 5% (w/w) and it was also found that the gum is pH sensitive and may, therefore, be considered in the formulation of intestinal drug delivery systems [84].

2.2.20. Mimosa Scabrella Gum

This gum is obtained from the seeds of *Mimosa scabrella* and contains a highly hydrophilic galactomannan consisting of mannose and galactose [85]. The mannose:galactose ratio is approximately 1.1:1.0 [86].

Mimosa scabrella gum has been studied for its controlled release matrix forming properties. Theophylline tablets containing xanthan and *Mimosa scabrella* gum showed decreased drug release with an increase in polymer concentration and formulations with 25% (w/w) of the mixture of the two gums exhibited sustained release. The sustained drug release was considered to be due to a combination of diffusion through hydrated gum and relaxation of the polymer molecules [87].

2.2.21. Moi Gum

Moi gum is obtained from various parts of the *Lannea coromandelica* tree such as the leaves, stems, fruits and bark of the stem. The water-soluble, neutral polysaccharide found in moi gum is composed of galactose and arabinose in the ratio 4:1 [88].

Studies have been performed on moi gum to investigate its microencapsulation capacity, as well as its ability to provide sustained drug release. Microspheres were prepared by solvent evaporation using lamivudine as the model drug. Spherical microcapsules without aggregation were obtained with a circularity factor of 1.00. The mean geometric particle size ranged from 23.76 to 31.34 µm. The *in vitro* drug release profile and release kinetics were studied, using 0.1N HCl and it was found that microspheres of moi gum exhibited sustained release beyond 10 h. The study concluded that the gum possesses substantial rate controlling properties and could be used for sustained oral drug delivery [88].

2.2.22. Moringa Oleifera Gum

Moringa oleifera gum is found in various parts (e.g. seeds) of the horseradish or drumstick tree *(Moringa oleifera)* native to the sub-Himalayan region of northwest India. The purified, whole-gum exudate of *Moringa oleifera* consists of arabinose, galactose, glucuronic acid, rhamnose, mannose, and xylose [89]. Horsedadish is Generally Recognized as Safe (GRAS) by the FDA [22].

Moringa oleifera gum has been used as binder, mucoadhesive agent and disintegrant [90]. *Moringa oleifera* gum was investigated for its potential as binder in tablet formulations. Chloroquine phosphate tablets were formulated using different concentrations of the gum as binding agent in comparison with starch. It was found that an increase in the gum concentration, increased the hardness and disintegration time, decreased the friability and the percentage cumulative release. *Moringa oleifera* gum was proven to be as good as starch as binder in this particular tablet formulation [91].

Tablet disintegration, a property dependent on binding characteristics, were investigated by formulating aceclofenac tablets using *moringa oleifera* gum as disintegrant in various concentrations. The disintegration time was found to be faster than that of tablet formulations prepared from synthetic disintegrants (e.g. sodium starch glycolate and croscarmellose sodium) and the dissolution profile was comparable with those of formulations using synthetic disintegrants. The study concluded that the gum exhibited better results in comparison to other super disintegrants [92].

In another study, the mucoadhesive properties of *moringa oleifera* gum were evaluated by measuring the pH, swelling index, viscosity and solubility. The gum was also tested for its adhesive characteristic by physical studies such as shear stress. The evaluation concluded that the gum is comparable to synthetic polymers such as hydroxyl propyl methyl cellulose (HPMC) and Carbopol® 934 and its use was proposed for oral mucoadhesive drug delivery systems [93].

2.2.23. Neem Gum

Neem gum is obtained from the trunk of *Azadirachta indica*. The gum consists of mannose, glucosamine, arabinose, galactose, fucose, xylose, and glucose [94].

The binding properties of neem gum were compared with those of acacia gum in paracetamol tablets. Inclusion of neem gum improved the balance between binding and disintegration properties of the paracetamol tablets and led to both a faster onset and higher amount of plastic deformation during compression than acacia gum. Neem gum also produced tablets with lower disintegration and dissolution times than those containing acacia gum [95].

Co-processing of neem gum with other excipients such as rice starch and lactose has also been shown to enhance the packing and flow properties of these excipients [94].

2.2.24. Okra Gum

Okra gum is obtained from the fresh fruit of the *Abelmoschus esculentus* or *Hibiscus esculentus* plant. It is a polysaccharide containing galactose, galacturonic acid and rhamnose with some fractions of arabinose, glucose, mannose and xylose [96]. When extracted in water, it produces a highly viscous solution, which has been proven useful as a drug-release retarding polymer and has therefore been used in sustained-release drug delivery matrices [97]. In a study by Sinha *et al.* [98] drug loaded beads consisting of okra gum mixed with sodium alginate were prepared and evaluated as a potential sustained release drug delivery system. The glibenclamide-loaded okra gum/alginate beads exhibited high drug entrapment and relatively slow drug release over 8 h. The beads also exhibited good mucoadhesiveness on goat intestinal mucosa [98].

Okra gum has also been investigated as constituent of a gastric floating dosage form containing metformin HCl [99]. The study showed that, although the formulation containing okra gum had lesser floating capacity, it exhibited sustained drug release when compared with a metformin HCl floating tablet containing hydroxypropyl methyl cellulose (HPMC). The study concluded that the physicochemical parameters of the gum showed good characteristics as a pharmaceutical excipient for use in the formulation of floating tablets. The floating of the tablet in the gastric fluid is achieved due to the swelling properties of the gum. Furthermore, this gum facilitates controlled release of the drug by maintaining the tablet in a floating position in the gastric fluids. This is achieved by the matrix forming capability of *okra gum* [99].

This gum has also been investigated for its suitability as suspending agent and for its disintegrating properties [100].

2.2.25. Tamarind Gum

Tamarind gum is found in the tamarind plant (*Tamarindus indica*) seeds and consists of a glucan backbone substituted with side chains of xylose and galactose linked to glucose residues. This tamarind seed polysaccharide is regarded as a galactoxyloglucan. It swells in water [101] and has been used as a binder, gelling agent, emulsifier and suspending agent [102]. Tamarind is Generally Recognized as Safe (GRAS) by the FDA [22].

The use of tamarind gum in comparison with established binders (e.g. tragacanth gum and acacia gum) has been investigated by evaluating the physical properties of the granules, the tableting performance and the physical characteristics of prepared tablets. The granules obtained from the gum were stronger than those obtained from the other gums. The tablet hardness and friability were also improved. From the results it is clear that tamarind gum has a high binding capacity and can therefore be used as a binder in tablet formulations [103].

Tamarind gum has been studied for its mucoadhesive properties. The gum was mixed with a dye and applied to the nasal cavity of rabbits in powder form. The residue of the dye was then observed through a thin fiberscope. The residence time of tamarind

gum in the cavity proved that this gum can be useful as a base for mucoadhesive powder formulations [104].

The use of tamarind gum as an alternative excipient for formulation of pharmaceutical emulsions was investigated by using castor oil as a model drug. Castor oil was emulsified with the gum and compared with acacia gum emulsions. It was found that the emulsions prepared with 2% (w/v) tamarind gum were more effective than emulsions prepared by using 10% (w/v) of acacia gum [21].

Tamarind gum was investigated as a suspending agent in the formulation of various Nimesulide suspensions. The formulations were compared with a commercial product. The tamarind formulations were redispersed uniformly without any deposits. The rheological study indicated that as the shear rate increased the viscosity decreased, which confirmed the shear thinning nature of the suspension. The suspensions were found to be stable. The results showed that this gum can be used as an effective suspending agent [105].

2.2.26. Tara Gum

Tara gum is obtained from the seed endosperm of the *Caesalpinia spinosa* tree, which is native to Peru. The major component of tara gum is galactomannan, consisting of mannose and galactose units. The ratio of mannose to galactose in tara gum is 3:1 [6].

Tara gum has been investigated for its use in the formulation of gastro-retentive tablets. Drug free tablets were prepared by wet granulation and evaluated mainly for hardness, *in vitro* buoyancy and floating time. This gum provided good results regarding these parameters and was considered to have a significant influence on the floating behavior of gastro-retentive tablets [106]. The gastro-retentive properties of tara gum have also been investigated in controlled release tablets and emulsions for drugs like metformin hydrochloride, ciprofloxacin hydrochloride nimodipine, nifedipine, carvedilol and clozapine [107].

Controlled release matrix tablets of ambroxol HCl using tara gum as excipient was prepared by wet granulation. The study revealed that the release followed Non-Fickian diffusion which includes a combination of diffusion and erosion mechanisms. The drug-polymer ratio played an important role in the overall drug release, which was found to decrease with an increase in drug-polymer ratio. Tara gum was considered to be a suitable candidate for formulation of controlled release matrix tablets for a period up to 8 h [108].

2.2.27. Terminalia Catappa Gum

Terminalia catappa gum is obtained from exudates of the *Terminala catappa* tree [109].

The gum has been investigated as a release retarding excipient in oral controlled drug delivery systems. Matrix tablets containing dextromethorphan hydrobromide as a model drug and *Terminalia catappa* gum were prepared by direct compression, wet granulation and solid dispersion techniques. The wet granulated tablet showed a maximum sustained release of more than 8 h. This was attributed to the excellent swelling properties of the gum in water. The study concluded that this gum might be used as a release-retarding polymer in controlled drug delivery systems [109].

2.2.28. Tragacanth Gum

Tragacanth gum is obtained from the *Astragalus gummifer* tree and is one of the most abundant biopolymers and eco-friendly polysaccharides. The gum consists of an anionic carbohydrate, which is stable over a wide pH-range. It consists of galactose, galacturonic acid and rhamnose with traces of ketohexose [110]. Tragacanth gum is Generally Recognized as Safe (GRAS) by the FDA [22].

The sustained release properties of tragacanth gum were evaluated by formulating diclofenac sodium tablets. Tablets were prepared by using wet granulation and the *in vitro* drug release of the gum formulation was compared with a commercially available formulation and a formulation containing polyvinylpirrolidone. *In vivo* drug release was studied in healthy volunteers using a non-blinded cross over, two period design using Diclofenac sodium SR tablets as a reference product. Formulations where the polyvinylpirrolidone was partially replaced with tragacanth gum yielded sustained release of the drug for 12 h in both the *in vitro* and *in vivo* studies [111].

Another study also evaluating the release properties provided by tragacanth gum involved the direct compression of chlorzoxazone with the gum. *In vitro* drug release showed sustained release up to 12 h, which suggests that tragacanth gum can be used in the formulation of sustained release tablets prepared by direct compression [112].

Tragacanth gum has also been studied for its mucoadhesive properties by combining synthetic (e.g. hydroxypropyl methylcellulose) and natural (tragacanth) hydrophilic polymers. Various mucoadhesive tablet formulations containing combinations of different synthetic and natural polymers were prepared by wet granulation using famotidine as a model drug. Results of *in vitro* drug release and wash-off studies suggest that the tablets containing hydroxypropyl methylcellulose and tragacanth yielded better mucoadhesive properties than the other polymer combinations [113].

2.2.29. Xanthan Gum

Xanthan gum is produced by fermentation of sugars by *Xanthomonas campestris* and consists of an anionic, high molecular weight, microbial exo-polysaccharide. Its basic chain structure consists of a glucose backbone with mannose and glucose units. Xanthan gum is considered as one of the most widely used biopolymers of natural origin. Xanthan gum is soluble in both cold and hot water, hydrates quickly and produces high viscosity dispersions at low concentration [114]. Xanthan gum is Generally Recognized as Safe (GRAS) by the FDA [22].

The sustained release properties of this gum were studied by formulating different drug-matrix ratios of propranolol HCl tablets. The tablets were prepared by direct compression using xanthan gum and lactose. *In vitro* dissolution studies were performed and an inverse relationship between the amount of xanthan gum and drug release rate was observed. The drug release gradually increased as the amount of lactose increased and the amount of gum decreased. Increasing the amount of xanthan gum could control the drug release from the matrix tablets. Increasing the amount of soluble diluent could increase the release rate [115].

A study to investigate the suspending properties of xanthan gum was conducted by preparing loratadine suspensions with different types and concentrations of suspending agents. From the results it was clear that the drug release rate was dependent on the type and concentration of the suspending agent. Xanthan gum exhibited the best drug release from the five suspending agents (e.g. xanthan gum, sodium carboxymethylcellulose, aluminum magnesium silicate and sodium alginate) that were investigated and also proved to be stable with an expected shelf-life of more than 36 months [116].

Sustained-release matrix tablets were developed by injection moulding using metoprolol tartrate as model drug and ethylcellulose as sustained-release agent. Dibutyl sebacate was selected as plasticiser. The drug release from the ethylcellulose/metoprolol tartrate matrices was found to be too slow (less than 50 % in 24 h), therefore xanthan gum was added to the formulation. Increasing the xanthan gum concentrations provided faster metoprolol tartrate release rates characterised by zero-order release kinetics with no burst release effect. *In vivo* evaluation was performed by administering the formulations to male mixed breed dogs in a cross-over sequence with a wash out period of at least 8 days. Blood was collected at predetermined intervals up to 24 h. The formulations composed of xanthan gum and ethylcellulose in a ratio of 1.0:1.5 and 30% (w/w) metoprolol tartrate had a low relative bioavailability

compared with the commercial product (Lopressor®). However, the relative bioavailability improved significantly at higher concentrations of metoprolol tartrate (50%, w/w). These injection moulding tablets were able to sustain metoprolol plasma levels in dogs, however, the *in vivo* performance depended on the dug loading [117].

2.2.30. Xyloglucan

Xyloglucan is a polysaccharide found in the primary cell walls of monocotyledons and in some dicotyledonous seeds, where they function as storage polysaccharides. Xyloglucan is mostly extracted from *Tamarindus indica* seeds, although other plant sources such as *Hymenaea courbaril* seeds have also been proposed. Its chemical structure consists of a glucan backbone substituted with xylose and galactose units [20].

Xyloglucan has been proposed as mucoadhesive material and also in sustained release formulations (i.e. indomethacin suppositories and oral formulations of cimetidine). This polymer has also been used as a vehicle for sustained release of percutaneous formulations of non-steroidal anti-inflammatory drugs such as ibuprofen and ketoprofen and in oral formulations containing indomethacin and diltiazem [20, 118, 119]. The use of a layered double hydroxide system to release drug in the stomach is limited due to the low pH in the stomach. This system readily dissolves in the stomach (pH ~1.2). However, when coated with xyloglucan it passes through the stomach to release the drug in the small intestine. In addition, the coated system was efficient in obtaining a slow release of enalaprilate [18].

Xyloglucan was studied by Avachat *et al*. [119] for its mucoadhesive properties. Mucoadhesive buccal films were developed for the systemic delivery of razatriptan benzoate. It was concluded from the results of this study that xyloglucan is a mucoadhesive polymer suitable for inclusion in buccal delivery systems for highly water-soluble drugs.

3. NATURAL MUCILAGES

3.1. Classification of Mucilages

Since mucilages are products of normal physiological processes, their classification basically refers to the location in the plant on a cellular level (e.g. intracellular, cell membrane or secreting hair), as well as the part of the plant where they are formed and stored (e.g. stem, bark, seed-coat, leaf, corn, rhizome, flower) [1, 3, 13]. Table **4** provides information regarding the source, shape of the polysaccharide chain and chemical structure/chemical constituents of different mucilages.

3.2. Pharmaceutical Applications of Natural Mucilages

3.2.1. Alginates

Alginates or alginic acids are linear, un-branched polysaccharides found in brown seaweed and marine algae such as *Laminaria hyperborea, Ascophyllum nodosum* and *Macrocystis pyrifera* [16]. Alginate polysaccharides are composed of guluronate and mannuronate and are arranged as linear homopolymeric and heteropolymeric blocks [136]. Algae (brown and red) are Generally Recognized as Safe (GRAS) by the FDA [22].

Alginate has been used for encapsulation purposes, mainly in the form of controlled release drug delivery systems including microspheres, beads, liposomes, tablets and buccal films. The gelling properties of the guluronic residues with polyvalent ions (i.e. calcium or aluminium) found in alginate allow cross-linking with subsequent formation of gels that can be employed to prepare matrix systems [137]. Sodium alginate acts as a thickening agent and has been used in the preparation of pastes and creams. It has also been used as bioadhesive, disintegrant, binder and sustained release agent in tablet formulations [138]. Many examples exist in literature where alginates have been investigated as functional pharmaceutical excipients in the formulation of novel dosage forms and only a few of the most recent reports are discussed below.

Martin *et al.* [139] investigated and formulated antifungal mucoadhesive systems containing nystatin and alginate microspheres for the treatment of oral candidiasis. The microspheres were prepared using the emulsification/internal gelation method. Mucoadhesive properties and swelling behaviour, as well as effective antifungal mucosal activity, were achieved against *Candida albicans* strains.

Lacerda *et al.* [140] encapsulated rifampicin in sodium alginate/chitosan microparticles and studied the drug release thereof. The results of the study showed that the sodium alginate/chitosan microparticles provided controlled release of rifampicin. The controlled release was related to diffusion, swelling, relaxation and erosion processes. The release and swelling were also found to be pH-dependent.

Nanoparticles based on thiolated alginate and disulfide bond reduced albumin were synthesised by using the coacervation phase-separation method. Cubic shaped nanoparticles with a certain spherical tendency were obtained with a size range between 42 and 388 nm. The nanoparticles were loaded with tamoxifen and *in vitro* drug release studies were conducted. Total release of tamoxifen could not be achieved and only 23-61% of the drug was released between 7 and 75 h. These nanoparticle formulations can, however, still be considered as potential drug delivery candidates for antitumor drug administration [141].

3.2.2. Aloe Leaf Gel or Mucilage

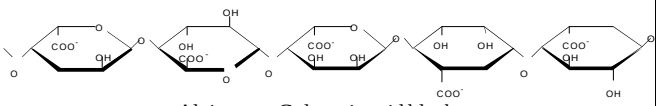
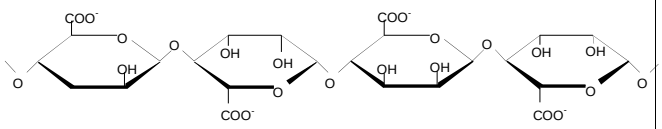
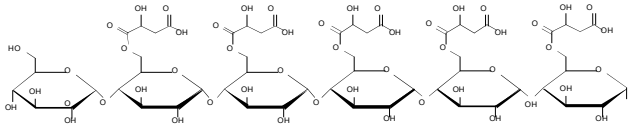
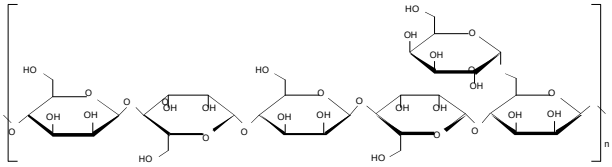
Aloe mucilage is obtainable from the leaves of various Aloe species. The mucilage obtained from the leaves of *Aloe barbadensis* contains aloin which is a mixture of barbaloin, isobarbaloin, aloe emodin, and resins. It also contains aloetic acid, galactouronic acid, glucosamine, monosaccharides, and polysaccharides [142]. Aloe is Generally Recognized as Safe (GRAS) by the FDA [22]. Aloe mucilage has been used as a gelling agent and sustained release agent [41]. Controlled release delivery systems of glibenclamide and diclofenac using aloe mucilage have been studied. Tablet formulations containing *Aloe barbadensis* leave mucilage with glibenclamide and diclofenac respectively have been prepared by direct compression techniques and both formulations exhibited controlled drug release [142, 143]. The mucilage extracted from *Aloe barbadensis* appears to be a suitable excipient for use in pharmaceutical sustained-release matrix products due to its good swelling and good flow properties. This mucilage is also suitable for direct-compression formulations. Jani *et al.* [143] came to the conclusion that the dried mucilage from *Aloe barbadensis* can be used as an excipient for sustained-release, modified-release, and fast-release tablets with suitable modifications.

Zapata *et al.* [144] studied and compared the leaf characteristics and gel chemical composition of eight aloe species (i.e. *Aloe arborescens* Mill., *Aloe aristata* Haw., *Aloe claviflora* Strydenburg, *Aloe ferox* Mill., *Aloe mitriformis* Mill., *Aloe saponaria* Ait., *Aloe striata* Haw., and *Aloe vera* L.). *Aloe vera* and *Aloe claviflora* yielded the highest gel percentage, followed by *Aloe ferox* and *Aloe metriformis*. Very low amounts of aloin exist in the internal pulp mass (i.e. the mucilage or gel) of the aloe leaf, but is generally contained in the bitter exudate of the freshly cut leaves.

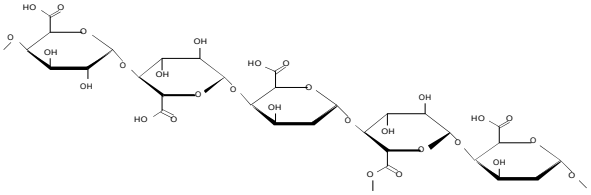
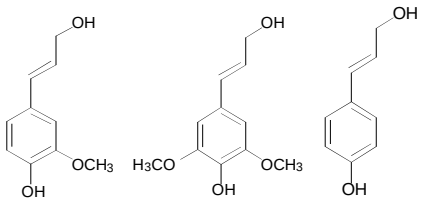
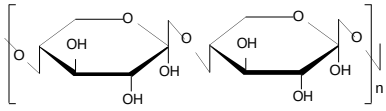
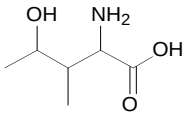
Dried mucilage or gel extracted from *Aloe vera* leaves showed potential to be used as a direct compressible material for sustained release matrix type tablets [142]. The gel and whole leaf materials from *Aloe vera* and *Aloe ferox* have been found suitable as pharmaceutical excipients in the formulation and preparation of matrix-type tablets for modified drug release [145].

Another potential pharmaceutical application of aloe mucilage materials includes its use as a functional excipient to enhance drug bioavailability. *Aloe vera* gel exhibited the ability to open tight

Table 4. Summary of the origin and chemical characteristics of natural mucilages.

Mucilage	Site of formation/Source	Shape of polysaccharide chain	Chemical Constituents/ Chemical Structure	Charge	Refs.
Alginates	*Laminaria hyperborea, Ascophyllum nodosum, Macrocystis pyrifera.* (Brown seaweed and marine algae)	Linear, unbranched	 Alginates – Guluronic acid block  Alginates – Mannuronic acid block	Anionic	[24]
Aloe leaf gel or mucilage	*Aloe barbadensis* (Plant leaves)	-		-	
Althaea officinalis mucilage (Marshmallow)	*Althaea officinalis* L. (Plant roots)	Highly branched	Arabinin	-	[120]
Cassia tora mucilage (Sickle senna)	*Cassia tora* (Plant seeds)	-		-	[121]
Cinnamomum mucilage (Cinnamon)	*Cinnamomum tamala nees* (Plant leaves)	-	-	-	[122]
Cocculus hirsutus mucilage (Moonseed)	*Cocculus hirsutus* (Plant leaves)	-	-	-	[123]
Cordia obliqua mucilage (Assyrian Plum)	*Cordia obliqua* (Plant fruit)	-	Arabinose and Glucose	-	[124]
Cydonia vulgaris mucilage (Quince seed)	*Cydonia vulgaris Pers.* or *Cydonia oblonga Miller* (Plant seeds)	-	-	-	[125]
Dendrophthoe falcate mucilage (Honey Suckled Mistletoe)	*Dendrophthoe falcate* (Stem parasite)	-	-	-	[126]

(Table 4) Contd….

Mucilage	Site of formation/Source	Shape of polysaccharide chain	Chemical Constituents/ Chemical Structure	Charge	Refs.
Hibiscus sp. mucilage (Shoe-flower plant or China rose)	*Hibiscus rosa-sinensis* (Plant leaves) *Hibiscus moscheutos* (Plant roots)	-	Galactose, galacturonic acid, glucuronic acid and rhamnose	-	[127]
Mimosa pudica seed mucilage (Touch me not)	*Mimosa pudica* (Plant seeds)	-	Glucuronic acid and xylose)	-	[85]
Musa paradisiacal mucilage (Banana)	*Musa paradisiacal* peel	-	Arabinose, galacturonic acid and xylose together with traces of galactose, glucose, mannose and rhamnose residues	-	[128]
Ocimum americanum mucilage (Sweet basil)	*Ocimum americanum* (Plant seeds)	Linear	Arabinose, galacturonic acids rhamnose and xylose	Anionic	[15, 129]
Pectin	(Plant cell walls)	-		-	[130]
Phoenix dactylifera mucilage (Date palm)	*Phoenix dactylifera* (Plant fruit)	-	- 	-	[131]
Psyllium mucilage (Flea seed)	*Plantago psyllium* (Plant seeds)	-		-	[132]
Sinapsis sp. mucilage (Yellow mustard and black mustard)	*Sinapsis alba* and *Sinapsis nigra* (Plant seeds)	-	Glucans and pectic polysaccharide containing galactose, rhamnose, galacturonic acid and non-reducing end glucuronic acid	-	[133]
Trigonella foenum-graceum mucilage (Fenugreek)	*Trigonella foenum-graceum* (Plant seeds)	Branched		Non-ionic	[134]
Urginea sp. mucilage (Squill)	*Urginea maritima* and *Urginea indica* (Plant cell content of bulb)	-	-	-	[135]

junctions in epithelial cell monolayers and thereby could facilitate absorption of large macromolecular drugs such as insulin [24, 146].

3.2.3. Althaea Officinalis Mucilage

The mucous material of the roots of the marshmallow plant (*Althaea officinalis* L.) contains water-soluble arabinan, which has a highly branched structure of arabinofuranosyl residues [119]. Althea flowers and root are Generally Recognized as Safe (GRAS) by the FDA [22].

This mucilage has been investigated for its bioadhesive properties and used for the treatment of irritated mucosa. The clinically proven effects are related to the presence of bioadhesive and mucilaginous polysaccharides, leading to the physical formation of mucin-like substances on top of the irritated mucosal tissue [147].

3.2.4. Cassia Tora Mucilage

This mucilage is obtained from the seeds of *Cassia tora*, which consists of cinnamaldehyde, polysaccharides, tannins, mannitol, coumarins and essential oils (aldehydes, eugenol, and pinene) [120]. Cassia is Generally Recognized as Safe (GRAS) by the FDA [22].

Cassia tora mucilage has been studied for its binding and disintegration properties as well as for its properties as suspending agent compared with tragacanth gum, acacia gum, and gelatin. *Cassia tora* mucilage had better suspending properties than tragacanth gum and acacia gum [40] but exhibited similar binding properties as guar gum [148].

This mucilage has also been used as a binder in the formulation of uncoated tablets using zidovudine as a model drug. The tablets were prepared by wet granulation using different concentrations (2 to 8%, w/v) of this mucilage and were compared with 8% (w/v) guar gum. The tablets exhibited good physicochemical properties with a drug release rate of more than 85% within 4 h. An increase in mucilage concentration resulted in an increase in tablet hardness and a decrease in the disintegration time. Stability studies were also conducted for three months at ambient (25°C/60% RH) and accelerated (40°C/75% RH) conditions, yielding results that confirmed that *Cassia tora* mucilage can be used as a binder in tablet formulations. The study concluded that tablet formulations using 8% (w/v) *Cassia tora* mucilage exhibited binder properties almost equivalent to tablet formulations using 8% (w/v) guar gum [148].

3.2.5. Cinnamomum Mucilage

This mucilage can be obtained by soaking and boiling the leaves of the plant *Cinnamomum tamala nees* in water. The mucilage contains tannins, saponins, sugars, acidic compounds and chlorides [121].

Cinnamomum mucilage has been studied for its binding properties in tablet formulations. Paracetamol tablets were prepared by wet granulation using different concentrations (5 to 15%, w/v) of this mucilage, polyvinylpyrrolidone (PVP) and starch. The mucilage was found to exhibit significant swelling properties as well as good binding properties in the range between 10 to 15% (w/v) [121].

3.2.6. Cocculus Hirsutus Mucilage

The leaves of *Cocculus hirsutus* contain a high proportion of mucilage which consists of polysaccharides and a gelatinous type of material [123].

Rao *et al.* [123] investigated the use of *Cocculus hirsutus* leaf powder as a gel base for a topical delivery system. They prepared and tested a flurbiprofen gel using the powder of dried *Cocculus hirsutus* leaves and concluded that the quantity of flurbiprofen released from this preparation was higher than that of the commercially available topical gel product. Their formulation also showed a better anti-inflammatory activity than the commercially available topical gel product [123].

3.2.7. Cordia Obliqua Mucilage

Cordia mucilage is obtained from the raw fruits of *Cordia obliqua*. It consists mainly of glucose and arabinose [124].

This mucilage has been evaluated for its efficacy as a novel sustained release matrix forming material in tablet formulations. Different diclofenac sodium matrix tablet formulations were prepared using 1, 2, 5 and 10% (w/w) of cordia mucilage. The tablets were prepared by wet granulation using non-aqueous solvents. The tablets were evaluated and yielded results comparable to those of the commercial formulation. The *in vitro* drug release studies were performed using 0.1 N HCl for 0 to 2 h and phosphate buffer (pH 6.8) for 2 to 24 h. The dissolution results indicated sustained drug release up to 24 h. An increase in the percentage of mucilage resulted in a decrease in the drug release rate. The mucilage may therefore be suitable as a matrix forming agent in the formulation of gastric resistant and sustained release tablet formulations [149].

The ability for tablet binding, sustained and controlled drug release was also evaluated in other studies [150-152].

Nanoparticles for ophthalmic delivery of fluconazole were prepared using cordia mucilage. The fluconazole-loaded cordia mucilage nanoparticles were prepared by emulsion-cross-linking and were compared with a commercially available formulation. The nanosuspension formulation provided comparable *in vitro* corneal permeability of fluconazole across isolated goat cornea, indicating that the nanosuspension formulation containing cordia mucilage is suitable for ophthalmic delivery of fluconazole [153].

3.2.8. Cydonia Vulgaris Mucilage

Cydonia vulgaris Pers. (also known as *Cydonia oblonga Miller*) is a small shrub belonging to the family Rosaceae. The mucilage from this shrub can be obtained by soaking the dried seeds in water followed by boiling [125].

Cydonia mucilage has been evaluated for its binding properties in tablet formulations. Paracetamol tablets were prepared by wet granulation using cydonia mucilage and compared with tablets prepared with acacia gum. The binding efficiency of this mucilage was found to be equivalent to that of acacia gum [125].

3.2.9. Dendrophthoe Falcate Mucilage

Dendrophthoe mucilage is obtained from the fresh or dried stem parasite *Dendrophthoe falcate* commonly known as 'Vanda' found on *Magnifera indica* [126].

This mucilage has been evaluated as a binder in solid oral dosage forms. Different concentrations of this mucilage were used in wet granulation tablet formulations with paracetamol as a model drug. An increase in the concentration of mucilage resulted in slower drug release from the tablet and a concentration of 6% (w/w) of this mucilage showed optimal results as a tablet binder [126].

3.2.10. Hibiscus sp. Mucilage

Hibuscus mucilage is obtained from the fresh leaves of *Hibiscus rosa-sinensis* or from the roots of *Hibiscus moscheutos* and contains rhamnose, galactose, galacturonic acid and glucuronic acid [127].

One of the uses that have been studied using mucilage from *Hibiscus rosa-sinensis* is the sustained release properties in a matrix tablet formulation containing diclofenac sodium. This study evaluated the physicochemical properties and examined the effect of different polymer blends on the release kinetics of diclofenac from matrix type tablets. The mucilage showed good swelling capacity, which was found to be pH independent. It was concluded from the study that Hibuscus mucilage can be used in the formulation of sustained-release tablets [154].

3.2.11. Mimosa Pudica Seed Mucilage

Mimosa mucilage is obtained from the seeds of the plant *Mimosa pudica*. The polymeric material of this mucilage consists of

xylose and glucuronic acid. This mucilage hydrates and swells rapidly when exposed to water [85]. Mimosa flowers are Generally Recognized as Safe (GRAS) by the FDA [22].

Matrix tablets containing diclofenac sodium as active ingredient were prepared by wet granulation and different proportions of mimosa mucilage and dibasic calcium phosphate were investigated in the formulation of the tablets. An increase in the proportion of mucilage in the tablet matrix resulted in a corresponding decrease in the release rate of the model drug, which is possibly due to the increase in swelling and decrease in erosion of the tablets. Furthermore, the dissolution profiles of the tablets prepared from mimosa mucilage were similar to those of the commercially available sustained release diclofenac sodium tablet [85].

3.2.12. Musa Paradisiacal Mucilage

This mucilage is obtained by drying banana (*Musa paradisiacal*) peel, soaking it in water containing metabisulphate and then boiling the peel [128]. This water-soluble polysaccharide contains arabinose, xylose and galacturonic acid together with traces of galactose, glucose, mannose and rhamnose residues [128].

Banana peel or *Musa paradisiacal* mucilage has been investigated as binder and suspending agent. Aceclofenac tablets were prepared by wet granulation and the mucilage powder was used as binding agent. The tablet friability and hardness as well as disintegration time studies yielded satisfactory results, while the release rate of the drug decreased with an increase in mucilage powder percentage in the formulation [155]. In the same work aceclofenac suspensions were also prepared with banana peel mucilage powder, this time acting as suspending agent. The sedimentation volume, pH, degree of flucculation and re-dispersibility were found to be satisfactory. Banana peed mucilage powder can therefore be considered as a suitable pharmaceutical excipient in the formulation of tablets and suspensions [155].

3.2.13. Ocimum Americanum Mucilage

The seeds of *Ocimum americanum* (also known as *Ocimum canum*) yield ocimum mucilage, which contains arabinose, rhamnose, xylose and galacturonic acids [129]. *Ocimum americanum* (basil) is Generally Recognized as Safe (GRAS) by the FDA [22].

Seed mucilage from *Ocimum americanum* was studied for its tablet disintegrating properties and compared with starch. Tablets containing propranolol as a model drug showed that the disintegration time of tablets containing 10% (w/w) mucilage was much faster than the disintegration time of the tablets containing starch as disintegrant, while the drug release was not influenced [129].

3.2.14. Pectin

Pectin is a collective name for a group of closely associated polysaccharides found in plant cell walls [130]. The main component of pectin is a linear polysaccharide composed of galacturonic acid units, but the linear structure is interrupted with highly branched regions. The pectin polysaccharides are rich in neutral sugars such as rhamnose, arabinose, galactose, xylose and glucose [24]. Pectin is Generally Recognized as Safe (GRAS) by the FDA [22].

Pectin remains intact in the upper gastrointestinal tract and is degraded by colonic microflora [156]. Pectin has therefore been investigated for its use in film coating of colon-specific drug delivery systems. Pandey *et al.* [156] prepared a polyelectrolyte complex between chitosan and pectin and used it as a coating for tablets intended for colon delivery. The results showed a high swelling ability of the complex and drug release was restricted to the alkaline pH environment, which indicated that pectin could be used as an excipient in colon targeted drug delivery [157].

3.2.15. Phoenix Dactylifera Mucilage

Phoenix mucilage is obtained from the dried date fruit of *Phoenix dactylifera*, which consists of carbohydrates, pectin, starch and cellulose. Phoenix mucilage was evaluated and compared with acacia gum and tragacanth gum for its binding properties in tablet formulations. The study found that the tablet binding ability improved with an increase in concentration of the phoenix mucilage. Furthermore, the tablets manufactured using phoenix mucilage as excipient were found to be less friable than those containing acacia gum and tragacanth gum as excipients. The tablet formulation containing phoenix mucilage as binder did not disintegrate, but the drug release from the tablets still complied with the dissolution criteria of the pharmacopoeia [131].

3.2.16. Psyllium Mucilage

The mucilage extracted from *Plantago psyllium* seeds or from the seed coat of *Plantago ovata* is known as psyllium mucilage. The gel-forming polysaccharides of this mucilage are composed of arabinose, xylose and traces of other sugars [132]. Psyllium seed is Generally Recognized as Safe (GRAS) by the FDA [22]. Psyllium mucilage has been assessed as binder in pharmaceutical tablets and it was compared with polyvinylpyrrolidone and tragacanth gum in tablets formulated with paracetamol as a model drug. The tablets containing 5% (m/m) psyllium mucilage was found to be comparable with the tablets containing 3% (m/m) polyvinylpyrrolidone [132].

Singh *et al.* [158] found that the swelling of modified psyllium-based hydrogels is affected by the composition of the hydrogels and the pH of the swelling medium. An increase in the cross-linker concentration resulted in a decrease in the swelling of the hydrogel, whereas the swelling of the polymers increased with an increase in the pH of the swelling medium. The release of the drug from the polymer gel matrix also increased with an increase in pH of the releasing medium. The drug loaded samples initially showed slow release from the hydrogels but an increase in the rate of diffusion was observed over time. These hydrogels can therefore be used in colon targeted drug delivery systems, because the pH in the colon is higher than in other parts of the gastrointestinal tract.

3.2.17. Sinapsis sp. Mucilage

Sinapsis mucilage is obtained from the seed-coat of *Sinapsis alba* (yellow mustard) and *Sinapsis nigra* (black mustard) [135]. Sinapsis mucilage is composed mainly of glucans and pectic polysaccharide containing galactose, rhamnose, galacturonic acid and non-reducing end glucuronic acid [133]. Yellow and black mustard are Generally Recognized as Safe (GRAS) by the FDA [22]. *Sinapsis alba* mucilage has been evaluated and compared with other mucoadhesive polymers (e.g. hydroxypropylmethylcellulose and Carbopol® 934P). Diltiazem buccal adhesive tablets were formulated using *Sinapsis alba* mucilage and the results showed that this mucilage could be considered as a mucoadhesive polymer in the formulation of buccal adhesive tablets [159].

3.2.18. Trigonella Foenum-Graceum Mucilage

The mucilage derived from the seeds of *Trigonella foenum-graceum* L yields fenugreek mucilage. This mucilage contains polysaccharides, steroidal sapogenins, triterpenoids, alkaloids, flavonoids and phenolic acids [134]. Fenugreek is Generally Recognized as Safe (GRAS) by the FDA [22].

Fenugreek mucilage has been tested for its potential as excipient in oral controlled-release matrix type tablets. Fenugreek mucilage was compared with a standard controlled release polymer (e.g. Methocel™ K4M). The effect of lactose on the release behaviour of propranolol HCl from matrices formulated to contain fenugreek mucilage was also investigated. It was found that an increase in the concentration of the fenugreek mucilage resulted in a decrease in the release rate of propranolol HCl compared with that observed with Methocel™ K4M [134].

Fenugreek mucilage has also been investigated as disintegrant for use in mouth dissolving formulations. Metformin HCl was used as a model drug in fast disintegration tablet formulations containing

different concentrations of fenugreek mucilage compared with synthetic superdisintegrants (e.g. crosscarmellose sodium). The study concluded that fenugreek mucilage in the concentration of 4% (w/w) showed better disintegration properties than synthetic superdisintegrants [160].

3.2.19. Urginea sp. Mucilage

Urginea mucilage is obtained from the cell content of the bulb of *Urginea maritima* and *Urginea indica* [137].

The mucilage from the bulbs of *Urginea indica* can be separated by an acetone precipitation method and this mucilage has been investigated for its disintegration properties. Tramadol HCl directly compressed tablets were formulated with different concentrations of urginea mucilage. The tablets were compared with a standard disintegrant (e.g. starch). The results of the study showed that urginea mucilage has good disintegration properties and could be used as a disintegrant in tablet formulations [161].

CONCLUSION

Gums and mucilages are found in, or produced by a variety of natural sources such as plants, animals, fungi and microbial organisms. Numerous gums and mucilages have been investigated for their use as excipients in different pharmaceutical applications in diverse types of dosage forms. They have been proven to be effective binders, suspending agents, mucoadhesive agents and have been used in the formulation of modified release dosage forms, matrix type tablets, gastro-retentive systems, microparticulate systems, nanoparticles, bioadhesive systems and stimuli responsive drug delivery systems. These natural polymers are cost-effective and usually safe to use and are available as renewable sources. The natural origin of gums and mucilages also increases the biocompatibility potential.

A limited number of these gums and mucilages, however, are available on the market (e.g. acacia gum and tragacanth gum) and are used in commercially available pharmaceutical products. Most of the research that has been performed on gums and mucilages has only been performed on laboratory scale batches, therefore providing huge potential for further investigation and formulation to be performed on production scale batches. Furthermore, most of the drug release studies have only been performed *in vitro*, necessitating further *in vivo* studies. Stability data is also lacking regarding active compounds in formulations containing natural gums and mucilages and further stability studies should therefore be conducted on the production scale batches. Another concern when using plant material is the variation in chemical composition of plants obtained from different regions, collection of plant material in different seasons, as well as the positive and correct identification of the plants. Development of DNA-based identification methods of plants are currently ongoing and could be useful in the routine identification of plant species in future.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Chapter 3: Review Article: "*Multiple-unit pellet systems (MUPS)*: *Production and applications and advanced drug delivery systems*"

Chapter 3 is presented in the form of a review article entitled "*Multiple-unit pellet systems (MUPS)*: *Production and applications and advanced drug delivery systems*" which was published in the journal entitled *"Drug Delivery Letters"* in 2017 (volume 7, issue number 3, p 201–210; DOI: 10.2174/2210303107666170927161351). The complete guide for authors for this journal is given in Appendix E.

Conventional solid oral dosage forms (i.e. tablets and capsules) are the most common drug delivery systems, however, in recent years multiple unit pellet systems (MUPS) have become important and successful dosage forms which offer various advantages over conventional solid oral dosage forms. Part of this PhD study was to produce pellets and MUPS tablets. The aim of this review article was to provide an overview of the principles and applications of MUPS formulations, their various production methods and the challenges involved in the production of MUPS tablets or capsules.

REVIEW ARTICLE

Multiple-Unit Pellet Systems (MUPS): Production and Applications as Advanced Drug Delivery Systems

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Abstract: ***Background and Objective*:** Single-unit solid oral dosage forms such as tablets and capsules are considered the most common and acceptable form of immediate release systemic drug delivery systems. On the other hand, multiple-unit pellet systems (MUPS) have in recent years become an important dosage form that offers various advantages over conventional single-unit solid oral dosage forms.

***Discussion*:** These advantages include, amongst others, reduced risk of local irritation and toxicity, more predictable bioavailability, reduced likelihood of dose dumping and minimised fluctuations in the plasma concentration of the drug. MUPS comprise of relatively small uncoated or coated spherical particles (pellets or beads) compressed into tablets (MUPS tablets) or filled into hard gelatine capsules (MUPS capsules).

***Conclusion*:** Application of MUPS technology has led to the successful formulation of various marketed products such as omeprazole in Losec® MUPS tablets, which has resulted in increased drug bioavailability and improved pharmacological response. Another application of MUPS technology is controlled drug release, for example theophylline MUPS capsules (Elixophyline®), which offer sustained drug release.

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1. INTRODUCTION

Multiple-unit pellet systems (MUPS) are dosage forms comprising of coated and/or uncoated pellets (also referred to as beads), which are filled into hard gelatine capsules (*i.e*. MUPS capsules) or compressed into tablets (*i.e*. MUPS tablets) together with the appropriate excipients. MUPS capsule formulations present fewer challenges than MUPS tablet formulations and are therefore more frequently available as commercial products. The production costs of MUPS capsules are, however, higher than that of MUPS tablets. The higher cost can be related to the lower production rate of capsule filling machines compared to that of modern tablet compression machines [1]. It should be noted, however, specialised tablet compression machines or attention during formulation may be required for the production of MUPS tablets to prevent damage to the pellets during compaction and to ensure that the MUPS tablets comply with content uniformity and mass variation specifications. Furthermore, tablets can easily be scored and divided into sub-units without compromising their drug release characteristics, thus providing a more flexible dosage form than capsules [1]. In general, tablets are considered more convenient and patient friendly dosage forms than capsules and better patient compliance is therefore expected for tablets [2].

MUPS tablets and MUPS capsules provide several pharmacokinetic and pharmacodynamic advantages over conventional solid oral single-unit dosage forms prepared from powders or granules [3]. The pharmacokinetic advantages of MUPS include a smooth transit of the relatively small pellets from the stomach into the duodenum combined with an even distribution of the pellets in the small intestine, which provides a platform for more uniform drug absorption. Furthermore, improved bioavailability and a reduction in local irritation are beneficial consequences of the even distribution of the relatively small units in the gastrointestinal tract. MUPS designed for controlled drug release purposes often produce a more uniform drug release rate and a reduced risk of dose dumping with a lower tendency of inter-subject variation. MUPS can also be designed for delayed-release by enteric coating of the individual pellets. Uniform emptying of pellets from the stomach into the small intestine followed by dissolution of the coating at a higher pH will then produce relatively fast release of the drug after the initial delay [1, 2]. Pharmacodynamic advantages include a more consistent pharmacological action due to a more uniform and predict-

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able drug absorption from MUPS compared to conventional dosage forms [2].

The combination of more than one active pharmaceutical ingredient (drug substance) with different release profiles is possible with MUPS dosage forms. In addition, more than one incompatible drug can be incorporated in a single MUPS dosage form [1].

2. PELLET PRODUCTION METHODS

Pellets manufactured for pharmaceutical applications are generally sized between 0.5 and 1.5 mm in diameter and can be produced by means of different methods, which include powder layering, cryopelletisation, freeze pelletisation, spray drying, compression, spherical agglomeration and extrusion spheronisation. New and innovative methods of pellet production include Controlled Release Pelletising (CPS™), Fluidised Bed MicroPx™ and ProCell™ Technology. The various pellet production methods are illustrated in Fig. (**1**).

2.1. Drug Layering Method

This method entails the deposition of successive layers of a drug in the form of a dry powder, solution or suspension onto a core or nuclei with the aid of a binding/application medium (e.g. maltodextrin, polyvinylpirrolidone (PVP), gelatine or hydroxy propyl methyl cellulose (HPMC)). The core may be crystals or granules of the same material or may consist of an inert material. The dissolved binding material crystallises and thereby forms bridges between the core and layers of the drug substance. In powder layering, the binding liquid helps with the formation of successive layers of dry powder of drug and other components on starting cores by forming liquid bridges, which are eventually replaced by solid bridges [4, 5].

2.2. Cryopelletisation Method

Pellets are formed by converting liquid formulations into solid pellets through snap-freezing of droplets with the use of liquid nitrogen. The droplets are instantly and uniformly frozen due to the rapid heat transfer, which occurs between the droplets and liquid nitrogen. The water or organic solvent can be removed by drying the pellets in freeze dryers. The critical step is droplet formation and is influenced by formulation related variables such as viscosity, surface tension and solid content, equipment design and process variables [4, 5].

2.3. Freeze Pelletisation Method

Molten solid carriers together with dispersed active ingredient are introduced as droplets into a column of inert and immiscible liquid (*e.g.* aqueous glycerol solutions, vegetable or mineral oils). The equipment for freeze pelletisation contains a column that is divided into two parts. The first part maintains the molten solid carrier at a temperature between 20 to 100°C and in the second part of the column the droplet solidification takes place at a temperature between 0 to -40°C. This temperature is maintained by using a mixture of acetone and dry ice [6].

The active ingredient and other excipients are mixed with the molten carrier to form a solution or dispersion. Needles or nozzles are used to introduce the solution or dispersion into a column of liquid. Depending on the density of the droplets with respect to the liquid in the column, the droplets can either move in an upward or downward direction before solidifying into spherical pellets. When the density of the solid carrier is higher than the density of the liquid used in the column, the molten solid carrier is introduced from the upper portion of the column and the carrier solidifies in the bottom portion. However, when the density of the solid carrier is lower in comparison to that of the liquid used in the column, the molten solid carrier is introduced from the bottom of the column [5, 6].

2.4. Spray Drying and Spray Congealing Method

During the spray drying process, the suspended or dissolved drug without any excipient is sprayed into a hot

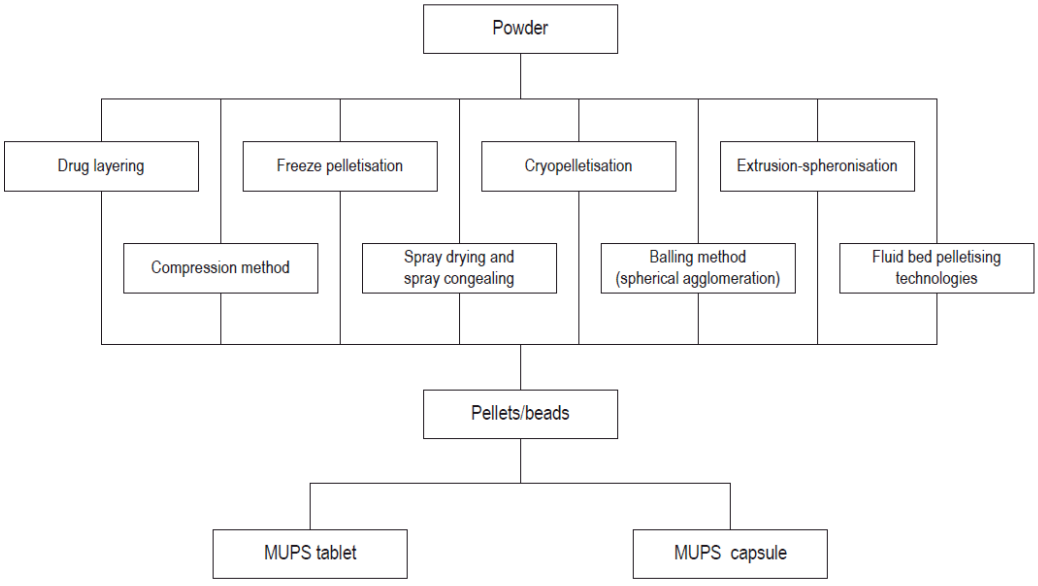

Fig. (1). Diagram illustrating pellet production methods.

stream to produce dry, spherical particles. As the atomised droplets come into contact with the hot air, the liquid medium evaporates. This drying process continues through a series of stages. The viscosity of the droplets constantly increases until solid particles are formed because the application medium is completely driven off [4, 5].

During the spray congealing process, a drug is allowed to melt, disperse or dissolve in hot melts or gums, waxes or fatty acids and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components to produce spherical congealed pellets [4, 5]. Suitable commercial excipients that can be used in the spray congealing process can be divided into two basic groups: hydrophobic and hydrophilic carriers. Hydrophobic carriers include beeswax, carnauba wax, cetostearyl alcohol, cetyl palmitate, fats (*i.e*. glyceryl behenate, glyceryl palmitostearate, glyceryl stearate, glyceryl palmitate), hydrogenated castor oil, microcrystalline wax, paraffin wax, stearic acid, and stearic alcohol. Hydrophilic carriers include esters of polyethylene glycol (*i.e.* Stearate 6000 WL1644), polyethylene glycols (PEGs) 2000–20000 and polyoxylglycerides. The selection of a carrier with a hydrophilic/hydrophobic character has a pronounced effect on the dissolution behaviour of the drug from the pellets. Hydrophobic carriers should be used to control the release of drug with a short half-life (*e.g.* theophylline and verapamil hydrochloride). Hydrophilic carriers should be used when enhancement of the dissolution rate of poorly water-soluble drugs is required (*e.g.* carbamazepine, diclofenac, and praziquantel) [7].

2.5. Compression Method

Powder mixtures or blends that contain both the active ingredient(s) and excipients are compacted under pressure to produce pellets of definite sizes and shapes. The formulation and process variables controlling the quality of the pellets prepared by means of the compression method are similar to those used in tablet manufacturing [5].

2.6. Balling Method (Spherical Agglomeration Method)

The balling method entails the formation of pellets from powders by continuous rolling or tumbling in pans, discs, drums or mixers. The pellets are formed with the addition of liquid or with exposure to high temperatures. Finely divided particles are converted into spherical particles upon addition of the appropriate amounts of liquid during application of physical forces [4, 5].

2.7. Extrusion-spheronisation Method

Of all the methods applied in pelletisation, extrusion-spheronisation is the most widely used pelletisation method because it is a simple, fast and versatile process for producing pellets and offers advantages over other pelletisation methods in terms of efficiency and pellet quality [6]. Extrusion spheronisation is a multi-step process, which consists of the following steps: dry mixing of all the powder ingredients; wet mass preparation; shaping the wet mass into cylinders (extrusion); breaking up the extrudate and rounding of the particles into spheres (spheronisation) and lastly drying of the pellets. Extrusion is the stage where pressure is applied to a wet powder mass (*e.g.* paste) until it passes through the calibrated openings of a screen or die plate of the extruder to form cylindrical segments with a uniform diameter. Spheronisation is the stage in which the small cylinders are rolled into solid spheres [4, 6].

Microcrystalline cellulose (MCC) is the excipient that is most often used in pellet formulation via extrusion-spheronisation. MCC provides many advantages in the formulation of solid dosage forms such as pellets. MCC aids the process by absorbing and retaining a large quantity of water, which binds and lubricates the material thus improving the plasticity and enhancing the rheological properties. The interactions between the wetting fluid (*e.g*. water) and the large surface area of MCC is responsible for producing strong spherical pellets with smooth surfaces [8, 9]. However, MCC has some characteristics which limit its use in the formulation of solid dosage forms *e.g*. sensitivity to lubricants, reduction of compactability after wet granulation, moderate flowability and low bulk density. Various other polymers of natural origin have therefore been investigated as potential excipients in pellet formulations intended for production by extrusion spheronisation, alone or in combination with MCC [3]. These excipients include chitosan, cross-linked polyvinyl pyrrolidone, glycerol monostearate, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, kappa-carrageenan, lactose, pectinic acid, powdered cellulose, polyethylene oxide and starch [10].

The excipients listed in Table **1** have been used in combination with MCC to improve pellet disintegration and/or drug release from MCC-based pellets [9].

Table 1. Excipients used in combination with MCC to improve the drug delivery properties of pellets [9].

Fillers	Disintegrants	Surface Active Agents
Lactose	Sodium starch glycolate	Glycerol monostearate
Dicalcium diphosphate	Croscarmellose sodium	Polyethylene glycol
Mannitol		Sodium lauryl sulphate
Starch and derivatives		Polysorbate 80, glyceryl and sorbitan mono-oleate, sorbitan mono-palmitate
Glucose		
β-Cyclodextrin		

Several excipients have been suggested and researched as an alternative for MCC in pellet production by means of extrusion spheronisation. The excipients listed in Table **2** have been reviewed for their suitability and capability of producing good quality pellets [8, 9].

2.8. Innovative Fluid Bed Pelletising Technologies

2.8.1. Controlled Release Pelletising (CPS™) Technology

CPS™ technology allows for the preparation of matrix pellets utilising low-dosed and high potent active pharmaceutical ingredients (API's) as well as high-dosed API's. Advanced fluid bed rotor technology, incorporating a conical shaped rotating disk and additional devices are used in CPS™ technology. Basic excipients such as microcrystalline cellulose powder is used as starting material, negating the use of starter beads. Other polymers, disintegrants and solubilisers may also be incorporated in the formulation. The starting powders are wetted with liquid (*i.e*. water and/or organic solvents) followed by a rolling particle movement (spheronisation step) yielding spherical pellets which are finally dried in the CPS™ or in a classical fluid bed dryer. This technology yields pellets with a high density and smooth surface which makes it ideal for coating applications [11, 12].

2.8.2. Fluidised Bed MicroPx™ Technology

The MicroPx™ technology is a continuous fluid bed agglomeration process suitable for high-dose API's, yielding matrix type pellets. Starting beads are not a requirement and all the components (*i.e*. API, binder material and other functional excipients) are contained in a liquid. The liquid is sprayed through spray guns into the empty MicroPx™ fluid bed unit generating initial particles which are then stepwise agglomerated to seeds. Onion-like structured pellets are formed through continuously layering of droplets onto the seeds. Pellets of the desired size, classified by an online sigzig air sifter are continuously discharged through a rotary valve. High density, low porosity spherical pellets produced by the MicroPx™ technology have smooth surfaces and a narrow particle size distribution. This technology is ideal for coating applications such as taste-masking (*i.e*. for use in oral suspensions or bitter tasting API's) [11, 12].

2.8.3. ProCell™ Technology

The ProCell™ technology is a direct granulation and pelleting process used for the preparation of pellets with a high drug load. This high-throughput and cost effective spouted bed type process requires no additional excipients since the pellets consists of pure API. Solutions, suspensions, emulsions or melts containing API can be processed. The conventional fluid bed with air entrance through a bottom screen is altered in this technology to allow the air to enter the processing chamber through slots at the sides and spray nozzles are arranged in the bottom spray position allowing spray to commence at the point of highest energy input inside the unit. Although pellets produced by this technology may be less spheronised than pellets produced by the CPS™ and MicroPx™ technologies, the ProCell™ technology is capable of producing pellets with a very high drug load (up to 100%), with a narrow particle size distribution, low friability and attrition and which is particularly suitable for processing of products with inherent stickiness (*e.g*. ibuprofen).

3. PRODUCTION PRINCIPLES OF MUPS TABLETS AND CAPSULES

Coated or uncoated pellets can be filled into hard gelatine capsules using the same principles and equipment that are used in the filling of conventional hard gelatine capsules with powder mixtures. The surface of the pellets may sometimes be rough, which can cause a problem during the capsule filling process. MUPS capsule formulations can be prepared by pellets only, however, pellets can be mixed with excipients such as lubricants to improve flow properties and to prevent fill mass variation. Automatic capsule filling machines are able to produce MUPS capsules with relatively low weight variation, however, electrostatic surface charges may result in pellet flow problems as well as the presence of agglomerates that may cause weight variation problems. Under-filled capsules are more common than over-filled capsules during production of MUPS capsules [13].

A typical formulation for MUPS tablets for direct compression consists of 30-40% w/w pellets (containing the active), 20-60% w/w MCC (filler) and 0.5-5.0% w/w magnesium stearate (lubricant). It is important to note that pellets and powders of the same material react differently when subjected to compaction forces [14]. There are four steps involved in the compaction of granules that are also applicable to the compaction of pellets into MUPS tablets namely repositioning or re-arrangement of the pellets, deformation (a change in shape of individual pellets), densification (a reduction in pellet porosity) and fragmentation with bonding (fracturing of pellets into small aggregates) [1]. During the re-

Table 2. Excipients suggested as alternatives for MCC for the production of pellets by means of extrusion spheronisation [8, 9].

Celluloses	Saccharides and Oligosaccharides	Polysaccharides	Synthetic Polymers
Powdered cellulose	Lactose	Starch	Poly-acrylates
Hydroxy-propyl methyl-cellulose (HPMC)		Alginates	Polyvinyl-pyrrolidone (PVP)
Hydroxy-ethyl cellulose (HEC)		Chitosan	Cross-linked polyvinyl-pyrrolidone
Polyethylene oxide (PEO)		Pectinic acid	
		Carrageenans	

arrangement and the deformation stages there is a reduction of volume, but the strength of the compressed bed is relatively low. The bulk deformation of pellets results in stronger inter-granular bonding, which is further increased during the bonding stage of the compaction process. The volume reduction during the bulk deformation and bonding stages are relatively small [1, 2]. It has been suggested that permanent deformation and densification are the relevant compaction mechanisms involved in the formation of MUPS tablets during compaction of pellets, while pellet fragmentation and abrasion are relatively low or non-existent [1, 2].

3.1. Deformation of Pellets During Compaction

Deformation of the pellets depends on three deformation characteristics namely the capacity for deformation, the mode of deformation and the resistance to deformation. The mode of deformation depends on the material composition of the pellets. Surface deformation refers to the ability of the pellets to conform to the surfaces of surrounding pellets (i.e. the external pellet surface is flattened against the adjacent pellets). In pellets containing a soft waxy material, the primary particles can reposition within the agglomerate and the inter-granular pore space is filled. In pellets consisting of a hard material, the compaction stress may result in deformation to the pellet surfaces [14]. The compression behaviour and desired compaction profile of pellets can be improved by including soft waxy materials such as polyethylene glycol (PEG) or wax in the uncoated pellets [15].

3.2. Pellet Size

The size of the pellets plays an important role in their compaction behaviour. Larger pellets are not as strong, relative to their size, as smaller pellets, therefore larger pellets are more readily deformed due to the reduced number of force transmission points and the resulting increased contact force on each pellet [16]. A screen size of 0.8 mm diameter aperture was shown to be the most suitable for the wet mass extrusion of pellets to be compressed into tablets [3]. Pellets with this size had a low tendency of segregation. A MUPS tablet formulation containing 30-40% w/w of pellets was also proven to behave like rapidly disintegrating tablets, while tablets containing 60% w/w of pellets did not show this type of behaviour [3].

3.3. Pellet Excipient Type

Excipients are used in pellet formulations mainly to facilitate the manufacturing process of the products, to ensure that satisfactory levels of the drug is delivered to the intended site and to produce a dosage form with favourable characteristics (e.g. dissolution, disintegration, release profile *etc*.). Pellets are intended to be administered orally, therefore the excipients used in pellet formulations are similar to those used in conventional tablet or capsule formulations. Excipients that are typically used in pellet formulations include binders, fillers, lubricants, disintegrants, surfactants, separating agents, pH adjusters, spheronisation enhancers, glidants and release modifiers [17].

Binding/application mediums such as maltodextrin, gelatine and polyvinylpirrolidone (PVP) are used in the drug layering method and helps with the formation of layers of drug and other components on the starting cores [4, 5]. The freeze pelletisation method utilises liquids (*e.g.* aqueous glycerol solutions, vegetable or mineral oils) together with molten carriers and dispersed active ingredients to form spherical pellets [6].

Hydrophobic carriers (*e.g*. beeswax, carnauba wax, cetostearyl alcohol and cetyl palmitate) or hydrophilic carriers (e.g. esters of polyethylene glycol, polyethylene glycols and polyoxylglycerides) are used as excipients in the spray congealing process. The dissolution behaviour of the drug is determined by the selection of the carrier [7].

Cellulosic (*e.g*. ethylcellulose) and acrylic polymers (*e.g*. Eudragit® or Kollicoat®) are popular as fillers in the production of pellets. Ethylcellulose has weak mechanical properties, therefore, compaction of pellets coated with ethylcellulose often leads to damage to the coating resulting in a loss of sustained-release properties. Acrylic polymers are flexible and allow for compaction of coated pellets without rupturing of the pellet's coating film [1].

As mentioned before, MCC is considered one of the most commonly used excipients in the production of pellets and is considered the golden standard in the production of pellets by means of extrusion spheronisation [9]. MCC is reported to aid the spheronisation process by trapping the moisture in the microfibrils, which adds plasticity to the extrudate resulting in spherical pellets [18, 19].

4. APPLICATION OF MUPS IN DRUG DELIVERY

4.1. Fast Disintegrating MUPS Formulations

The effect of formulation and process variables on the properties of fast disintegrating MUPS tablets were investigated by preparing starch based pellets by extrusion-spheronisation using riboflavin as model drug, starch as filler, HPMC as binder and sorbitol as plasticiser. Excipient granules containing MCC, lactose, internal disintegrant (*e.g*. croscarmellose sodium, sodium starch glycolate or crospovidone) and polyvinylpyrrolidone K-30 were prepared by wet granulation. The pellets, granules and external disintegrant (*i.e*. silicium dioxide and sodium stearyl fumerate) were then mixed and compressed, yielding fast disintegrating MUPS tablets. Evaluation of the tablets showed that a lower concentration of starch pellets and higher compression force was required to yield tablets with a high hardness, low friability and a short disintegration time (< 3 min). It was also found that crospovidone containing tablets were harder, less friable and disintegrated faster compared to croscarmellose sodium and sodium starch glycolate containing tablets. The study concluded that the selection of excipients and process parameters are of utmost importance in the formulation of fast disintegrating MUPS tablets [20].

A multi-particulate fast disintegrating system consisting of MCC pellets containing acetaminophen was also successfully developed. The pellets were prepared using the extrusion-spheronisation technique. Pellets were characterised in terms of size distribution, sphericity, friability and drug release. Pellets containing a high drug load (25-75% w/w) and exhibiting instantaneous disintegration upon contact with water were produced with a disintegration time of less

than 5 s. An acetaminophen release rate of more than 90% in 15 min was achieved. The researchers attributed their success to the combination of extrusion/spheronisation and freeze-drying [21]. Prospective research should include the formulation of fast disintegrating MUPS dosage forms by compression or encapsulation of fast disintegrating pellets into MUPS tablets or capsules to ease drug administration and to ensure correct dosing.

4.2. Modified Drug Release MUPS Formulations

Modified drug release can either refer to delayed drug delivery or controlled/sustained/extended/prolonged drug delivery. Delayed drug delivery is aimed at protecting the drug from an unfavourable environment in the gastrointestinal tract, to protect the gastrointestinal tract from high, local concentrations of an irritating drug compound, or to target a specific region of absorption or action. Delayed drug release products are often enteric coated and targeted to the small intestines or colon. Controlled drug delivery is aimed at releasing the drug continuously at a predetermined rate. This is done to reduce the frequency of dosing and thereby increasing patient compliance [22].

Modified drug delivery can be achieved by applying a film coating to pellets. Film coating pellets with a polymer (e.g. cellulosic or arcrylic polymers), which regulates the drug release rate, is a common way of designing multiple-unit oral modified/extended drug release delivery systems. The coated pellets can be filled into hard gelatine MUPS capsules or compacted into MUPS tablets. The modified drug release MUPS should have a short disintegration time to maintain the multi-particulate function of the MUPS [23].

Enteric film coating (*e.g*. methacrylic acid co-polymers, hydroxypropylmethylcellulose phthalate and hydoxypropylmethylcellulose acetate succinate) provides a barrier that protects the drug from the acidic pH in the stomach. The enteric coating layer presents a surface that is stable in the highly acidic environment of the stomach but that breaks down rapidly in the less acidic environment of the small intestine thus resulting in drug release targeted to the small intestine [24].

Bioavailability studies were performed on two venlafaxine sustained-release pellet formulations to explain the effect of the film coating composition on the *in vitro* drug release profiles and *in vivo* pharmacokinetics. The organic solvent and aqueous dispersion coatings exhibited similar *in vitro* drug release behaviour, but due to the complex *in vivo* environment, the *in vivo* drug release was significantly different. The study concluded that differences in the film micro-structure and roughness of the pellet surface caused by two different coating techniques influenced the *in vivo* drug release and oral absorption [25].

Non-gastric resident sustained release pellets containing dipyridamole has also been developed. Dipyridamole, a coronary vasodilator, is a weak basic drug, which exhibits good solubility at relatively low pH values (*e.g*. pH 1.0 in the stomach) and poor solubility at relatively high pH values (*e.g*. pH 7.0 in the small intestine). These pellets were prepared by incorporating a pH-modifier into the core of the pellets to modify the micro-environment and by coating the pellets with a retarding film layer consisting of a mixture of enteric soluble and insoluble polymers. *In vivo* studies with the sustained release pellets were performed in beagle dogs using commercially available immediate release dipyridamole tablets as reference product. Both the rate and extent of drug release in the small intestine increased, which was associated with an increase in the bioavailability for the pellets when compared to that of the reference product [26].

4.3. Matrix Type MUPS Formulations

Matrix type drug delivery systems are controlled drug delivery systems, which release the drug in a continuous manner by both dissolution controlled as well as diffusion controlled mechanisms. To control the drug release rate, the drug is dispersed in either swellable hydrophilic substances or insoluble matrices consisting of rigid non-swellable hydrophobic materials or plastic materials [27].

In another study, ibuprofen MUPS tablets with a sustained drug release rate over an extended period of 24 h was formulated. The authors concluded from the results of the study that compression force, pellet to filler ratio, composition of filler blend and granulation of fillers had a significant influence on the tablet strength, friability, and disintegration time, but had no effect on drug release rate from the compacted pellets. The compacted pellets showed no apparent damage to the pellet coating as a result of the compaction process [28].

An oral anti-diabetic agent (repaglinide) with a short half-life of about 1 h was prepared in sustained release matrix pellets using the extrusion-spheronisation technique. The pellets were composed of MCC, lactose and sodium lauryl sulphate. *In vitro* drug release and *in vivo* blood glucose studies were carried out and the results obtained showed that the pellets had acceptable physical properties with regard to pellet size distribution, flowability and friability and 94% of the drug content was released after 12 h. The repaglinide formulation was able to decrease blood glucose levels in normal rats and those with diabetes throughout 8-12 h. The study concluded that controlled release matrix pellets offered sustained and more effective blood glucose control than conventional repaglinide tablets, but further clinical studies in humans were suggested [29].

4.4. Targeted Drug Delivery MUPS Formulations

4.4.1. Gastro-retentive MUPS Systems

Gastro-retentive drug delivery systems enhance the bioavailability and effectiveness of drugs with a relatively narrow absorption window in the upper gastrointestinal tract or when drugs have a local effect in the stomach and duodenum [30]. The main approaches to achieve gastro-retention include: (i) high density systems with prolonged gastric retention time in the lower part of the antrum, (ii) swelling and expanding systems which swells and unfold to prevent their passage through the pyloric sphincter, (iii) muco-adhesive systems which adhere to the gastric epithelial cells and (iv) floating systems which float on the surface of the gastric fluid [31].

In a study by Martins and co-workers, mucoadhesive pellets on a thiolated pectin base was developed. Pellets containing pectin, MCC and ketoprofen were prepared by using the extrusion-spheronisation technique and their mucoadhesive properties were evaluated through a wash-off test using porcine intestinal mucosa. The pellets were still adhering to the intestinal mucosa after 480 min. *In vitro* drug release indicated gradual release of ketoprofen. The study concluded that thiolated pectin-based pellets could potentially be considered as a platform for the development of an oral mucoadhesive MUPS drug delivery system [32].

Another study aimed to develop a novel gastro-floating multi-particulate system based on floatable, porous and low-density matrix type pellet cores. Pellet cores containing MCC and mannitol were prepared by using the extrusion-spheronisation technique. Porous matrix cores were prepared by coating the pellets with a coating solution containing ethyl cellulose and polyvinyl pyrrolidone in a fluid bed coater. A drug layer (i.e. dipyridamole), sub-coating layer (HPMC solution plasticised by polyethylene glycol 6000) and retarding layer (Eudragit® NE 30D) was then spayed onto the matrix type pellet cores in a fluid bed coater. An *in vitro* buoyancy study, *in vitro* dissolution test and *in vivo* pharmacokinetic study in beagle dogs were carried out on these pellets. The formulation showed immediate floatability without a lag time and floatability was maintained for 12 h. First order drug release up to 12 h was achieved. The *in vivo* pharmacokinetic study demonstrated prolonged gastric retention time, sustained drug release and also better control over peak plasma concentration when compared to conventional sustained release pellets. The study concluded that the novel gastro-floating pellets had the potential to be developed into a gastro-retentive drug delivery system [31].

4.4.2. Colon Targeted Drug Delivery

Both local and systemic delivery of drugs can take place in the colon. Local drug delivery allows topical treatment of inflammatory bowel disease. Oral colon specific drug delivery systems have the advantages that local drug concentrations are improved and dosage and drug side effects are reduced. These systems could also enhance the systemic bioavailability of poorly absorbed drugs due to the long retention time in the colon. Low efficacy due to premature drug release in the stomach or small intestines can be overcome by colon targeted drug delivery of drugs such as budesonide. Colon targeted drug delivery systems could also be advantageous in the treatment of inflammatory bowel disease [33]. Colon targeted drug delivery has been achieved by focusing on three basic approaches namely pH-dependent release, time-dependent release, or bacterial degradation in the distal ileum/colon [34].

A carrier system for herbal medicines with low water solubility and bioavailability was also developed. Common diseases associated with oxidative stress can effectively and safely be treated by herbal medicines. Layered pellets containing *Petroselinum crispum* extract on MCC inert pellet cores were prepared and coated with enteric coatings (*e.g.* Eudragit® L 30 D-55 and Eudragit® FS 30 D) to achieve colonic drug delivery. Eudragit® contain carboxyl groups which remain unionised in the acidic pH of the stomach, but which are transformed to carboxylate groups when the pH increases in the colon. The study concluded that colon site-specific pellets containing flavonoid extract could successfully be prepared. The site-specific delivery of *Petroselinum crispum* could allow for increased effectiveness and further *in vitro* antioxidant activity measurements was suggested [35].

Ibuprofen and furosemide MUPS capsule drug delivery systems for site specific drug release in the colon was developed by formulating pellets containing various polymers as binder agent and then coating the pellets with an enteric coating. The pellets were then filled into hard gelatine capsules. The ibuprofen MUPS capsule formulation had a lag-time of about 2 h before release of the active ingredient commenced. Furosemide is normally absorbed only in the upper parts of the gastrointestinal tract. The furosemide MUPS capsule formulation showed decreased bioavailability, which could be explained by the fact that the formulation carried the furosemide to the lower parts of the gastrointestinal tract, where absorption of furosemide is lower. The authors concluded that site specific drug release (*i.e.* in the distal part of the small intestine and the colon) can be achieved by formulating film-coated pellets in which enteric polymers (dissolving at pH≈7) are used as binders and as coating materials [36].

Metronidazole colon targeted pellets has also been developed. The objective of the study was to develop pellets which will maximise the amount of metronidazole at the targeted site (*e.g.* colon) thus minimising side effects, toxic effects and to avoid hepatic metabolism. This study aimed to prepare colon targeted drug delivery by using a combination of time and pH dependent polymethacrylate polymers that offer protection to the drug until it leaves the stomach and major drug release in the small intestine. Metronidazole pellets were prepared by the extrusion-spheronisation process using MCC and super-disintegrants and a double layer coating was applied to the pellets using Eudragit® RS 100 (inner coat) and Eudragit® S100 (outer coat). The pellets were evaluated in terms of friability, sphericity, aspect ratio and *in vitro* drug dissolution. A drug release rate of not more than 10% at 5 h and more than 90% at 7 h was achieved. The study concluded that desirable drug release can be obtained by applying a double layer coating to pellet cores [34]. These pellets should be formulated into MUPS capsules for future *in vivo* research purposes.

Applications of MUPS tablets and capsules in drug delivery is illustrated in Fig. (**2**).

5. MUPS PRODUCTS AVAILABLE ON THE MARKET

MUPS capsules are widely used in solid dosage form design and numerous MUPS capsule products are available on the market. The compaction of pellets presents more challenges than filling capsules with pellets, but various MUPS tablet formulations are also available on the market. Table **3** contains the trade names and active pharmaceutical ingredients (API's) of some of the MUPS products (both capsules and tablets), which are available on the market [15, 37].

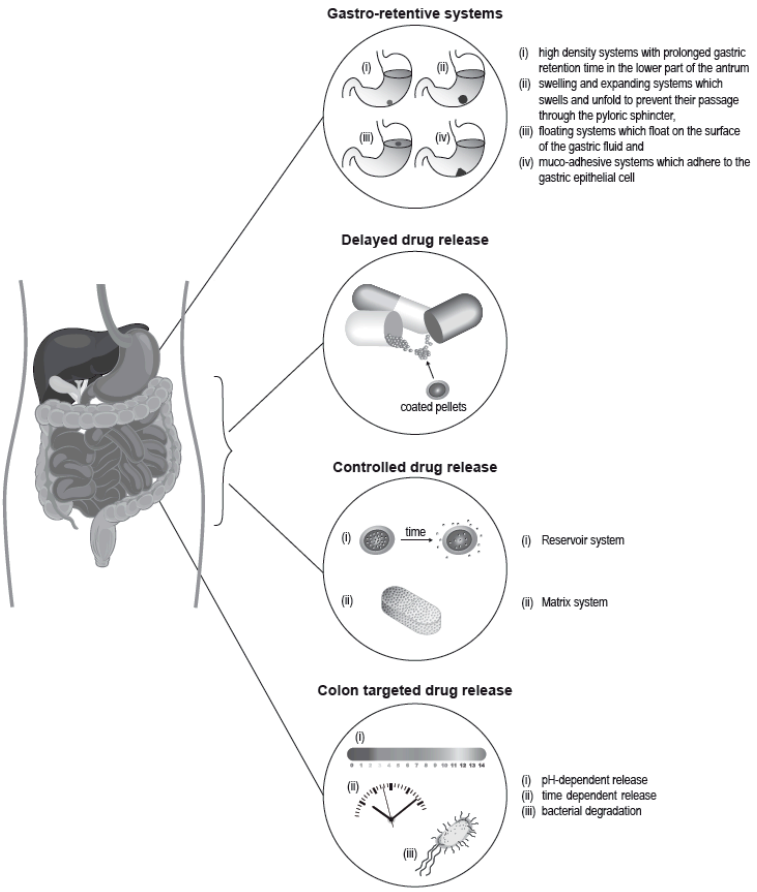

Fig. (2). Different applications of MUPS drug delivery systems.

Table 3. MUPS products available on the market [adapted from 15, 37].

Product Name	Dosage Form	Active Pharmaceutical Ingredient	Manufacturing Company
Antra®	MUPS tablet	Omeprazole magnesium	AstraZeneca
Beloc-Zok®	MUPS tablet	Metoprolol succinate	AstraZeneca
Bontril SR®	MUPS capsule	Phendimetrazine	Valeant Pharmaceuticals
Brexin L.A.®	MUPS capsule	Chlorpheniramine/Pseudoephedrine	Savage Laboratories
Compazine®	MUPS tablet	Prochlorperazine	GlaxoSmithKline
Dilgard XL 180®	MUPS capsule	Diltiazem	Cipla
Elixophyline®	MUPS capsule	Theophylline	Cipla
Fastin®	MUPS capsule	Phentermine	GlaxoSmithKline
Hispril®	MUPS capsule	Diphenylpyraline hydrochloride	GlaxoSmithKline
Ibugesic SR 300®	MUPS capsule	Ibuprofen	Cipla
Indocin SR®	MUPS capsule	Indomethacin	Merck
Losec® MUPS Tablets	MUPS tablet	Omeprazole magnesium	AstraZeneca
Nicobid TS®	MUPS tablet	Niacin	US Vitamin
Zenical®	MUPS capsule	Orlistat	Roche Laboratories
Ornade®	MUPS capsule	Chlorpheniramine/Phenylpropanolamine	GlaxoSmithKline
Prevacid SoluTab®	MUPS tablet	Lansoprazole	Takeda Pharmaceuticals
Prilosec®	MUPS capsule	Omeprazole	AstraZeneca

6. CHALLENGES IN MUPS FORMULATIONS

Variation in fill mass is one of the problems which may occur during the production of MUPS capsules. Fill mass variation can be attributed to flow related issues of the pellets, which are caused by pellets with rough surfaces, electrostatic charges and the presence of agglomerates. This problem can easily be solved by adding excipients such as lubricants or glidants (*e.g.* 1% talcum powder) [12].

The formulation and manufacturing of MUPS tablets presents challenges such as content uniformity and weight variation. These problems mainly occur due to differences in the density and size of the excipients and pellets. Selecting pellets with a narrow size distribution together with excipients of similar shape and size may minimise these problems, but practically challenging because the excipients are in powder from with relative small particles compared to that of pellets [3]. Homogeneous blends of excipients and pellets are of utmost importance in order to obtain tablets of uniform drug content and weight [2].

Fragmentation or deformation of the pellets as a result of the compaction forces is another problem, which may occur during the manufacturing of MUPS tablets. Deformation of coated pellets may lead to cracked or ruptured coating with a loss of the coating functionality, resulting in an undesirable effect on the drug release properties of the pellets. By changing the composition and characteristics of the pellets or by including excipients such as cushioning agents (*e.g*. polyethylene glycol), this problem can be minimised. The size of the pellets is an important variable that can be controlled in order to minimise fragmentation and deformation. Small, mechanically strong pellets that are less porous and have a uniform particle size distribution are more suited for compaction without deformation than larger pellets with a wide particle size distribution, great porosity and which are mechanically soft [2]. The rate and magnitude of compaction force applied must also be monitored and optimised to minimise fragmentation or deformation and to ensure the desired drug release profile [1]. The MUPS tablets should, however, be mechanically strong, but should still have a relative short disintegration time to maintain the multi-particulate function of the MUPS [23].

CONCLUSION

MUPS tablet and capsule formulations have become important drug delivery systems due to the advantages they offer over conventional tablet and capsule formulations as well as their applications in specialised drug delivery settings. Their pharmaceutical applications include immediate release, controlled/sustained release and site specific dosage forms. Although the MUPS formulation and manufacturing processes present various challenges, it is evident that these challenges can be overcome by formulation factors such as addition of excipients. Various MUPS products have been successfully formulated and are available on the market internationally.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Chapter 4: Research Article: "*Development of multiple-unit pellet system tablets by employing the SeDeM expert diagram system I: pellets with different sizes*"

Chapter 4 is presented in the form of a full length research article entitled "*Development of multiple-unit pellet system tablets by employing the SeDeM expert diagram system I: pellets with different sizes"* which was published (early on-line) in 2017 in the journal entitled *"Pharmaceutical Development and Technology"* (DOI: 10.1080/10837450.2017.1342657). The complete guide for authors for this journal is given in Appendix F.

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RESEARCH ARTICLE

Development of multiple-unit pellet system tablets by employing the SeDeM expert diagram system I: pellets with different sizes

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ABSTRACT

Multiple-unit pellet systems (MUPS) provide several pharmacokinetic and pharmacodynamic advantages over single-unit dosage forms, however, compression of pellets into MUPS tablets present certain challenges. Although the SeDeM Expert Diagram System (SeDeM EDS) was originally developed to provide information about the most appropriate excipient and the minimum amount thereof that is required for producing direct compressible tablets, this study investigated the possibility to apply the SeDeM EDS in the production of MUPS tablets. In addition, the effect of pellet size (i.e. 0.5, 1.0, 1.5, 2.0, and 2.5 mm) on SeDeM EDS predictions regarding the MUPS tablet formulations was investigated. The compressibility incidence factor values were below the acceptable value (i.e. 5.00) for all the pellet sizes. Kollidon® VA 64 was identified as the most appropriate excipient to improve compressibility. The compression indices, namely, the parameter index (IP), parametric profile index (IPP), and good compression index (GCI) indicated that acceptable MUPS tablets could be produced from the final pellet-excipient blends based on predictions from the SeDeM EDS. These MUPS tablets complied with specifications for friability, hardness, and mass variation. The SeDeM EDS system is therefore applicable to assist in the formulation of acceptable MUPS tablets.

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Introduction

The SeDeM Expert Diagram System (SeDeM EDS) is used in formulation studies to develop direct compressible tablets. This system provides information about the suitability of active pharmaceutical ingredients (API) and excipients required to successfully produce direct compressible tablet formulations. In essence, the SeDeM EDS indicates the degree to which powder substances can be successfully compressed and the properties of the end product that need to be adjusted to yield the best possible tablet formulation for direct compression (Suñé-Negre et al. 2008).

Multi-particulate delivery systems are receiving renewed interest by pharmaceutical scientists to improve the delivery and performance of therapeutic compounds (Jose et al. 2012; Pagariya and Patil 2013). Such dosage forms include mini-tablets, pellets, granules, and microparticles (Ghebre-Sellassie 1994; Barakat and Ahmad 2008). Pellets (or beads) are spherical or semi-spherical free flowing solid units with a relatively narrow size distribution, which are often used in drug delivery systems called multiple-unit pellet systems (MUPS). Pellets in multiple-unit drug delivery systems offer various technological as well as therapeutic advantages over conventional dosage forms. Technological advantages include a narrow particle size distribution, strong spheres with low friability, a smooth surface and improved flow properties (Reddy et al. 2011). Pharmacokinetic advantages of MUPS include rapid but uniform transit of the relatively small pellets from the stomach into the small intestine (i.e. gastric emptying), which results in a lower possibility of localized irritation as well as better and more uniform drug absorption. Furthermore, potentially improved bioavailability and a reduction in toxicity and side-effects are expected due to the even distribution of the spheres in the gastrointestinal tract. MUPS designed for controlled-release purposes produce a more uniform drug release rate and a reduced risk of dose dumping with a lower tendency for inter-subject variation (Ghebre-Sellassie 1994; Abdul et al. 2010; Aulton and Summers 2013). Pharmacodynamic advantages include consistent and controlled pharmacological action due to a more uniform and predictable drug release and subsequently more consistent drug absorption from MUPS. Reduced inter- and intra-individual variability in drug absorption and clinical response is therefore achieved (Vervaet et al. 1995 Dukić-Ott et al. 2007, 2009; Pai et al. 2012).

Pellets manufactured for pharmaceutical applications are generally sized between 0.5 and 1.5 mm in diameter (Ghebre-Sellassie 1994) and can be produced with different methods, e.g. drug layering, cryopelletization, freeze pelletization, globulation method, spray drying, and spray congealing, compression, balling method/spherical agglomeration, and the extrusion–spheronization method (Aulton and Summers 2013). Upon successful preparation of multiparticulates (e.g. pellets) intended for drug delivery, the pellets are usually processed into MUPS.

The particles of multiple-unit dosage forms can be filled into hard gelatin capsules (MUPS capsules) or compressed into tablets (MUPS tablets). MUPS capsules are more common but the production costs of capsules are relatively high. Furthermore, the production rate of capsules is lower when compared to that of tablets due to the lower output of capsule filling machines. Capsules, as opposed to tablets, cannot be divided into sub-units

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(Abdul et al. 2010). Easy adjustment of the dosage strength is therefore not possible with capsules and tablets provide a more flexible dosage regimen. MUPS tablets include lower tendency of adhesion of the dosage form to the oesophagus during swallowing (Abdul et al. 2010).

Challenges in content uniformity and weight variation may be experienced during MUPS tablet production. These problems mainly occur due to differences between excipients and pellets in terms of size and density (Pai et al. 2012). Another problem that may be experienced is the fragmentation of pellets during compaction into MUPS tablets. The choice of excipients as well as homogeneous blends of excipients and pellets is important factors that may impact on the quality of MUPS tablets (Reddy et al. 2011).

Although the SeDeM EDS was originally developed for the formulation of conventional direct compressible tablets consisting of powders as well as validation of powder properties as described in detail in previous publications (Pérez et al. 2006; Suñé-Negre et al. 2011a,b), this study investigated the applicability of the SeDeM EDS for the formulation of MUPS tablets consisting of pellets (produced by means of extrusion spheronization) with different sizes.

Materials and methods

Materials

MicroceLac® 200, Cellactose® 80, Tablettose® 80, and talc were donated by Meggle (Molkerei Meggle, Wasserburg GmbH & Co, Germany) and were used as pharmaceutical excipients in the formulation of the pellets and/or MUPS tablets. The other excipients employed in the formulation of the MUPS tablets included colloidal silicon dioxide (Aerosil® 200, Degussa, Paeisipanny, New Jersey, USA), copovidone (Kollidon® VA 64, BASF, Ludwigshafen, Germany), croscarmellose sodium (Ac-di-Sol®, FMC Corporation Little Island, Cork, Ireland), and microcrystalline cellulose (Avicel® PH 200, FMC Corp, Brussels, Belgium). Ethanol (Associated Chemical Enterprises (ACE), Johannesburg, South Africa) and purified water were used during the wetting of powders prior to extrusion during pellet preparation.

Methods

Production of pellets

The pellets for this study were prepared by means of extrusion–spheronization in five different sizes (i.e. 0.5, 1.0, 1.5, 2.0, and 2.5 mm based on the aperture size of the extrusion screen) and consisted of co-processed lactose-microcrystalline cellulose (MicroceLac® 200) without any active ingredient (placebo pellets). The MicroceLac® 200 powder was wetted with a mixture of ethanol and water (60:40), while the powder bed was mixed in the bowl of a Kenwood planetary mixer (Kenwood Chef Mixer, Kenwood Ltd, Havant Hants, Britain). The wetted powder mass was extruded with a Caleva extruder (Caleva Process Solutions Ltd, England) at a speed of 30 rpm to render cylindrical extrudates. Each pellet size was produced by using an extruder screen with a different aperture size that vary in 0.5 mm increments from 0.5 mm up to 2.5 mm. Each extrudate was spheronized for 5 min at a speed of 2000–2550 rpm in a Caleva spheronisator (Caleva Process Solutions Ltd, England). The pellets were then freeze dried using a Virtis Advantage bench-top freeze dryer (SP Industries Ins., PA). For freeze-drying the pellets were frozen at −80 °C for 5 h, after which a vacuum of 45 mTorr was applied for 48 h in order to sublime off the wetting agent.

Characterization of the pellets and excipients

The pellets (i.e. five different sizes) and selected excipients were characterized in terms of the parameter tests required by the SeDeM EDS as explained below. The mean value of each parameter test was obtained and used in the radius calculations as described below. A SeDeM diagram was drawn for each pellet size and selected excipient (Pérez et al. 2006; Suñé-Negre et al. 2008, 2011a,b).

Briefly, the methods used to determine each of the SeDeM parameter tests for the pellets and excipients are as follows (Pérez et al. 2006):

- Bulk density (Da): Determined for each pellet size and selected excipient powder according to the United States Pharmacopeia (USP) method described in Section 616 (United States Pharmacopeia 2015).
- Tapped density (Dc): Determined for each pellet size and excipient powder according to the USP method described in Section 616 (United States Pharmacopeia 2015). The volume was the value obtained after 2500 taps using a settling apparatus with a graduated cylinder (i.e. voluminometer).
- Inter-particle porosity (Ie): Calculated from Da and Dc by using the following equation: $Ie = (Dc - Da)/(Dc \times Da)$.
- Carr index (IC): Calculated from Da and Dc by using the following equation: $IC = (Dc - Da/Dc) \times 100$.
- Cohesion index (Icd): Determined by directly compressing the respective selected excipient powders and pellets each at maximum compression force. An eccentric press was used as recommended. The hardness (N) of the tablets obtained from this compression step was determined with a hardness tester (Erweka TBH 425 TD, Germany). Initially, the excipient powders and pellets were each tested on their own, but if found to be abrasive, a 3.5% w/w of the following standard lubricant mixture was added as previously recommended (Pérez et al. 2006): talc (2.36%), colloidal silicon dioxide (0.14%), and magnesium stearate (1.00%).
- Hausner ratio (IH): This was calculated from Da and Dc by using the following equation: $IH = Dc/Da$.
- Angle of repose (α): Was determined according to the USP method described in Section 1174 (United States Pharmacopeia 2015).
- Flowability (t″): Was determined according to the USP method described in Section 1174 (United States Pharmacopeia 2015) using an electronic balance and recording device. It is expressed in seconds and tenths of a second per 100 g of sample.
- Loss on drying (%HR): This was determined by the USP method described in Section 731 (United States Pharmacopeia 2015). Briefly, a sample from each excipient powder or pellet formulation was dried in an oven at 105 °C ± 2 °C, until a constant weight was obtained.
- Hygroscopicity (%H): Determined by measuring the percentage increase in sample weight after being kept in a humidifier at relative humidity of 76% (± 2%) and a temperature of 22 °C ± 2 °C for 24 h.
- Percentage of particles measuring <45 μm (%Pf): Particle size was determined by means of the USP sieve test as described in Section 786 (United States Pharmacopeia 2015). The % of particles that passed through a 45 μm sieve was determined when the sieve was loaded with 100 g powder/pellets and vibrated for 10 min at a speed setting of 10 on the apparatus (Fritsch Analysette, Germany).

- Homogeneity index (Iθ): This was determined in accordance with the general USP method described in Section 786 (United States Pharmacopeia 2015) for determining particle size range by means of the sieve test. A 100 g sample of each respective excipient powders and pellets from each size was determined by submitting a sieve stack to vibration for 10 min at a speed setting of 10 on the apparatus (Fritsch Analysette, Germany). Sieve sizes that were used included 2800, 2360, 2000, 1700, 1200, 1000, 850, 710, 500, 355, 212, 106, and 45 μm. The percentage of powder/pellet retained on each sieve and the quantity that passed through the 45 μm sieve was measured. The following equation was applied to the data obtained in order to calculate the homogeneity index (Pérez et al. 2006):

$$I\theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}} \quad (1)$$

Where:

$I\theta$ = Relative homogeneity index, which is the particle-size homogeneity in the range of the fractions and sieve sizes used in the study.

F_m = Percentage of particles in the majority range.

F_{m-1} = Percentage of particles in the range immediately below the majority range.

F_{m+1} = Percentage of particles in the range immediately above the majority range.

n = Order number of the fraction under study, within a series, with respect to the majority fraction.

d_m = Mean diameter of the particles in the majority fraction.

d_{m-1} = Mean diameter of the particles in the fraction of the range immediately below the majority range.

d_{m+1} = Mean diameter of the particles in the fraction of the range immediately above the majority range.

The SeDeM parameters described above were grouped into five incidence factors based on the physical characterization of each of the selected excipients and pellet sizes. The parameters and equations used to calculate the incidence factor values as well as the conversion of SeDeM parameters into radii values are shown in Table 1 (Pérez et al. 2006; Suñé-Negre et al. 2008, 2011a,b).

The excipients that were investigated in this study for correction of inadequacies of the pellets before compression included Avicel® PH 200, Cellactose® 80, Kollidon® VA 64, MicroceLac® 200 and Tablettose® 80. SeDeM diagrams were drawn for each of these selected excipients. The most appropriate excipient, when used in the smallest possible amount to yield a formulation that should be suitable for compression was identified for each pellet size by means of the SeDeM EDS as previously described by Suñé-Negre et al. (2008) and briefly outlined below.

Radius calculations for construction of the SeDeM diagram

A specific factor value (shown in Table 1) was used to calculate diagram radii values, which were used to draw the SeDeM diagrams. These diagrams indicated the characteristics of the material under investigation in terms of its suitability for compression (Pérez et al. 2006; Suñé-Negre et al. 2008, 2011a,b).

Compressibility indices to predict material compressibility

The following indices were calculated to determine whether a material can be considered suitable for compression.

Table 1. Parameters and equations used to calculate the SeDeM EDS incidence factor values and conversion of SeDeM parameters into radii values (Pérez et al. 2006; Suñé-Negre et al. 2008, 2011a,b).

Incidence factor	Parameter	Symbol	Unit	Equation	Acceptable range	Factor applied to the parameter value (v)
Dimension	Bulk density	D_a	g/ml	$D_a = P/V_a$	0–1 g/ml	10v
	Tapped density	D_c	g/ml	$D_c = P/V_c$	0–1 g/ml	10v
Compressibility	Inter-particle porosity	Ie	–	$Ie = (D_c - D_a)/(D_c \times D_a)$	0–1.2	10v/1.2
	Carr index	IC	%	$IC = [(D_c - D_a)/D_c] \times 100$	0–50%	v/5
	Cohesion index	Icd	N	Hardness of MUPS at maximum compression force	0–200 N	v/20
Flowability/Powder flow	Hausner ratio	IH	–	$IH = D_c/D_a$	3–1	10 – (10v/3)
	Angle of repose	(α)	°	$\alpha = \tan^{-1}$ h/r	50–0°	10 – (v/5)
	Powder flow	t″	s	Time taken for 100 g to flow through funnel	20–0 s	10 – (v/2)
Lubricity/Stability	Loss on drying	%HR	%	%HR = (weight before drying – weight after drying)/weight before drying] × 100	10–0%	10 – v
	Hygroscopicity	%H	%	%H = (weight after exposure/weight before exposure) x 100	20–0%	10 – (v/2)
Lubricity/Dosage	Particle size <45 μm	%Pf	%	Percentage that passed through 45 μm sieve	50–0%	10 – (v/5)
	Homogeneity index	(Iθ)	–	$I\theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$	$0–2 \times 10^{-2}$	500 v

$$\text{Parameter index (IP)} = \frac{\text{Number of parameters having } r \geq 5}{\text{Total number of parameters}} \quad (2)$$

The index is acceptable when IP $\geq$0.5.

$$\text{Parameter profile index (IPP)} = \text{Mean value of all the parameters} \quad (3)$$

The index is acceptable when IPP $\geq$5.

$$\text{Good compression index(GCI)} = \text{IPP} \times f \quad (4)$$

Where:

f = Reliability factor and $f = \frac{\text{polygon area}}{\text{circle area}}$

The index is acceptable when GCI $\geq$5.

Application of the SeDeM expert diagram system to determine the amount of excipient required

Besides the radii values as well as indices that should be >5.00, an equation was also proposed that can be used to identify the most appropriate excipient when used in the smallest possible amount, to yield a formulation that should be suitable for compression (Suñé-Negre et al. 2008), namely:

$$CP = 100 - \left(\frac{RE - R}{RE - RP} \times 100\right) \quad (5)$$

Where:

CP = % w/w of corrective excipient required to render a tablet formulation,

RE = mean incidence value of the corrective excipient,

R = mean incidence value to be obtained in the blend (R = 5 as 5 is the minimum value that is regarded as necessary in order to achieve good compression),

RP = mean incidence value of the API to be corrected.

Preparation of final MUPS tablet formulations

Based on the SeDeM parameter test results, the most appropriate excipient was identified for each pellet size. A mixture of each pellet size and the optimal amount of the excipient was prepared. Each pellet size and identified excipient was mixed with a Turbula T2B mixer (Willy A Bachofen Maschinenfabrik, Basel, Schweiz) for 5 min to yield an intermediate blend. Each intermediate blend was characterized in terms of the parameter tests required by the SeDeM EDS and a SeDeM diagram for each intermediate blend was constructed. Subsequently, a final blend for each of the pellet formulations was prepared in the Turbula T2B mixer by adding additional excipients as recommended by the SeDeM EDS, namely, talc (2.36%), colloidal silicon dioxide (Aerosil® 200) (0.14%), and magnesium stearate (1.00%) in addition to the identified corrective excipient (Pérez et al. 2006). Croscarmellose sodium (Ac-di-Sol®) (5.00%) was also added as another disintegration aid.

These final blends or MUPS tablet formulations were also characterized in terms of the parameter tests required by the SeDeM EDS and the SeDeM diagrams were constructed. Finally, the compressibility indices were calculated for each of the final MUPS tablet mixtures.

MUPS tablet preparation

The final blends were compressed on a Korch XP 1 (Korsch AG, Berlin) single punch tablet press, using a 10 mm diameter round, flat faced, bevelled edge punch. All the MUPS tablets were compressed at a similar compression force and fill volumes to produce tablets of similar mass.

Characterization of the MUPS tablets

All the MUPS tablets were characterized in terms of uniformity of mass, tablet hardness, friability, and disintegration using the methods as indicated in the pharmacopoeias (United States Pharmacopeia 2015; British Pharmacopoeia Commission 2015).

Results and discussion

SeDeM EDS results of the pellets and excipients

The SeDeM diagrams as well as the incidence factor values for the pellets with different sizes are shown in Figure 1 and Table 2,

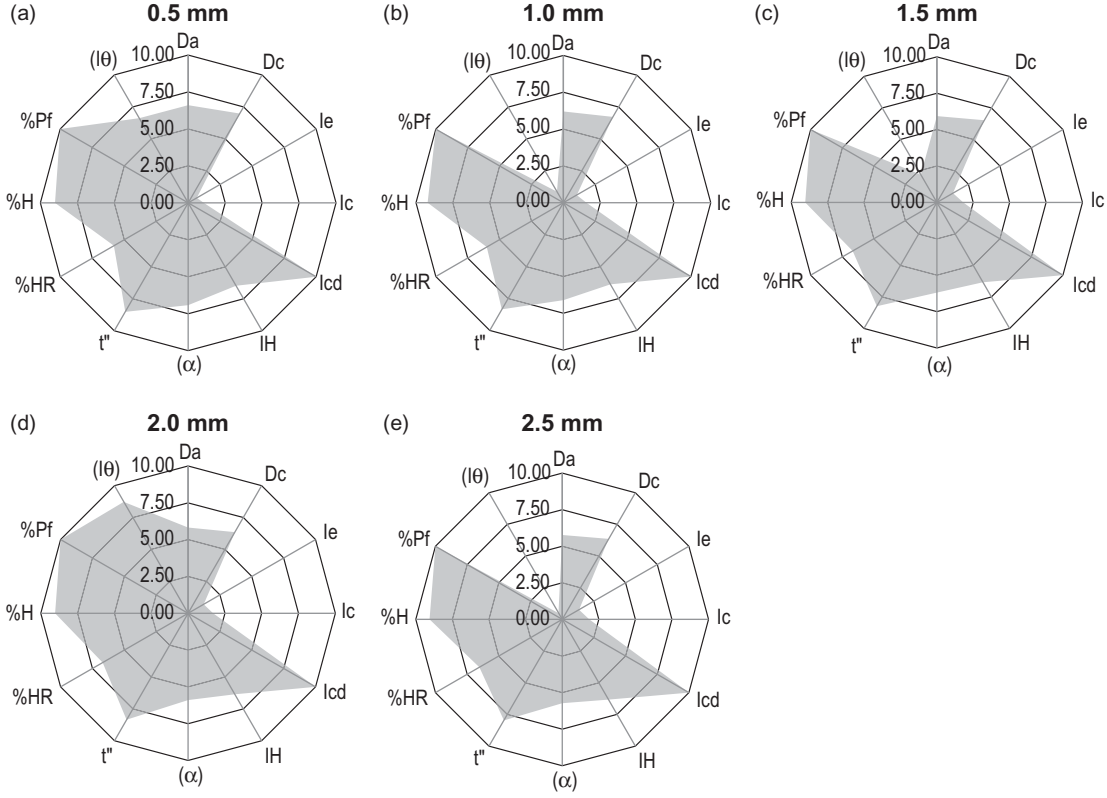

Figure 1. SeDeM diagrams for the MicroceLac® 200 pellets with different sizes.

while those for the selected excipients are shown in Figure 2 and Table 3, respectively.

It is clear from Figure 1 that all the pellet sizes exhibited certain characteristics as reflected by the diagram radius values (which were calculated from the SeDeM parameter test results) that did not meet the minimum criterion (i.e. radius values >5.00). The inter-particle porosity (Ie) and Carr index (IC) radii values of all the pellets were consistently below 3.00, while the homogeneity index (Iθ) radii values varied as a function of pellet size. Although the Iθ results obtained for the 0.5 and 2.0 mm pellets were acceptable with radii values >5.00, the radii values for the 1.0, 1.5, and 2.5 mm pellets were below 2.50. The relatively high cohesion index (Icd) values indicated that the pellets should cohere under compression forces. However, Icd alone does not indicate compressibility because Ie as well as IC contribute to the calculation of the compressibility incidence factor value. As expected, the radii values of all the pellet sizes complied with the minimum criterion for all the powder flow parameters (i.e. Hausner ratio, angle of repose, and powder flow).

The radii values for the percentage of particles measuring <45 μm (%Pf) were all showing the highest possible value for the SeDeM diagram polygon radius (i.e. 10.00) for all the pellet sizes. This was expected as the pellets have been prepared in sizes ranging from 0.5 to 2.5 mm as determined by the aperture sizes of extrusion sieves.

It is clear from Table 2 that the incidence factor values in all the categories were above the minimum acceptable value of 5.00 except for compressibility. The acceptable flow of the pellets as indicated by the flowability/powder flow incidence factor may be attributed to their overall spherical nature as well as their relative large size. In general, the compressibility incidence factor values increased as the pellet size increased, but were all below the minimum acceptable value of 5.00. Compressibility was therefore identified as a potential inadequacy for compression of MUPS tablets composed of MicroceLac® 200 pellets of different sizes. It was therefore important to use the SeDeM EDS to identify the amount of a suitable corrective excipient to overcome this inadequacy in order to produce compressible MUPS tablets of acceptable quality with acceptable physical properties.

The SeDeM diagrams indicate the strengths and weaknesses of the selected excipients in terms of the characteristics as measured by the SeDeM parameters. From Figure 2, it is clear that all the selected excipients exhibited acceptable radii values exceeding 5.00 for cohesion index (Icd), Hausner ratio (IH) and the

Table 2. Incidence factor values for the MicroceLac® 200 pellets prepared with different screen sizes.

	Incidence factor				
Pellet size	Dimension	Compressibility	Flowability/ powder flow	Lubricity/ stability	Lubricity/ dosage
0.5 mm	6.79	3.91	7.31	7.41	8.31
1.0 mm	6.46	4.21	7.11	7.61	5.43
1.5 mm	6.23	4.37	6.92	7.86	6.10
2.0 mm	6.09	4.31	6.87	7.86	9.37
2.5 mm	6.06	4.39	6.67	7.80	5.25

Table 3. Incidence factor values for excipients investigated with the SeDeM EDS.

	Incidence factor				
Pellet size	Dimension	Compressibility	Flowability/ powder flow	Lubricity/ stability	Lubricity/ dosage
Avicel® PH 200	4.07	5.44	5.99	6.28	4.43
Cellactose® 80	4.92	5.59	5.88	5.50	4.89
Kollidon® VA 64	3.87	6.55	4.92	5.48	4.70
MicroceLac® 200	5.34	4.92	5.85	6.88	6.31
Tablettose® 80	6.83	5.65	5.64	2.89	3.55

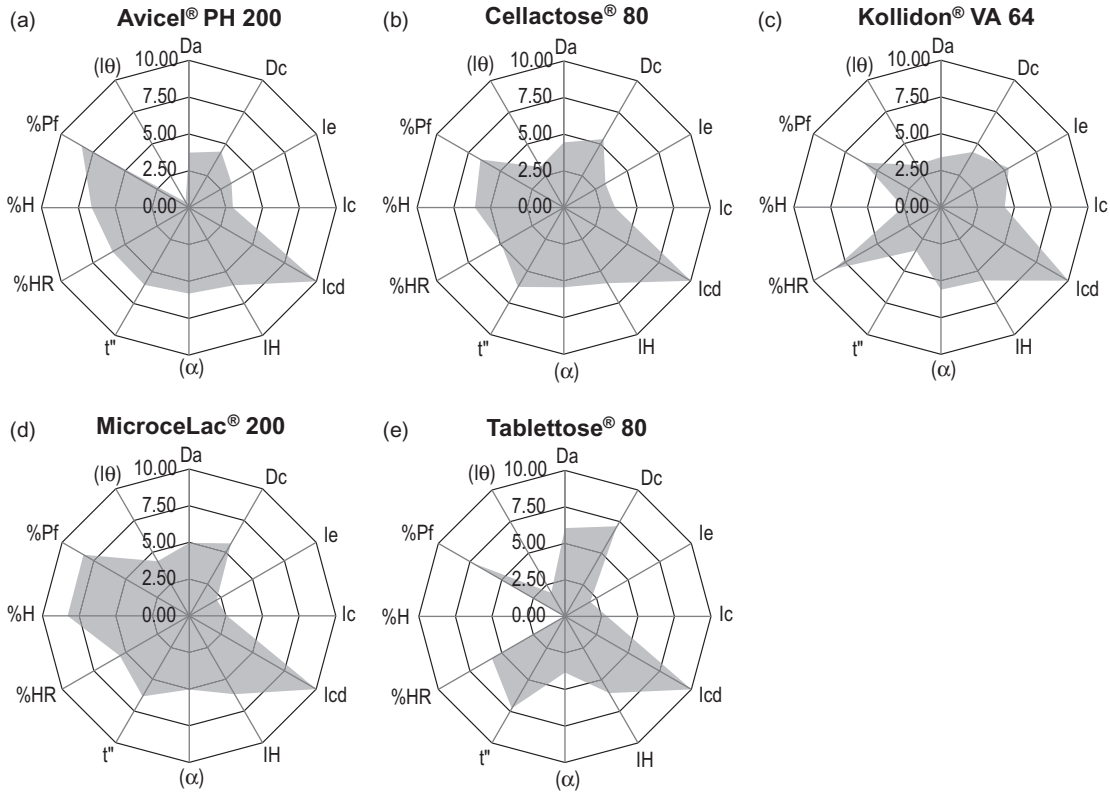

Figure 2. SeDeM diagrams for the selected excipients.

percentage of particles measuring <45 μm (%Pf), however, radii results lower than 5.00 were obtained for Carr index (IC) and homogeneity index (Iθ). Kollidon® VA 64 yielded the highest radii value of all the selected excipients for inter-particle porosity (Ie), Carr index (IC) and loss on drying (%HR), while Tablettose® 80 yielded the highest radii values for bulk density (Da), tapped density (Dc), and flowability (t″).

The incidence factor for compressibility yielded acceptable results with values higher than 5.00 for all the excipients except for MicroceLac® 200, while the incidence factor for flowability/powder flow for all the selected excipients exceeded a value of 5.00, except for Kollidon® VA 64 that exhibited a value of 4.92. Tablettose® 80 was the only excipient that did not meet the minimum acceptable value for lubricity/stability. The incidence factor for lubricity/dosage was generally below 5.00 for all the selected excipients, except for MicroceLac® 200 that yielded a value of 6.31 and the incidence factor values for dimension ranged from 4.07 to 6.83.

Selection of the most suitable excipients for the various pellet sizes

The most appropriate excipient and the smallest possible amount thereof that is required to yield a formulation that should be suitable for compression into MUPS tablets were identified for each pellet size. The amount of each selected excipient required as calculated from the SeDeM EDS results to formulate suitable pellet intermediate blends for compression into MUPS tablets are given in Table 4.

From the CP % w/w values obtained, it was evident that Kollidon® VA 64 is the most suitable excipient for correcting the deficient property (i.e. compressibility) of all of the pellet sizes in the smallest possible amount. The pellets with the smallest size (0.5 mm) required the largest amount of Kollidon® VA 64 (41.29% w/w), while the largest pellet size (2.5 mm) required the smallest amount of Kollidon® VA 64 (28.24% w/w) to produce compressible MUPS formulations. This trend was also apparent for all the other excipients, except for MicroceLac® 200, which required more than the maximum amount that can be incorporated into the MUPS formulation (i.e. >100% w/w). This was expected since compressibility was already identified as a weakness of this excipient when used in the pellets with different sizes.

Table 4. Amount of each selected excipient required (CP % w/w) to correct inadequacies of pellets prepared with different screen sizes.

Pellet size	Avicel® PH 200	Cellactose® 80	Kollidon® VA 64	MicroceLac® 200	Tablettose® 80
0.5 mm	71.24	64.88	41.29	107.92	62.64
1.0 mm	64.23	57.25	33.76	111.27	54.86
1.5 mm	58.88	51.64	28.90	114.55	49.22
2.0 mm	61.06	53.91	30.80	113.12	51.49
2.5 mm	58.10	50.83	28.24	115.09	48.41

SeDeM EDS results of intermediate blends

The most suitable corrective excipient (Kollidon® VA 64) was added according to the quantities recommended by the CP % w/w values to the various pellet sizes to obtain intermediate blends on which the SeDeM EDS tests were then performed. The SeDeM diagrams as well as the incidence factor values obtained for the intermediate blends are shown in Figure 3 and Table 5.

It is evident form Figure 3 that all the intermediate blends still exhibited some radii values that did not meet the minimum criterion for acceptable compression, however, the inter-particle porosity (Ie) and Carr index (IC) radii values of all the intermediate blends showed higher results than those obtained for the pellets prior to addition of any excipient. The bulk density (Da) and tapped density (Dc) values of the various final blends were still

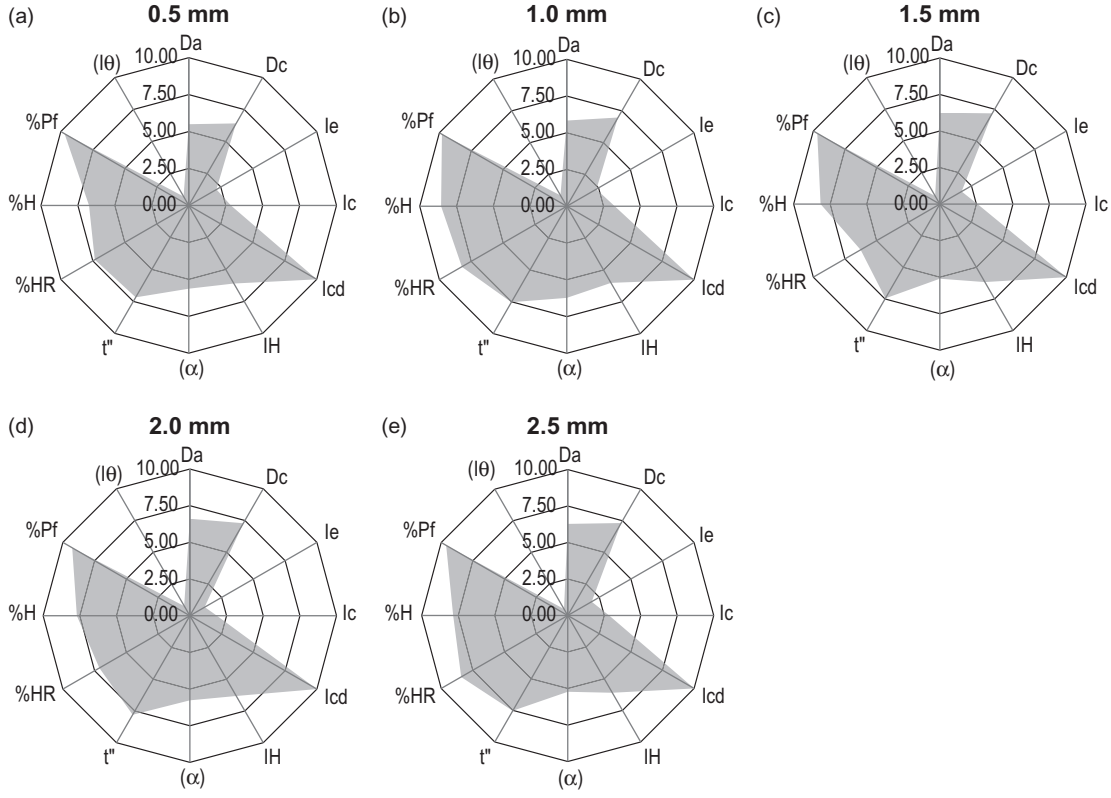

Figure 3. SeDeM diagrams for intermediate blends of the MicroceLac® 200 different size pellets with Kollidon® VA 64.

acceptable with radii values exceeding 5.00. The radii values of the homogeneity index (Iθ) of all the intermediate blends showed less variability, but were all below a value of 1.00 irrelevant to the pellet size. The cohesion index (Icd) results were still acceptable with maximum radii values of 10.00 for all the intermediate blends.

Most of the incidence factor values yielded acceptable results with values higher than 5.00 for all the intermediate blends, with the exception of compressibility. Although the incidence factor value of compressibility was lower than 5.00 for the pellets with sizes 1.5, 2.0, and 2.5 mm, the values improved when compared to the values of the pellets prior to addition of Kollidon® VA 64. Furthermore, the compressibility incidence value of the intermediate blends of the two smallest pellet sizes (i.e. 0.5 and 1.0 mm) complied with the minimum acceptable value.

The incidence factor for lubricity/dosage showed lower results than those obtained for the pellets (prior to addition of any excipient) indicating greater variance in particle size distribution which can be explained by the relatively large variance between the size of the pellets and the size of the added excipient powder particles (Kollidon® VA 64).

Table 5. Incidence factor values for intermediate blends containing Kollidon® VA 64 in combination with MicroceLac® 200 pellets prepared with different screen sizes.

	Incidence factor				
Pellet size	Dimension	Compressibility	Flowability/ powder flow	Lubricity/ stability	Lubricity/ dosage
0.5 mm	5.95	5.01	6.31	7.04	5.20
1.0 mm	6.41	5.20	6.59	8.39	5.33
1.5 mm	6.71	4.77	6.24	7.21	5.16
2.0 mm	6.95	4.34	6.63	7.42	5.01
2.5 mm	6.80	4.91	6.29	8.13	5.09

SeDeM EDS results of the final blend

A final blend for each of the pellet sizes was prepared with the recommended additional excipients (i.e. the standard lubrication mixture) to produce MUPS tablet formulations. The SeDeM parameter tests were then performed on all the final pellet-excipient blends. The SeDeM diagrams as well as the incidence factor values and compressibility indices obtained for the final blends are shown in Figure 4 and Table 6, respectively.

The final blends still exhibited some radii values that did not meet the minimum criterion for acceptable compression [i.e. homogeneity index (Iθ), inter-particle porosity (Ie) and Carr index (IC)]. However, the inter-particle porosity (Ie) and Carr index (IC) radii values of all the final blends generally showed higher values than those obtained for the pellets prior to addition of any excipient as well as the intermediate blends. The bulk density (Da) and tapped density (Dc) values of the various intermediate blends were still acceptable with radii values exceeding 5.00. The radii values for flowability (t″) of all the final blends showed lower results than those obtained for the intermediate blends. The radii values of the homogeneity index (Iθ) of all the final blends were below 1.00 irrelevant of the pellet size, which can be expected due to the relatively large difference in size between the pellets and the excipient powder particles. The cohesion index (Icd) results were acceptable with values exceeding the minimum acceptable value.

All of the incidence factor values of the final blends yielded acceptable results with values higher than the minimum acceptable value (i.e. 5.00) for all the final blends except for lubricity/dosage, which ranged between 3.98 and 4.59. The incidence factor for lubricity/dosage showed even lower values than those obtained for the pellets prior to addition of any excipient as well as the intermediate blends, which can be explained by the relatively large variance between the size of the pellets and the size

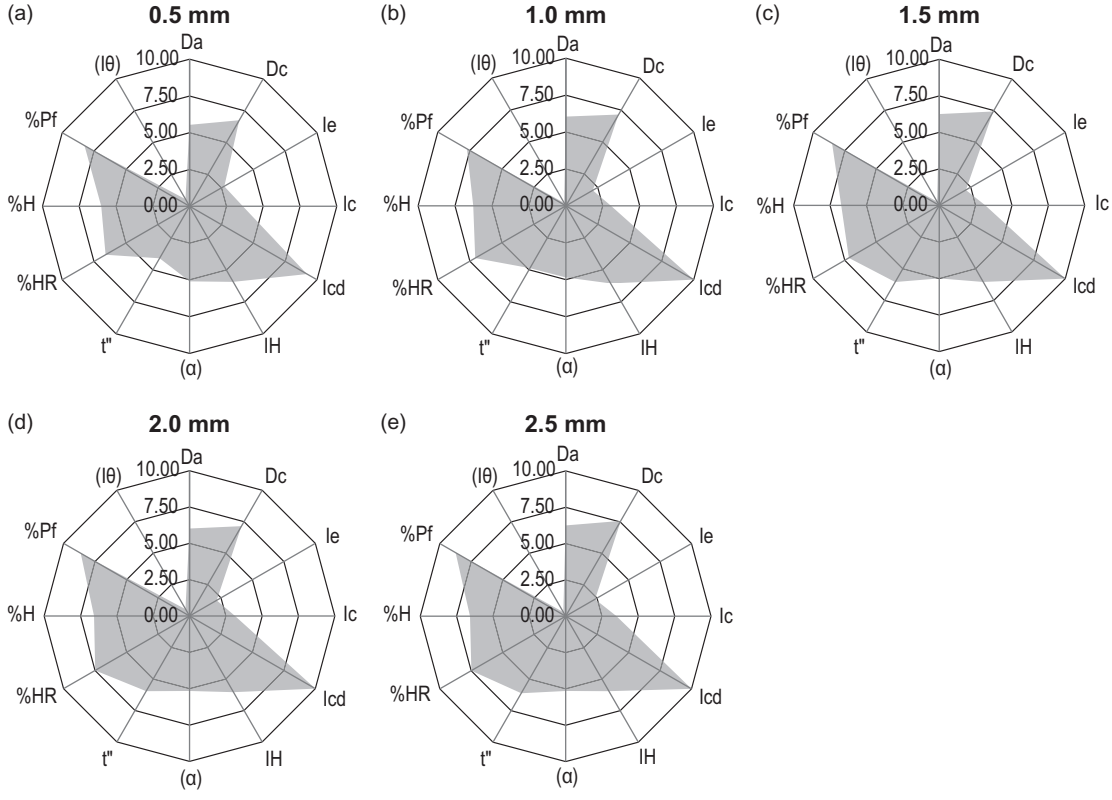

Figure 4. SeDeM diagrams for the MicroceLac® 200 final blends.

Table 6. Incidence factor values and compressibility indices for the final MicroceLac® pellet blends.

	Incidence factor					Compressibility indices		
Pellet size	Dimension	Compressibility	Flowability/powder flow	Lubricity/stability	Lubricity/dosage	IP	IPP	GCI
0.5 mm	6.15	5.18	5.04	6.30	4.41	0.667	5.364	5.107
1.0 mm	6.60	5.06	5.26	6.67	3.98	0.583	5.455	5.194
1.5 mm	6.84	5.09	5.69	5.96	4.40	0.667	5.728	5.453
2.0 mm	6.58	5.10	5.72	7.03	4.59	0.750	5.741	5.465
2.5 mm	6.91	5.28	5.74	7.03	4.53	0.750	5.834	5.554

IP: parameter index; IPP: parametric profile index; GCI: good compression index.

Table 7. Uniformity of mass, hardness, friability, and disintegration time of the different MUPS tablets produced from the final pellet blends.

Pellet size	Uniformity of mass Average (%RSD)	Hardness Average (std dev)	Friability	Disintegration time
0.5 mm	448.50 mg (0.63%)	71.5 N (2.80%)	0.30%	21.00 min
1.0 mm	446.65 mg (1.31%)	85.6 N (10.56%)	0.31%	25.53 min
1.5 mm	446.05 mg (0.92%)	89.4 N (10.56%)	0.45%	24.28 min
2.0 mm	450.65 mg (1.17%)	125.4 N (14.08%)	0.16%	16.63 min
2.5 mm	445.55 mg (1.25%)	72.8 N (13.03%)	0.15%	> 45.00 min

of the added excipients powder particles. The incidence factor values for compressibility for all the pellet sizes complied with the minimum value and were higher for the final blends when compared to the results obtained for the intermediate blends.

The compressibility indices [i.e. parameter index (IP), parametric profile index (IPP) and good compression index (GCI)] yielded values that indicated that all the final blends should be suitable for compression into MUPS tablets since they have met the minimum criteria for acceptable compression, namely, IP $\geq$0.5; IPP $\geq$5 and GCI $\geq$5.

This indicated that the SeDeM EDS was able to predict the correct excipient and amount thereof to overcome the inadequacy of low compressibility of the initial pellets.

Experimental confirmation of the MUPS tablet formulations

The final blends that were based on the predictions and recommendations made by the SeDeM EDS were compressed into MUPS tablets and evaluated with respect to uniformity of mass, tablet hardness, friability, and disintegration, which are shown in Table 7.

The uniformity of mass of all the MUPS tablets complied with the specification as set in the BP (British Pharmacopoeia Commission 2015), which means that none more than two tablets deviated from the average mass by 5% and none deviated more than 10% from the average mass. The hardness of the MUPS tablets were all above 70 N and increased with an increase in pellet size up to 2.0 mm, after which the hardness value decreased. The hardness of the MUPS tablets produced from the 2.5 mm pellets was similar to those produced from the 0.5 mm pellets. The friability results of all the MUPS tablets were less than 1.0%, which complied with the USP (United States Pharmacopeia 2015) specifications for uncoated tablets. The disintegration times of all the MUPS formulations were consistently more than 15 min.

Conclusions

The SeDeM EDS was successfully applied to pellets of different sizes ranging from 0.5 mm to 2.5 mm to identify potential inadequacies for compression into MUPS tablets. The incidence factor that was identified as a potential shortcoming for compression into MUPS tablets of all the pellet sizes was compressibility. The SeDeM EDS was furthermore successfully applied to identify the smallest amount of corrective excipient that was required to produce compressible MUPS tablets from pellets of all the sizes investigated in this study. Kollidon® VA 64 was identified as the corrective excipient that can be added to MicroceLac® 200 pellets of all sizes in the smallest amount to produce acceptable MUPS tablets. The homogeneity index values indicated that proper blending of the excipient powder with the pellets may be challenging due to the relatively large difference in particle sizes. The compressibility indices [i.e. parameter index (IP), parametric profile index (IPP) and good compression index (GCI)] of all the final blends predicted that acceptable MUPS tablets could be produced from the pellets of all the sizes investigated in this study after addition of the corrective excipient and other excipients of the standard lubrication mixture. Acceptable MUPS tablets were produced from the final predicted blends of all the pellet sizes as indicated by the physical properties of the MUPS tablets that complied with minimum specifications for uncoated tablets.

Disclosure statement

Any opinion, findings and conclusions or recommendations expressed in this material are those of the authors and therefore the NRF do not accept any liability with regard thereto.

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Chapter 5: Research Article: "*Development of multiple-unit pellet system tablets by employing the SeDeM expert diagram system II: pellets containing different active pharmaceutical ingredients*"

Chapter 5 is presented in the form of a full length research article entitled "*Development of multiple-unit pellet system tablets by employing the SeDeM expert diagram system II: pellets containing different active pharmaceutical ingredients"* which was published (early on-line) in 2018 in the journal entitled *"Pharmaceutical Development and Technology"* (DOI: 10.1080/10837450.2018.1435691). The complete guide for authors for this journal is given in Appendix F.

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RESEARCH ARTICLE

Development of multiple-unit pellet system tablets by employing the SeDeM expert diagram system II: pellets containing different active pharmaceutical ingredients

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ABSTRACT

The SeDeM Expert Diagram System (SeDeM EDS) was originally developed to provide information about the suitability of powders to produce direct compressible tablets. Multiple-unit pellet systems (MUPS) are dosage forms consisting of pellets compressed into tablets or loaded into hard gelatin capsules. The aim of this study was to apply the SeDeM EDS to different size pellets (i.e. 0.5, 1.0, 1.5, 2.0, and 2.5 mm) containing different APIs (i.e. doxylamine, ibuprofen or paracetamol) to determine which properties should be corrected to yield MUPS tablet formulations. The SeDeM parameter tests were conducted on the pellets, selected excipients, intermediate blends, and final blends. The study showed that the properties of the pellets depended on the active ingredient and pellet size. The SeDeM compressibility indices indicated that the final pellet blends should be suitable for compression into MUPS tablets. MUPS tablets were prepared from the final blends and evaluated in terms of physico-chemical properties and dissolution profiles. Only three of the MUPS tablet formulations containing ibuprofen and one MUPS tablet formulation containing paracetamol failed content uniformity. The water solubility of the APIs as well as the pellet size (surface area exposed to the dissolution medium) attributed to the difference in drug dissolution rate.

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Extrusion–spheronization; multiple-unit pellet system (MUPS); SeDeM expert diagram system (EDS); content uniformity; hardness; dissolution

Introduction

The SeDeM Expert Diagram System (SeDeM EDS) is based on the quality by design concept and is used in formulation studies to determine the suitability of active ingredients and excipients for direct compression into tablets. The SeDeM EDS provides a profile of the formulation components and predicts whether they can be directly compressed or whether certain properties need to be corrected by adding additional excipients before compression (Suñé-Negre et al. 2008; Aguilar-Diaz et al. 2009; Suñé-Negre et al. 2011a, 2011b).

In multiple-unit drug delivery systems, the active pharmaceutical ingredient (API) is contained as portions in sub-units that are combined into a dosage form. A multiple-unit drug delivery system is for example obtained when solid spherical particles or pellets are compacted into tablets, which are dosage forms referred to as multiple-unit pellet systems (MUPS) and have many advantages over single-unit drug delivery systems. The pellets that are released from MUPS tablets shortly after administration can leave the stomach relatively quickly and will then distribute readily over a large surface area of the gastro-intestinal tract. This could potentially result in a lower local drug concentration, which subsequently reduce irritation and risk of toxicity. Inter- and intra-individual variations in drug bioavailability can also be reduced (Vervaet et al. 1995; Abdul et al. 2010; Reddy et al. 2011; Pai et al. 2012).

The SeDeM EDS was originally developed for the formulation of tablets by means of direct compression of powder mixtures. The SeDeM EDS comprises of the experimental determination of the SeDeM parameters (e.g. bulk density, tapped density, angle of repose, powder flow etc.), mathematical processing of the parameter results and graphical expression thereof in order to identify potential inadequacies of the powder blend for direct compression into tablets (Pérez et al. 2006; Suñé-Negre et al. 2008, 2011a, 2011b, 2013; Aguilar-Diaz et al. 2014; Suñé-Negre et al. 2013, 2014).

The work presented in this study is an extension of previous work (Hamman et al. 2017) indicating the value of the SeDeM EDS as a formulation tool in the formulation of multiple-unit pellet system (MUPS) tablets from different pellet sizes. The initial MUPS tablets evaluated in the previous work, however, were prepared without an active pharmaceutical ingredient (API). The aim of the current study is to apply the SeDeM EDS to the formulation of multiple-unit pellet system (MUPS) tablets containing different pellet sizes and active pharmaceutical ingredients (APIs) to evaluate the applicability of the SeDeM EDS in the formulation of MUPS tablets containing different APIs. The APIs were selected based on their physico-chemical properties such as solubility and compressibility and included doxylamine, ibuprofen, and paracetamol.

Materials and methods

Materials

Doxylamine (Uquifa Quimico Farmaceutica S.A., Barcelona, Spain), ibuprofen (Shasun Chemicals and Drugs Ltd, Periyakalapet, Pondicherry) and paracetamol (SRI Krishna Pharmaceuticals Ltd, Hyderabad, India) were used as APIs in the MUPS tablets. MicroceLac® 200, Cellactose® 80, Tablettose® 80, and talc were donated by Meggle (Molkerei Meggle, Wasserburg GmbH & Co,

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Germany) and were used as pharmaceutical excipients in the pellets and/or MUPS tablets. The other excipients employed in the formulation of the MUPS tablets included colloidal silicon dioxide (Aerosil® 200) (Degussa, Parsippany, NJ), copovidone (Kollidon® VA 64) BASF, Ludwigshafen, Germany), croscarmellose sodium (Ac-di-Sol®) FMC Corporation Little Island, Cork, Ireland), magnesium stearate (Kirsch Pharma, Johannesburg, South Africa), and microcrystalline cellulose (Avicel® PH 200) (FMC Corp, Brussels, Belgium). Ethanol (Associated Chemical Enterprises (ACE), Johannesburg, South Africa) and purified water were used during the wetting of powders prior to extrusion during pellet preparation.

Methods

Production of pellets

Three pellet formulations each containing one of the selected APIs was formulated at five different sizes as shown in Table 1, which shows the formulation composition and formulation numbers. All the pellets were prepared by means of extrusion–spheronization. Each API was pre-mixed by means of a Turbula T2B mixer (Willy A Bachofen Maschinenfabrik, Basel, Schweiz) for 5 min with co-processed lactose-microcrystalline cellulose (MicroceLac® 200) in a ratio of 1:3. A batch size of 150 g was used in this study. The powder mixture was then wetted with a mixture of ethanol and water (60:40), while the powder bed was mixed in the bowl of a Kenwood planetary mixer (Kenwood Chef Mixer, Kenwood Ltd, Havant Hants, Britain). The wetted powder mass was extruded with a Caleva extruder (Caleva Process Solutions Ltd, England) at a speed of 30 rpm to render cylindrical extrudates. Pellets with different sizes were produced for each API using five screen sizes in the extruder, namely, 0.5, 1.0, 1.5, 2.0, and 2.5 mm, respectively. Each extrudate was spheronized for 5 min at a speed of 2000–2550 rpm in a Caleva spheronizator (Caleva Process Solutions Ltd, England) using a spheronizer friction plate with a cross-hatch pattern. The pellets were then freeze dried using a Virtis Advantage bench-top freeze dryer (SP Industries Ins., Warminster, PA). For freeze-drying the pellets were frozen at −80 °C for 5 h, after which a vacuum of 45 mTorr was applied for 48 h in order to sublime off the wetting agent.

Characterization of the pellets and excipients

All the pellet formulations (Table 1) and selected excipients (listed below) were characterized in terms of the parameter tests required by the SeDeM EDS in triplicate. The mean value of each parameter test was obtained and used in the radius calculations as described below. A SeDeM diagram was drawn for each selected excipient and pellet formulation.

Table 1. Composition and sizes of the pellet formulations and their allocated formulation numbers (F1–F15).

API	Excipient	Wetting agent [water:ethanol (v/v)]	Extruder screen size (mm)	Formulation number
Doxylamine	MicroceLac® 200	60:40	0.5	F1
			1.0	F2
			1.5	F3
			2.0	F4
			2.5	F5
Ibuprofen	MicroceLac® 200	60:40	0.5	F6
			1.0	F7
			1.5	F8
			2.0	F9
			2.5	F10
Paracetamol	MicroceLac® 200	60:40	0.5	F11
			1.0	F12
			1.5	F13
			2.0	F14
			2.5	F15

Briefly, the methods which were used to determine each SeDeM parameter test are as follows (Pérez et al. 2006; Suñé-Negre et al. 2008, 2011a, 2011b).

- Bulk density (Da): Determined for each of the pellet formulations and selected excipient powders according to the United States Pharmacopeia (USP) method described in Section 616 (United States Pharmacopeia 2015).
- Tapped density (Dc): Determined for each of the pellet formulations and excipient powders according to the USP method described in Section 616 (United States Pharmacopeia 2015). The volume was the value obtained after 2500 taps using a settling apparatus with a graduated cylinder (i.e. voluminometer).
- Inter-particle porosity (Ie): Calculated from Da and Dc by using the following equation: $Ie = (Dc - Da)/(Dc \times Da)$.
- Carr index (IC): Calculated from Da and Dc by using the following equation: $IC = (Dc - Da/Dc) \times 100$.
- Cohesion index (Icd): Determined by directly compressing the respective selected excipient powders and pellet formulations each at maximum compression force. An eccentric press was used as recommended. The hardness (N) of the tablets obtained from this compression step was determined with a hardness tester (Erweka TBH 425 TD, Germany). Initially, the excipient powders and pellets were each tested on their own, but if found to be abrasive, 3.5% w/w of the following standard lubricant mixture was added as previously recommended (Pérez et al 2006): talc (2.36%), colloidal silicon dioxide (0.14%), and magnesium stearate (1.00%).
- Hausner ratio (IH): Calculated from Da and Dc by using the following equation: $IH = Dc/Da$.
- Angle of repose (α): Determined according to the USP method described in Section 1174 (United States Pharmacopeia 2015).
- Flowability (t"): Determined according to the USP method described in Section 1174 (United States Pharmacopeia 2015) using an electronic balance and recording device. It is expressed in seconds and tenths of a second per 100 g of sample.
- Loss on drying (%HR): Determined by the USP method described in Section 731 (United States Pharmacopeia 2015). Briefly, a sample from each excipient powders or pellet formulations was dried in an oven at 105 °C ± 2 °C, until a constant weight was obtained.
- Hygroscopicity (%H): Determined by measuring the percentage increase in sample weight after being kept in a humidifier at relative humidity of 76% (±2%) and a temperature of 22 °C ± 2 °C for 24 h. A Binder climatic chamber (Binder, KBF 240, Germany) was used.
- Percentage of particles measuring <45 μm (originally a 50 μm sieve was used) (%Pf): Particle size was determined by means of the USP sieve test as described in Section 786 (United States Pharmacopeia 2015). The % of particles that passed through a 45 μm sieve was determined when the sieve was loaded with 100 g powder/pellet and vibrated for 10 min at a speed setting of 10 on the vibrating apparatus or sieve shaker (Fritsch Analysette, Germany).
- Homogeneity index (IΘ): Determined in accordance with the general USP method described in Section 786 (United States Pharmacopeia 2015) for determining particle size

range by means of the sieve test. The size of a 100 g sample of each respective excipient powder and pellet formulation was determined by submitting a sieve stack to vibration for 10 min at a speed setting of 10 on the vibrating apparatus or sieve shaker (Fritsch Analysette, Germany). Sieve sizes that were used included 2800, 2360, 2000, 1700, 1200, 1000, 850, 710, 500, 355, 212, 106, and 45 μm. The percentage of powder/pellet retained on each sieve and the quantity that passed through the 45 μm sieve was measured. The following equation was applied to the data obtained in order to calculate the homogeneity index (Pérez et al. 2006):

$$I\theta = \frac{F_m}{100+(d_m - d_{m-1})F_{m-1}+(d_{m+1} - d_m)F_{m+1}+(d_m - d_{m-2})F_{m-2}+\ldots +(d_m - d_{m-n})F_{m-n}+(d_{m+n} - d_m)F_{m+n}} \quad (1)$$

where: $I\Theta$ = Relative homogeneity index, which is the particle-size homogeneity in the range of the fractions and sieve sizes used in the study. F_m = Percentage of particles in the majority range. F_{m-1} = Percentage of particles in the range immediately below the majority range. F_{m+1} = Percentage of particles in the range immediately above the majority range. n = Order number of the fraction under study, within a series, with respect to the majority fraction. d_m = Mean diameter of the particles in the majority fraction. d_{m-1} = Mean diameter of the particles in the fraction of the range immediately below the majority range. d_{m+1} = Mean diameter of the particles in the fraction of the range immediately above the majority range.

Based on the physical characterization of the pellets and selected excipients, the SeDeM parameters were grouped into five incidence factors. The incidence factor values and conversion of SeDeM parameters into radii values were calculated as previously described (Pérez et al. 2006; Suñé-Negre et al. 2008, 2011a, 2011b; Hamman et al. 2017).

Excipients that were selected to be investigated for addition to the pellets before compression into MUPS tablets included Avicel® PH 200, Cellactose® 80, Kollidon® VA 64, MicroceLac® 200, and Tablettose® 80. The most appropriate excipient, when used in the smallest possible amount, to yield a formulation that should be suitable for compression into MUPS tablets was identified for each pellet formulation by means of the SeDeM EDS as previously described (Suñé-Negre et al. 2008).

Radius calculations for construction of the SeDeM diagram

The radii values were calculated from the measured SeDeM parameters by applying a specific factor to each of the parameter values. These parameter values were then used to draw SeDeM diagrams which indicated the characteristics of the powders or pellet formulations in terms of their suitability for compression (Pérez et al. 2006; Suñé-Negre et al. 2008, 2011a, 2011b).

Compressibility indices to predict material compressibility

The parameter index (IP), parameter profile index (IPP), and good compression index (GCI) were calculated to determine whether a material can be considered suitable for compression (Suñé-Negre et al. 2008, 2011a, 2011b).

The following indices were calculated to determine whether a material can be considered suitable for compression.

$$\text{Parameter index (IP)} = \frac{\text{Number of parameters having } r \geq 5}{\text{Total number of parameters}} \quad (2)$$

The index is acceptable when IP $\geq$0.5.

$$\text{Parameter profile index (IPP)} = \text{Mean value of all the parameters} \quad (3)$$

The index is acceptable when IPP $\geq$5

$$\text{Good compression index (GCI)} = \text{IPPf} \times f \quad (4)$$

Where:

$$f = \text{Reliability factor and } f = \frac{\text{Polygon area}}{\text{Circle area}}$$

The index is acceptable when GCI $\geq$5.

Application of the SeDeM expert diagram system to determine the amount of excipient required

From the list of selected excipients, the most appropriate excipient that is required to yield a pellet formulation that should be suitable for compression when used in the smallest possible amount was also calculated by using the following equation (Suñé-Negre et al. 2008):

$$CP = 100 - \left(\frac{RE - R}{RE - RP} \times 100\right) \quad (5)$$

where: CP = % w/w of corrective excipient required to render a tablet formulation; RE = mean incidence value of the corrective excipient; R = mean incidence value to be obtained in the blend (R = 5 as 5 is the minimum value that is regarded as necessary in order to achieve good compression); and RP = mean incidence value of the API to be corrected.

Preparation of final MUPS tablet formulations

A mixture of each pellet formulation and the minimum amount of the excipient that was identified to correct for any inadequacies was prepared. Each pellet formulation and excipient was mixed with a Turbula T2B mixer (Willy A Bachofen Maschinenfabrik, Basel, Schweiz) for 5 min to yield an intermediate blend formulation. These intermediate blend formulations were characterized in terms of the parameter tests required by the SeDeM EDS and a SeDeM diagram for each mixture was constructed. Subsequently, a final blend formulation for each of the pellet formulations was prepared by adding the standard lubricant mixture consisting of talc (2.36%), colloidal silicon dioxide (Aerosil® 200) (0.14%), and magnesium stearate (1.00%) in addition to the selected corrective excipient (Pérez et al. 2006). Croscarmellose sodium (Ac-di-Sol®) (5.00%) was also added as an additional disintegration aid. Each of the final mixtures were mixed for 5 min on a Turbula T2B mixer (Willy A Bachofen Maschinenfabrik, Basel, Schweiz).

These final mixtures of the MUPS tablet formulations were also characterized in terms of the parameter tests required by the SeDeM EDS and the SeDeM diagrams were constructed. Finally, the compressibility indices were calculated for each of the final MUPS tablet mixtures to predict if these formulations could provide MUPS tablets.

MUPS tablet preparation

The final blend formulations were compressed on a Korch XP 1 (Korsch AG, Berlin) single punch tablet press, using a 10 mm diameter round, flat faced, and beveled edge punch. All the MUPS tablets were compressed at a similar compression force and fill volume to produce tablets of similar mass.

Characterization of the MUPS tablets

All the MUPS tablets were characterized in terms of uniformity of mass (20 MUPS tablets), hardness (10 MUPS tablets), friability

(MUPS tablets corresponding as near as possible to 6.5 g), disintegration (6 MUPS tablets), content uniformity (10 MUPS tablets), and dissolution profiles (3 MUPS tablets) using the methods as indicated in the pharmacopoeias (British Pharmacopoeia Commission 2015; United States Pharmacopeia 2015).

The content uniformity was performed by crushing 10 individual MUPS tablets from each formulation and dissolving it in selected volumes and solvents according to the monographs of the USP for each selected API. Samples were analyzed by means of high-performance liquid chromatography (HPLC) using a Hitachi Chromaster chromatographic system. The system consisted of a 5410 UV detector, an auto-sampler (5260) with a sample temperature controller and a solvent delivery module (5160). The content uniformity was performed according to the USP methods of which the linearity and precision were confirmed.

The MUPS tablet dissolution was performed using a Distek Model 2500 dissolution bath (Distek, New Jersey) equipped with a USP type II apparatus, a Distek Evolution 4300 Dissolution Sampler (Distek, New Jersey), and Distek Syringe Pump (Distek, New Jersey). A volume of 900 ml was used per dissolution vessel, the paddle speed was set at 50 rpm, and the sample volume was 7 ml. A specific dissolution medium was used for each of the active pharmaceutical ingredients namely 0.01 N hydrochloric acid for doxylamine, phosphate buffer (pH 7.2) for ibuprofen, and phosphate buffer (pH 5.8) for paracetamol. Samples were withdrawn at pre-determined time intervals of 5, 15, 30, 45, 60, 90, 120, and 150 min, which were analyzed by UV spectrophotometry (Shimadzu Corporation, Kyoto, Japan). The UV spectrophotometric analytical methods for all three the selected active pharmaceutical ingredients were validated in terms of linearity, recovery, precision (repeatability), and stability.

Mean dissolution time (MDT) is a statistical moment for the cumulative dissolution process and provides an accurate drug release rate using the following equation (Reppas and Nicolaides 2000):

$$MDT = \sum_{i=1}^{n} t_i \times M_t / M_\infty \quad (6)$$

where: M_t = the amount of the drug released at time t; t_i = the time (minutes) at the midpoint between i and $i-1$; M_∞ = the overall amount of the drug released.

Results and discussion

SeDeM EDS results of the pellets and excipients

The SeDeM diagrams as well as the incidence factor values for the pellet formulations with different API compositions are shown in Figure 1 and Table 2, respectively. The incidence factor values and SeDeM diagrams of the selected excipients were previously determined as described and reported (Hamman et al. 2017).

It is clear from Figure 1 that all the pellet formulations exhibited some radii values (i.e. SeDeM parameters) that did not meet the minimum criterion for acceptable compression, namely >5.00, while some radii values exhibited maximum radii values of 10.00. For example, the SeDeM diagrams indicated that the bulk density (Da) and tapped density (Dc) values of all the pellet formulations were acceptable with radii values exceeding 5.00. The inter-particle porosity (Ie) and Carr index (IC) radii values of all the pellet formulations were consistently below 3.00 for all three APIs, which indicated potential challenges with compressibility will be experienced irrespective of pellet composition or size. The homogeneity index (IΘ) radii values varied as a function of pellet size and were inversely correlated to pellet size for the pellets containing doxylamine, while no specific trend could be observed for the ibuprofen and paracetamol pellet formulations with respect to size. The cohesion index (Icd) radii values exhibited the maximum value of 10.00 for all the pellet formulations irrespective of API included, which indicated good inter-particle bonding during compression. However, this parameter does not consider other potential inadequacies that may occur during compression.

The pellets containing all three APIs exhibited incidence factor values for compressibility that were all below 5.00, indicating that challenges may be experienced with the pellet formulations during compression into MUPS tablets. The lowest compressibility incidence factor values were obtained for the pellets containing ibuprofen, which indicated that these pellets would need the highest amount of corrective excipient in order to get compressible MUPS tablet formulations. The incidence factor for flowability/powder flow yielded values higher than 5.00 for all the pellet formulations, which was expected due to the spherical nature as well as the relative large size of the pellet formulations when compared to that of powder particles. The incidence factor for lubricity/stability as well as lubricity/dosage also showed acceptable results with values higher than 5.00 for all the pellet formulations. The dimension incidence factor varied in accordance with the homogeneity index (IΘ) values in the SeDeM diagrams, which showed relatively great variance between the pellets with different sizes. The 2.5 mm pellet formulations had the lowest IΘ values indicating greater variance in particle size distribution irrespective of the API incorporated.

Selection of the most suitable corrective excipient for the various pellet formulations

The most appropriate excipient and the smallest possible amount thereof that was required to yield a formulation that should be suitable for compression into MUPS tablets was identified for each pellet formulation. According to the SeDeM EDS results (data not shown), the amount of each selected excipient required to formulate suitable blends for compression into MUPS tablets are given in Table 3.

From the results obtained it was evident that Kollidon® VA 64 was the most suitable excipient that could be added in the smallest possible amount for correcting the deficient incidence (compressibility) for all the pellet formulations (F1 – F15). It was also apparent that MicroceLac® 200 is not suitable as a corrective excipient for any of the pellet formulations, since more than 100% w/w is required to provide a compressible MUPS tablet formulation. Interestingly, for both the smallest size pellets containing doxylamine and paracetamol (F1 and F11), the smallest amount of corrective excipient was required while relatively high amounts were required for the pellets containing ibuprofen for all the pellet sizes (F6–F10). The highest amount of corrective excipient was required for the 2.5 mm pellets containing doxylamine (F5) to provide a compressible MUPS tablet formulation. Cellactose® 80 exhibited the potential to correct the inadequacies of the smallest pellets (F1 and F11) containing doxylamine and paracetamol in relatively small amounts. This indicated that the SeDeM EDS was able to identify not only pellet size, but also API composition as factors that play a role in the amount and type of excipient required to correct the inadequacies of the pellets to render them compressible into MUPS tablets.

SeDeM EDS results of the intermediate blend formulations

The percentage corrective excipient (Kollidon® VA 64) was added to the various pellet formulations to obtain intermediate blend

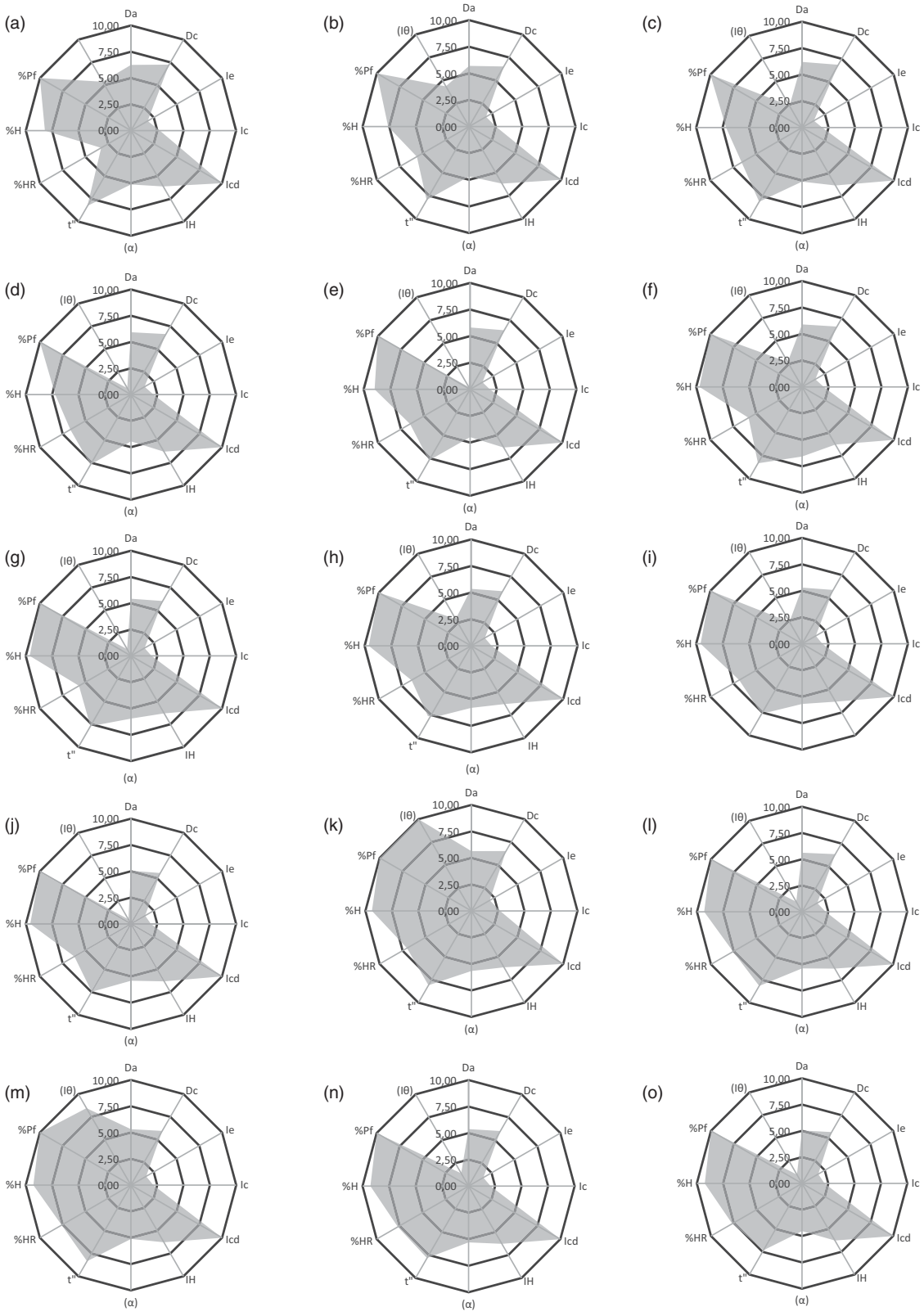

Figure 1. SeDeM diagrams for the pellets containing doxylamine (a–e), ibuprofen (f–j), and paracetamol (k–o).

formulations on which the SeDeM EDS tests could be performed. The SeDeM diagrams are shown in Figure 2. The incidence factor values for the intermediate blend formulations with different sizes and compositions were also calculated but are not shown here.

The intermediate blend formulations still exhibited some radii values that did not meet the minimum criterion for acceptable MUPS tablet compression [i.e. inter-particle porosity (Ie) and Carr index (IC)], while other radii values met the acceptance criteria exceeding 5.00 for bulk density (Da), tapped density (Dc), flowability (t''), and Hausner ratio (IH). The cohesion index (Icd) values were acceptable with values of 10.00 for all the intermediate blend formulations.

Table 2. Incidence factor values for the pellet formulations containing different active pharmaceutical ingredients.

Formulation number	Dimension	Compressibility	Flowability/ powder flow	Lubricity/ stability	Lubricity/ dosage
		Incidence factor – doxylamine pellets			
F1	6.75	4.86	6.51	5.73	7.69
F2	6.11	4.78	6.28	6.63	7.19
F3	6.52	4.39	6.51	6.89	6.19
F4	6.28	4.54	6.14	6.93	5.36
F5	6.11	4.40	6.18	7.75	5.13
		Incidence factor – ibuprofen pellets			
F6	6.24	4.50	7.07	7.76	6.36
F7	5.73	4.49	6.66	7.66	5.37
F8	5.64	4.48	6.68	8.03	6.45
F9	5.58	4.47	6.55	8.23	6.19
F10	5.31	4.48	6.40	7.90	5.25
		Incidence factor – paracetamol pellets			
F11	6.08	4.90	6.64	8.20	>10.00
F12	5.97	4.64	6.59	8.44	5.55
F13	5.64	4.60	6.58	8.44	9.23
F14	5.69	4.56	6.47	8.47	5.69
F15	5.34	4.64	6.04	8.45	5.49

Table 3. Amount of each selected excipient required (CP % w/w) to formulate suitable blends with the pellet formulations for compression.

Formulation number	Avicel® PH 200	Cellactose® 80	Kollidon® VA 64	MicroceLac® 200	Tablettose® 80
			Doxylamine pellet formulations		
F1	24.14	19.18	8.28	233.33	17.72
F2	33.33	27.16	12.43	157.14	25.29
F3	58.10	50.83	28.24	115.09	48.41
F4	51.11	43.81	22.89	121.05	41.44
F5	57.69	50.42	27.91	115.39	48.00
			Ibuprofen pellet formulations		
F6	53.19	45.87	24.39	119.05	43.48
F7	53.68	46.36	24.76	118.61	43.97
F8	54.17	46.85	25.12	118.18	44.44
F9	54.64	47.32	25.48	117.78	44.92
F10	54.15	46.85	25.12	118.18	44.44
			Paracetamol pellet formulations		
F11	18.52	14.49	6.06	500.00	13.33
F12	45.00	37.90	18.85	128.57	35.64
F13	47.62	40.40	20.51	125.00	38.95
F14	50.00	42.72	22.11	122.22	40.37
F15	45.00	37.90	18.85	128.57	35.64

The incidence factor for dimension yielded acceptable results with values of more than 5.00 for all the intermediate blend formulations. The incidence factor for compressibility generally improved for all the pellet blends after addition of the Kollidon® VA 64, although some intermediate blend formulations still exhibited incidence factor values for compressibility below 5.00. The incidence factor for flowability/powder flow showed acceptable results after the addition of Kollidon® VA 64 with values of higher than 5.00 for all the intermediate blend formulations.

The incidence factor for lubricity/stability still yielded acceptable results with values of higher than 5.00 for all the intermediate blend formulations. The incidence factor for lubricity/dosage generally showed values lower than 5.00 for pellets with larger sizes.

SeDeM EDS results of the final blend formulations

Final blend formulations were prepared where the corrective excipient (i.e. Kollidon® VA 64), and standard lubricant mixture [i.e. talc (2.36%), colloidal silicon dioxide (0.14%), and magnesium stearate (1.00%)] were added to the various pellet formulations. Croscarmellose sodium (Ac-di-Sol®) (5.00%) was also added as an additional disintegration. The SeDeM EDS tests were then performed on all the final blend formulations. The SeDeM diagrams as well as the incidence factor values for the final blend formulations with different API compositions are shown in Figure 3 and Table 4, respectively.

The final blend formulations still exhibited some radii values that did not meet the minimum criterion for acceptable compression, namely, homogeneity index (IΘ), inter-particle porosity (Ie), and Carr index (IC), however the inter-particle porosity (Ie) and Carr index (IC) radii values of all the final blend formulations generally showed higher results than those obtained for the pellet formulations prior to addition of any excipient. The radii values for flowability (t″) of all the final blend formulations showed lower results than those obtained for the intermediate blend formulations.

The incidence factor for dimension yielded acceptable results with values of more than 5.00 for all the final blend formulations. The incidence factor for compressibility yielded acceptable results with values of higher than 5.00 for most of the final blend formulations, except for the two smallest pellet formulations containing doxylamine (F1 and F2), the smallest pellet formulation containing ibuprofen (F6), and three of the pellet formulation containing paracetamol (F11, F14, and F15). The incidence factor for flowability/powder flow and for lubricity/stability showed acceptable results with values of higher than 5.00 for all the final blend formulations, while the incidence factor for lubricity/dosage did not yield acceptable results with values even lower than those obtained for the intermediate blend formulations. The ibuprofen final blend formulation F10 had the lowest incidence factor for lubricity/dose (3.90) and the paracetamol final blend formulation F11 had the highest value (6.25).

The compressibility indices [i.e. parameter index (IP), parametric profile index (IPP), and good compression index (GCI)] for all the final blend formulations yielded values that indicated that these formulations should be suitable for compression into MUPS tablets. The compressibility indices values obtained met the minimum criterion for acceptable compression, namely, IP $\geq$0.5; IPP $\geq$5, and GCI $\geq$5.

Evaluation of the MUPS tablet formulations

The final blend formulations were compressed into MUPS tablets and they were evaluated with respect to physical properties including uniformity of mass, tablet hardness (or breaking strength), friability, disintegration, content uniformity, and dissolution which are shown in Table 5. Area under the curve (AUC) and mean dissolution time (MDT) as parameters to describe dissolution behavior are also reported in Table 5. The dissolution profiles of the MUPS tablets containing different APIs are shown in Figures 4–6, respectively.

The validation results for the HPLC method (used in the content uniformity analysis of the MUPS tablets) yielded regression (R^2) values of 0.9997 for doxylamine, 0.9974 for ibuprofen, and 0.9926 for paracetamol indicating an acceptable degree of linearity. The % relative standard deviation (RSD) obtained for the retention time of the standard solutions of all three the APIs were 0.128, 0.093, and 0.032% respectively for doxylamine, ibuprofen, and paracetamol, indicating acceptable repeatability while the intermediate precision yielded % RSD of 0.532, 0.422, and 0.739%, respectively, indicating acceptable precision.

The validation results for the UV spectrophotometric method (used to analyze the dissolution samples) yielded regression (R^2) values of 0.9996 for doxylamine, 0.9988 for ibuprofen, and 0.9988

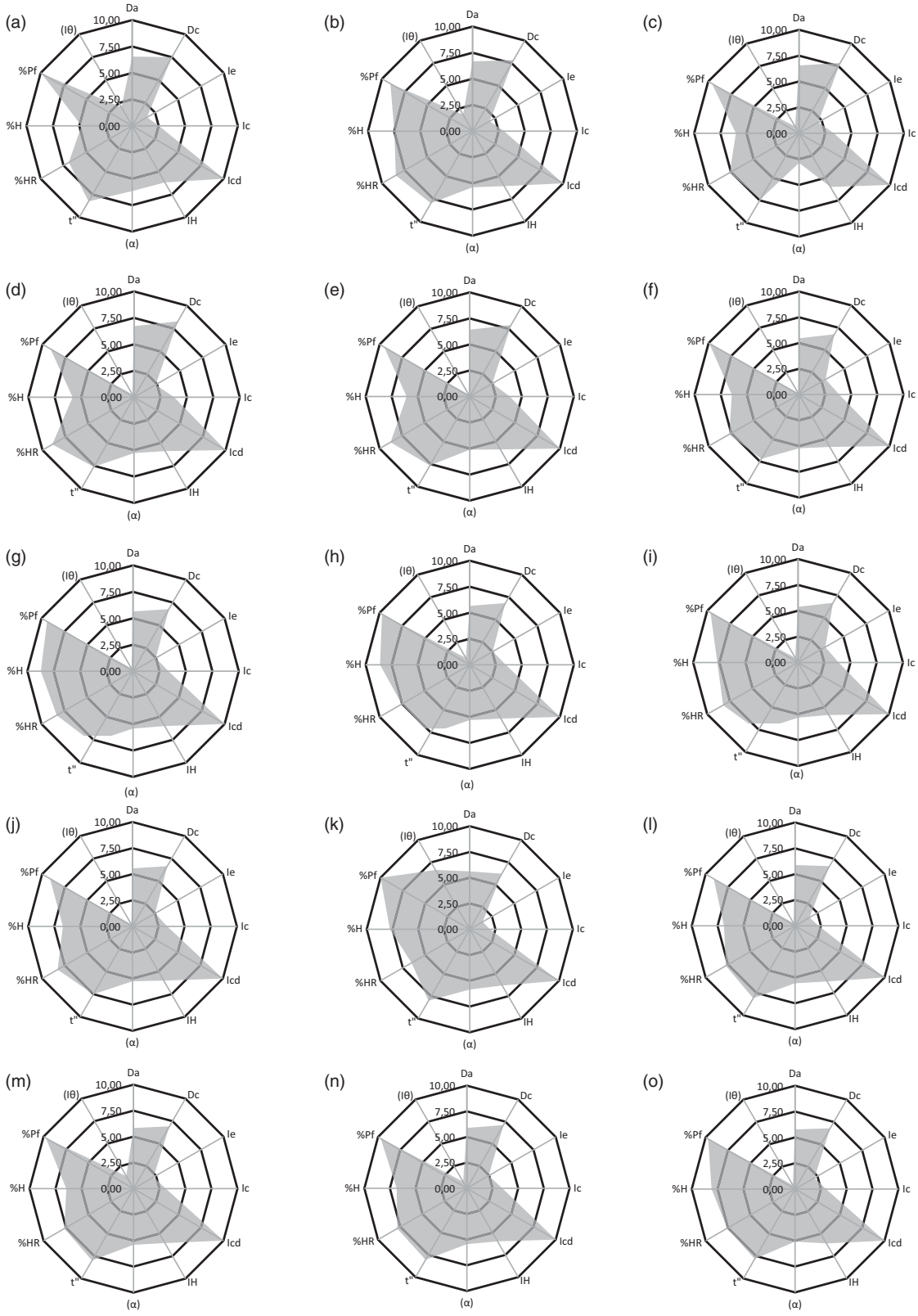

Figure 2. SeDeM diagrams for the intermediate blends consisting of the pellets containing doxylamine (a–e), ibuprofen (f–j), and paracetamol (k–o) and minimum amount of corrective excipient.

for paracetamol indicating an acceptable degree of linearity. The recovery obtained for doxylamine, ibuprofen, and paracetamol was between 95.29 and 102.58% of the amount added, indicating acceptable recovery. The % RSD obtained for three samples of the standard solutions of all three APIs were below 2.0%, indicating acceptable repeatability. The stability tests were carried out at 24 and 48 h, which yielded results between 98 and 102% of the initial concentration (0 h), indicating sufficient stability. The mass uniformity of all the MUPS tablet formulations complied with the specification as set in the BP (British Pharmacopoeia Commission

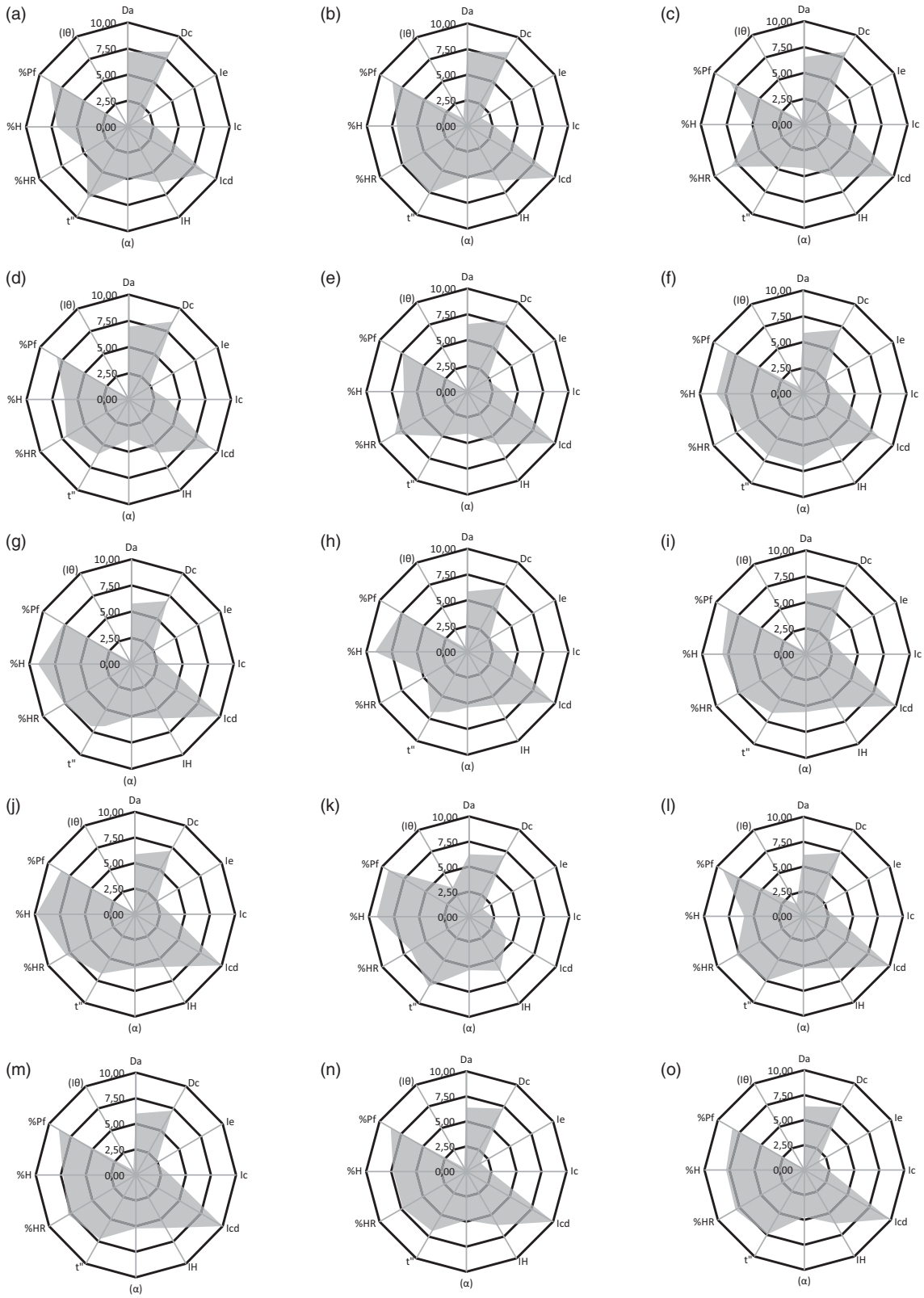

Figure 3. SeDeM diagrams for the final blend formulations containing doxylamine (a–e), ibuprofen (f–j), and paracetamol (k–o).

2015) with exception of one of the ibuprofen (F10) and one of the paracetamol (F15) MUPS tablets. Acceptable tablet hardness results, ranging from 67.4 ± 4.67 N (F11) to 125.7 ± 10.78 N (F1) were obtained for all of the MUPS tablet formulations. The tablet friability results of all the MUPS tablet formulations were less than 1.0% indicating results that complied with the USP (United States Pharmacopeia 2015) specifications for uncoated tablets, except for one of the paracetamol MUPS tablets (F11), which failed to comply with the specification. The disintegration time of all the MUPS formulations were generally more than 15 min and the disintegration time of the doxylamine MUPS tablet formulations were more than 45 min. The content uniformity results of all the MUPS tablet

Table 4. Incidence factor values and compressibility indices for the different final blend formulations.

Formulation number	Dimension	Compressibility	Flowability/ Powder Flow	Lubricity/ Stability	Lubricity/ Dosage	Parameter index (IP)	Parametric profile index (IPP)	Good compression index (GCI)
	Incidence factor values for final formulations containing doxylamine					Compressibility indices for final formulations containing doxylamine		
F1	7.76	4.43	6.34	5.79	4.48	0.583	5.694	5.421
F2	7.77	4.75	6.24	7.18	4.73	0.750	6.028	5.738
F3	7.34	5.52	4.91	6.49	4.40	0.500	5.647	5.376
F4	7.76	5.10	5.26	6.68	4.20	0.667	5.696	5.422
F5	7.26	5.29	5.00	7.29	3.76	0.667	5.625	5.355
	Incidence factor values for final formulations containing ibuprofen					Compressibility indices for final formulations containing ibuprofen		
F6	6.51	4.86	6.59	7.63	4.58	0.750	5.984	5.697
F7	6.36	5.28	6.10	8.37	3.99	0.750	5.965	5.678
F8	6.50	5.32	6.20	6.89	4.04	0.667	5.785	5.507
F9	6.49	5.42	6.01	7.78	4.51	0.750	5.990	5.703
F10	6.50	5.38	5.97	8.89	3.90	0.750	6.053	5.762
	Incidence factor values for final formulations containing paracetamol					Compressibility indices for final formulations containing paracetamol		
F11	6.63	2.71	6.54	7.96	6.25	0.667	5.790	5.512
F12	6.76	5.12	6.25	6.87	5.39	0.750	6.016	5.727
F13	6.62	5.28	6.14	7.52	4.71	0.750	5.995	5.707
F14	6.82	4.68	5.97	7.31	4.58	0.667	5.871	5.504
F15	6.82	4.62	6.12	7.90	3.99	0.667	5.801	5.522

Table 5. Uniformity of mass, hardness, friability, disintegration time, content uniformity, dissolution results, area under the curve (AUC) values and mean dissolution time (MDT) of the different MUPS tablet formulations.

	Uniformity of mass ± SD[a] (mg)	Hardness ± SD[a] (N)	Friability (%)	Disintegration time (min)	Content uniformity ± SD[a] (%) L1[b]	Dissolution (%)	AUC ± SD[a] (mg/ml min)	MDT ± SD[a] (min)
				Doxylamine MUPS tablet formulations				
F1 MUPS tablets	446.40 ± 2.16	125.7 ± 10.78	0.32	>45.00	104.11 ± 0.82 L1: 4.56	64.16 at 30 min 96.18 at 60 min 101.10 at 120 min	12268.30 ± 181.55	25.58 ± 1.12
F2 MUPS tablets	453.90 ± 6.83	87.7 ± 12.56	0.31	>45.00	104.19 ± 2.51 L1: 8.71	53.16 at 30 min 85.45 at 60 min 100.82 at 120 min	11574.43 ± 160.63	32.91 ± 2.16
F3 MUPS tablets	444.35 ± 5.95	109.1 ± 17.02	0.16	>45.00	111.03 ± 1.74 L1: 13.69	29.96 at 30 min 96.05 at 60 min 101.38 at 120 min	8486.71 ± 202.40	48.11 ± 2.71
F4 MUPS tablets	450.10 ± 10.01	92.6 ± 12.47	0.32	>45.00	109.87 ± 1.94 L1: 13.03	35.24 at 30 min 69.23 at 60 min 101.15 at 120 min	9000.78 ± 2510.21	47.08 ± 4.99
F5 MUPS tablets	438.90 ± 9.18	92.0 ± 12.04	0.15	>45.00	109.74 ± 2.54 L1: 14.33	25.09 at 30 min 50.53 at 60 min 98.23 at 120 min	7498.69 ± 640.72	59.04 ± 5.21
				Ibuprofen MUPS tablet formulations				
F6 MUPS tablets	446.95 ± 2.42	87.9 ± 9.00	0.11	14.82	98.01 ± 3.21 L1: 8.19	73.18 at 30 min 95.76 at 60 min 98.15 at 120 min	10218.05 ± 228.49	26.32 ± 2.66
F7 MUPS tablets	454.85 ± 5.80	100.4 ± 10.88	0.12	14.68	102.89 ± 3.04% L1: 8.70	45.68 at 30 min 82.75 at 60 min 94.34 at 120 min	9600.85 ± 334.31	41.33 ± 3.80
F8 MUPS tablets	459.15 ± 8.06	116.9 ± 20.78	0.19	15.15	109.53 ± 4.72 L1: 19.35	37.67 at 30 min 72.18 at 60 min 96.13 at 120 min	8717.48 ± 181.3	47.00 ± 0.87
F9 MUPS tablets	443.90 ± 4.44	109.5 ± 14.14	0.19	19.70	110.89 ± 4.27 L1: 19.65	48.82 at 30 min 73.20 at 60 min 93.42 at 120 min	9016.70 ± 459.80	45.71 ± 4.55
F10 MUPS tablets	457.10 ± 14.44	118.4 ± 17.15	0.20	>45.00	115.09 ± 5.27 L1: 26.24	46.06 at 30 min 69.64 at 60 min 90.23 at 120 min	8782.23 ± 423.90	45.87 ± 3.12
				Paracetamol MUPS tablet formulations				
F11 MUPS tablets	445.90 ± 2.36	67.4 ± 4.67	10.53	14.17	93.99 ± 2.50 L1: 10.50	93.14 at 30 min 99.88 at 60 min 100.88 at 120 min	12182.96 ± 876.22	14.77 ± 2.29
F12 MUPS tablets	462.45 ± 6.25	106.8 ± 7.57	0.31	12.87	109.47 ± 1.88 L1: 12.47	82.16 at 30 min 99.36 at 60 min 99.20 at 120 min	12255.41 ± 491.44	19.51 ± 2.02
F13 MUPS tablets	456.20 ± 7.40	111.9 ± 6.43	0.28	20.57	100.70 ± 3.01 L1: 6.42	69.87 at 30 min 97.40 at 60 min 100.30 at 120 min	10909.44 ± 212.83	25.35 ± 1.11
F14 MUPS tablets	450.10 ± 8.97	112.2 ± 13.60	0.13	16.48	90.05 ± 6.71 L1: 4.65	72.72 at 30 min 98.40 at 60 min 100.30 at 120 min	11138.57 ± 123.09	24.00 ± 2.32
F15 MUPS tablets	460.45 ± 13.18	85.4 ± 25.25	0.50	>45.00	101.69 ± 9.55 L1: 23.11	61.97 at 30 min 93.21 at 60 min 99.54 at 120 min	11537.26 ± 319.45	30.69 ± 1.97

[a]SD: standard deviation.
[b]L = Maximum allowed acceptance value (L1 = 15.0).

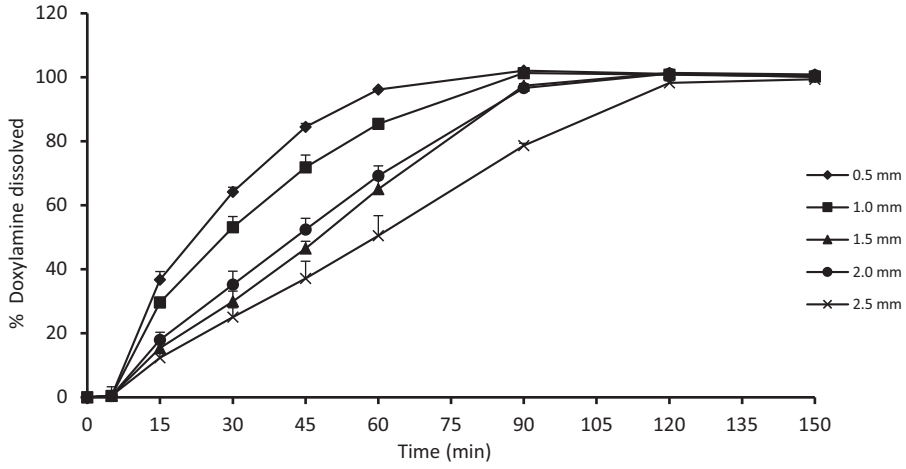

Figure 4. Dissolution profiles of the MUPS tablets containing doxylamine. Standard deviation (SD) is indicated by error bars.

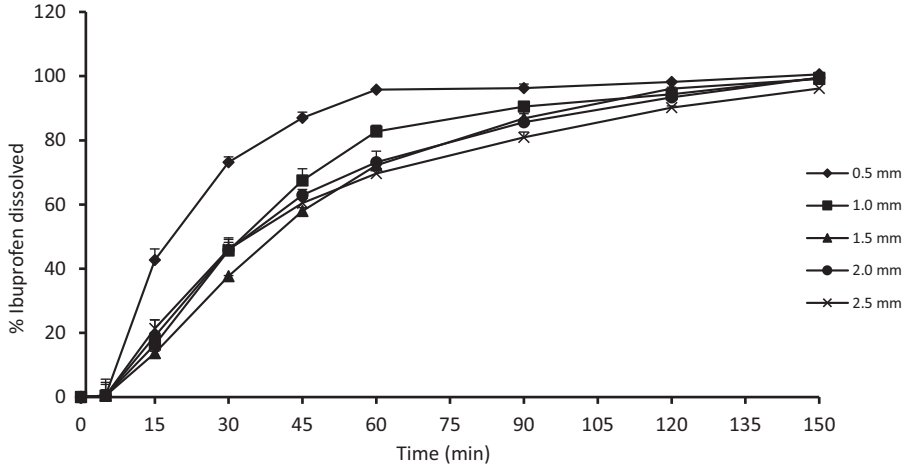

Figure 5. Dissolution profiles of the MUPS tablets containing ibuprofen. Standard deviation (SD) is indicated by error bars.

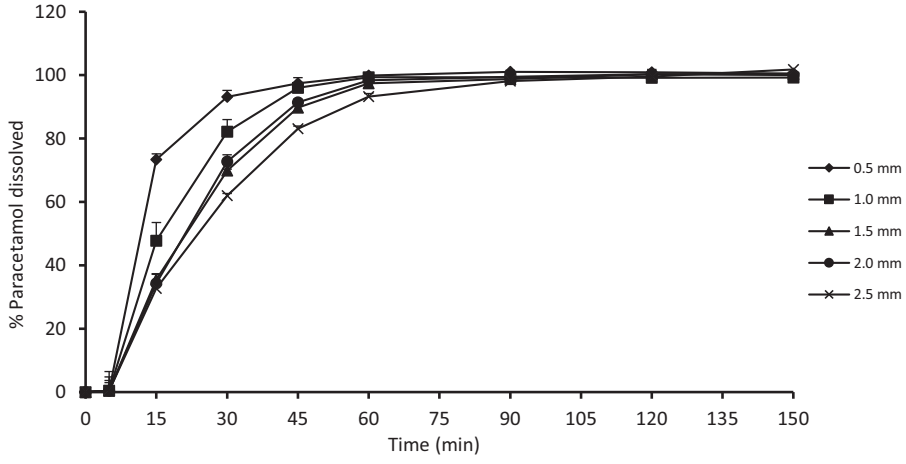

Figure 6. Dissolution profiles of the MUPS tablets containing paracetamol. Standard deviation (SD) is indicated by error bars.

formulations complied with the specification of the USP (United States Pharmacopeia 2015) with an acceptance value of less than or equal to L1 (L1 = 15.0), except for three of the ibuprofen MUPS tablet formulations (F8, F9, and F10) and one of the paracetamol MUPS tablet formulations (F15).

The dissolution profiles of the MUPS tablets containing doxylamine showed that >98% of the doxylamine content was released from all of the formulations after 120 min, albeit at different rates. The doxylamine release rates were in agreement with the size of the pellets that were compressed into the MUPS tablets. This was confirmed by an increasing trend in the average MDT values from 25.58 ± 1.12 to 59.04 ± 5.21 min for MUPS tablets comprising of pellets with a size of 0.5 mm to MUPS tablets comprising of pellets with a size of 2.5 mm. In general, the rate and quantity of doxylamine released (% dissolution) is less from the MUPS tablet formulations comprising of pellets with a larger diameter as evidenced

by a smaller AUC with an increase in pellet diameter (12268.30 ± 181.55 to 7498.69 ± 640.72 mg/ml min). As all the doxylamine tablet formulations complied with the test for uniformity of content, the lower extent of drug release was not due to a lower drug content and therefore, the lower extent of drug release may be attributed to a difference in average pellet size. A relatively large difference in doxylamine release rate was evident for the MUPS tablets produced from 0.5 mm pellets (64.16% at 30 min) and the MUPS tablets produced from 2.5 mm pellets (25.09% at 30 min). During disintegration of the MUPS tablets (although the disintegration time exceeded an average disintegration time of 45 min), the pellets were separated from each other, and the size of the pellets therefore determined the surface area that was exposed to the dissolution medium, which explains the difference in release rate. The smaller pellets exhibited a larger surface to volume ratio than the larger pellets and therefore exhibit a faster dissolution rate as the dissolution rate is directly proportionate to the surface area exposed to the dissolution medium (York 1988).

The dissolution profiles of the MUPS tablets containing ibuprofen showed that more than 90% of this active ingredient was released after 120 min from all the formulations. Although ibuprofen release was dependent on the size of the pellets, the release rate did not directly correlate with pellet size. From the MDT results it can be seen that the average MDT increased (26.32 ± 2.66 to 47.00 ± 0.87 min) for MUPS tablets comprised of pellets with an increase in pellet size up to a pellet size of 1.5 mm. However, this relationship was not seen for the MUPS tablets comprising of pellets with a size of 2.0 and 2.5 mm. The MUPS tablets comprising of pellets with a diameter of 2.0 and 2.5 mm exhibited average MDT values of 45.71 ± 4.55 and 45.87 ± 3.12 min, respectively. The same tendency was observed with regard to the extent of ibuprofen release. The average AUC value decreased from 10218.05 ± 228.49 mg/ml min for the MUPS tablets prepared from 0.5 mm diameter pellets to 8717.48 ± 181.37 mg/ml min for the MUPS tablets prepared from the 1.5 mm diameter pellets. The average AUC values for the MUPS tablets prepared from the 2.0 and 2.5 mm pellets were similar to the average AUC value of the tablets prepared from the 1.5 mm pellets. It is thus apparent that the ibuprofen release rate was not affected by pellet size to the same degree as doxylamine release, especially for the pellet sizes larger than 1.5 mm. It is not clear why the full range of pellet size did not influence the release rate of ibuprofen to the same extent as for doxylamine release. However, it could probably be attributed to the solubility of the drug, indicating that for pellet sizes exceeding 1.5 mm, the solubility of the drug is the rate limiting step rather than the specific surface area available for drug dissolution.

The dissolution profiles of the MUPS tablets containing paracetamol showed that more than 99% of this active ingredient was released after 120 min from all the formulations. In general, similar to the doxylamine release rates, the paracetamol release rates were in agreement with the size of the pellets that were compressed into the MUPS tablets. This was confirmed by a general trend of an increase in the average MDT values from 14.77 ± 2.29 to 30.69 ± 1.97 min for MUPS tablets comprising of pellets with a size of 0.5 mm to MUPS tablets comprising of pellets with a size of 2.5 mm. In general, the rate and quantity of paracetamol released (% dissolution) were less from the MUPS tablet formulations comprising of pellets with a larger diameter as evidenced by a smaller AUC with an increase in pellet diameter (12,182.96 ± 876.22 to 11,537.26 ± 319.45 mg/ml min).

Overall, at least 50% or more of the drug content was released after 60 min for all of the doxylamine MUPS tablet formulations, after 45 min for all of the ibuprofen MUPS tablet formulations and after 30 min for all of the paracetamol MUPS tablet formulations. This difference in drug release rate for the different APIs investigated can possibly be attributed to the physico-chemical properties (e.g. water solubility) of these APIs. Based on the water solubility of the APIs, it is expected that doxylamine (very soluble in water) should exhibit the highest % drug release in the shortest time, although this was not observed. This discrepancy may be attributed to the relatively long disintegration times (>45 min) of the doxylamine MUPS tablet formulations and the influence this may have on the specific surface area exposed to the dissolution medium (e.g. pellets not separated from the MUPS).

It should be noted that all the dissolution profiles for all three APIs exhibited a low percentage (<1%) release over the first 5 min period. This initial relatively low release may be attributed to the nature of the MUPS tablets (being not conventional tablets comprised of powders, but comprised of pellets). Therefore, the dissolution media needed to penetrate the beads before API can be dissolved and released resulting in a low initial release rate. In general, the MUPS tablet formulations prepared from a smaller pellet size exhibited a faster drug release rate than the formulations with a larger pellet size for all three APIs investigated in this study, however, the extent of this effect was apparently influenced by the solubility of the API and to the disintegration time of the MUPS tablets. The solubility of the API seems to have a more pronounced effect than the disintegration time. This pellet size dependent drug release rate can be explained by a larger total specific surface area of the smaller pellets exposed to the dissolution medium upon disintegration of the tablets compared to the total specific surface area of the larger pellets exposed to the dissolution medium.

Conclusions

Although the SeDeM EDS was developed as a tool to be used in the formulation of direct compression tablet formulations consisting of powder mixtures, the results of this study showed that the SeDeM EDS was successfully applied to pellets containing different active pharmaceutical ingredients for prediction of formulations for preparation of MUPS tablets with acceptable properties. Both the SeDeM diagram radii values as well as incidence factor values indicated that compressibility was an inadequacy that should be corrected by adding an excipient. Kollidon® VA 64 was identified as the excipient that could correct the inadequacy at the lowest amount.

The formulations recommended by the SeDeM EDS provided compressible MUPS tablet formulations for doxylamine, ibuprofen, and paracetamol as active ingredient. The analysis of the MUPS tablets confirmed that tablets with good physical properties were obtained. However, the content uniformity of some of the formulations did not comply with the content uniformity specifications, which can possibly be attributed to the difference in particle size of the pellets and the powder particles of the excipients. Dissolution results indicated that in general, an increase in dissolution rate and extent were obtained with a decrease in the pellet size used to compress the MUPS tablets. This relationship was, however, not evident in the total range of pellet sizes (i.e. 0.5 to 2.5 mm) for the ibuprofen MUPS tablet formulations and it appears that water solubility might also play a pronounced role in this case.

Disclosure statement

The authors report no declarations of interest.

Any opinion, findings, and conclusions or recommendations expressed in this material are those of the authors and therefore the NRF do not accept any liability with regard thereto.

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Chapter 6: Final conclusion and future prospects

1 Final conclusion

Tablet formulation can be a timeous process, especially when it is done by trial and error. The SeDeM EDS was developed to aid in the formulation of powders for direct compression into tablets (Aguilar-Diaz *et al*., 2014, Pérez *et al*., 2006, Suñé-Negre *et al*., 2008, Suñé-Negre *et al*., 2014). In this study, the SeDeM EDS was applied to pellets in the formulation of MUPS tablets. Properties of pellets with different sizes and containing different APIs were characterised and processed by employing the SeDeM EDS (i.e. parameters, incidence factors and diagram radii). The SeDeM EDS was also applied to selected excipients and the most suitable excipient, when used in the smallest possible amount, was identified for successful MUPS production by applying the mathematical equations suggested by the SeDeM EDS. The excipient identified by the SeDeM EDS was mixed with the pellets to provide formulations suitable for compression into MUPS tablets.

The placebo pellet formulation (without API) and separate pellet formulations each containing a different API (i.e. doxylamine, ibuprofen and paracetamol) were successfully compressed into MUPS tablets. Evaluation of the MUPS tablets confirmed that tablets with good physical properties were obtained from the predicted formulations. However, the content uniformity of four of the MUPS tablet formulations did not comply with the content uniformity specification of the United Stated Pharmacopeia (USP, 2015). The failure thereof could be attributed to the relatively large difference in particle size of the pellets and the particle size of the added excipient powders. From the results it is evident that content uniformity problems are more likely to be experienced with the larger pellets, probably due to the segregation of the powder particles of the excipients in the mixtures during handling and compression.

This study has shown that the SeDeM EDS can successfully be applied to pellets of different sizes in the formulation of MUPS tablets containing different APIs. A novel application of the SeDeM EDS was therefore identified in this research project that made a contribution to new knowledge in the field of MUPS tablet formulation and production.

2 Future prospects

Recommended future prospects for further investigation related to this project include the following:

- Further studies should be done using filler materials other than MicroceLac® 200 in the production of the pellets in order to investigate the effect of this variable on the predictions of the SeDeM EDS;
- Other manufacturing processes of pellets/granules (e.g. wet granulation, cross-linking, hot melt) should be employed to determine whether the SeDeM EDS could also be used in the formulation of MUPS tablets consisting of these different types of pellets;
- New requirements for SeDeM parameters should be developed for pellets (which should be different from those for powder particles) such as the cut-off for particle size;
- The possibility of the application of the SeDeM EDS for alternative solid oral dosage forms such as mini-tablet in capsule systems, matrix type tablets and gastro-retentive systems should be investigated;
- The application of the SeDeM EDS in powder mixtures with relatively large particle size differences should be investigated;
- The ability of the SeDeM EDS to predict the influence of newly developed excipients on formulation of directly compressible tablets should be investigated; and
- The deformation of pellets of different sizes and compositions during MUPS production should be investigated.

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Appendix A: SeDeM EDS results

A.1 Introduction

The SeDeM EDS parameter tests were performed on the following:

- Pellets;
- Excipients;
- Pellet formulations after addition of the most appropriate excipient (intermediate blend); and
- Pellet formulations after addition of the most appropriate excipient, disintegrant, lubricant and glidant (final blend).

A.2 Results

The results of the SeDeM EDS parameter values, diagrams and formulations are presented in Tables A.1–A.69 and Figure A.1–A.4.

Table A.1: SeDeM parameter values for 0.5 mm MicroceLac® 200 pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.67	0.66	0.66	0.66	6.608
Tapped Density (g/ml)	0.70	0.69	0.69	0.70	6.977
Inter-particle Porosity (-)	0.08	0.08	0.08	0.08	0.667
Carr's Index (%)	5.33	5.26	5.26	5.29	1.057
Cohesion Index (N)	-	-	-	491.00 (1)	24.550
Hausner Ratio (-)	1.06	1.06	1.06	1.06	6.481
Angle Of Repose (°)	15.29	15.40	15.50	15.40	6.921
Powder Flow (s)	2.90	3.00	3.00	2.97	8.517
Loss on Drying (%)	4.17	4.27	4.12	4.19	5.811
Hygroscopicity (%)	1.80	1.96	2.18	1.98	9.010
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.013223 (3)	6.611

(1) Cohesion Index average of 10 values (values: 493, 489, 495, 485, 493, 498, 487, 491, 490 and 489)

(2) Particle size results

Sieve size	% Retained
710	4.00
500	71.45
355	22.50
300	1.27
Tray	0.78
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.2: SeDeM parameter values for 1.0 mm MicroceLac® 200 pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.63	0.63	0.61	0.62	6.199
Tapped Density (g/ml)	0.68	0.68	0.67	0.67	6.727
Inter-particle Porosity (-)	0.12	0.12	0.14	0.13	1.056
Carr's Index (%)	7.50	7.50	8.54	7.85	1.569
Cohesion Index (N)	-	-	-	492.50 (1)	24.625
Hausner Ratio (-)	1.08	1.08	1.09	1.09	6.383
Angle Of Repose (°)	16.86	16.98	16.98	16.94	6.612
Powder Flow (s)	3.30	3.30	3.30	3.30	8.350
Loss on Drying (%)	4.25	3.92	3.80	3.99	6.007
Hygroscopicity (%)	1.38	1.78	1.57	1.58	9.212
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.001724 (3)	0.862

(1) Cohesion Index average of 10 values (values: 495, 489, 494, 496, 495, 499, 488, 485, 486 and 498)

(2) Particle size results

Sieve size	% Retained
1200	13.24
1000	11.48
850	30.06
710	27.80
Tray	17.42
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.3: SeDeM parameter values for 1.5 mm MicroceLac® 200 pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.60	0.60	0.59	0.59	5.929
Tapped Density (g/ml)	0.66	0.65	0.65	0.65	6.522
Inter-particle Porosity (-)	0.16	0.14	0.16	0.15	1.278
Carr's Index (%)	9.52	8.33	9.41	9.09	1.818
Cohesion Index (N)	-	-	-	469.00 (1)	23.450
Hausner Ratio (-)	1.11	1.09	1.10	1.10	6.333
Angle Of Repose (°)	18.17	19.77	19.11	19.01	6.197
Powder Flow (s)	3.60	3.50	3.50	3.53	8.233
Loss on Drying (%)	3.58	3.23	3.14	3.32	6.681
Hygroscopicity (%)	1.95	1.95	1.86	1.92	9.040
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.004408 (3)	2.204

(1) Cohesion Index average of 10 values (values: 416, 497, 493, 487, 478, 468, 472, 457, 449 and 473)

(2) Particle size results

Sieve size	% Retained
1700	3.44
1200	71.48
1000	10.00
850	8.02
Tray	7.06
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.4: SeDeM parameter values for 2.0 mm MicroceLac® 200 pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.58	0.58	0.58	0.58	5.814
Tapped Density (g/ml)	0.63	0.64	0.63	0.64	6.356
Inter-particle Porosity (-)	0.14	0.16	0.14	0.15	1.222
Carr's Index (%)	8.14	9.30	8.14	8.53	1.705
Cohesion Index (N)	-	-	-	426.90 (1)	21.345
Hausner Ratio (-)	1.09	1.10	1.09	1.09	6.356
Angle Of Repose (°)	20.85	19.63	21.04	20.51	5.899
Powder Flow (s)	3.30	3.30	3.30	3.30	8.350
Loss on Drying (%)	3.43	3.34	3.14	3.30	6.697
Hygroscopicity (%)	2.04	2.00	1.79	1.94	9.028
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.017465 (3)	8.733

(1) Cohesion Index average of 10 values (values: 442, 460, 417, 436, 460, 364, 403, 436, 438 and 413)

(2) Particle size results

Sieve size	% Retained
2360	0.00
2000	0.16
1700	0.36
1200	86.38
Tray	13.10
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.5: SeDeM parameter values for 2.5 mm MicroceLac® 200 pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.57	0.58	0.57	0.58	5.769
Tapped Density (g/ml)	0.63	0.64	0.63	0.64	6.356
Inter-particle Porosity (-)	0.16	0.16	0.16	0.16	1.333
Carr's Index (%)	9.20	9.30	9.20	9.23	1.846
Cohesion Index (N)	-	-	-	305.90 (1)	15.295
Hausner Ratio (-)	1.10	1.10	1.10	1.10	6.328
Angle Of Repose (°)	20.27	21.80	22.11	21.39	5.722
Powder Flow (s)	4.10	4.10	4.00	4.07	7.967
Loss on Drying (%)	3.52	3.46	3.42	3.46	6.537
Hygroscopicity (%)	1.84	1.87	1.93	1.88	9.060
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.000993 (3)	0.497

(1) Cohesion Index average of 10 values (values: 331, 301, 286, 315, 329, 297, 316, 287, 295 and 302)

(2) Particle size results

Sieve size	% Retained
2800	0.00
2360	0.48
2000	5.18
1700	35.34
1200	30.96
Tray	28.04
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.6: SeDeM parameter values for 0.5 mm doxylamine pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.63	0.63	0.63	0.63	6.250
Tapped Density (g/ml)	0.72	0.72	0.72	0.72	7.246
Inter-particle Porosity (-)	0.22	0.22	0.22	0.22	1.833
Carr's Index (%)	13.75	13.75	13.75	13.75	2.750
Cohesion Index (N)	-	-	-	494.10 (1)	24.705
Hausner Ratio (-)	1.16	1.16	1.16	1.16	6.135
Angle Of Repose (°)	24.38	24.04	24.78	24.40	5.120
Powder Flow (s)	3.50	3.50	3.40	3.47	8.267
Loss on Drying (%)	6.38	6.36	7.44	6.73	3.274
Hygroscopicity (%)	3.60	3.79	3.51	3.63	8.183
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.010752 (3)	5.376

(1) Cohesion Index average of 10 values (values: 498, 487, 489, 499, 496, 495, 499, 496, 496 and 489)

(2) Particle size results

Sieve size	% Retained
710	2.47
500	66.23
355	30.06
300	0.60
Tray	0.38
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.7: SeDeM parameter values for 1.0 mm doxylamine pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.57	0.57	0.57	0.57	5.704
Tapped Density (g/ml)	0.65	0.66	0.65	0.65	6.522
Inter-particle Porosity (-)	0.20	0.24	0.22	0.22	1.833
Carr's Index (%)	11.49	13.64	12.50	12.54	2.509
Cohesion Index (N)	-	-	-	480.30 (1)	24.015
Hausner Ratio (-)	1.13	1.16	1.14	1.14	6.188
Angle Of Repose (°)	26.57	26.92	26.21	26.56	4.687
Powder Flow (s)	4.00	4.10	4.10	4.07	7.967
Loss on Drying (%)	4.09	4.49	4.43	4.34	5.662
Hygroscopicity (%)	4.44	5.33	4.64	4.80	7.598
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.008741 (3)	4.370

(1) Cohesion Index average of 10 values (values: 475, 462, 475, 476, 463, 498, 487, 499, 479 and 489)

(2) Particle size results

Sieve size	% Retained
1200	79.42
1000	5.79
850	8.59
710	4.22
Tray	1.99
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.8: SeDeM parameter values for 1.5 mm doxylamine pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.63	0.62	0.62	0.62	6.199
Tapped Density (g/ml)	0.68	0.68	0.68	0.68	6.849
Inter-particle Porosity (-)	0.14	0.16	0.16	0.15	1.278
Carr's Index (%)	8.75	9.88	9.88	9.50	1.900
Cohesion Index (N)	-	-	-	471.00 [(1)]	23.550
Hausner Ratio (-)	1.10	1.11	1.11	1.11	6.317
Angle Of Repose (°)	24.44	25.11	23.72	24.43	5.115
Powder Flow (s)	3.80	3.80	3.80	3.80	8.100
Loss on Drying (%)	2.93	3.41	3.90	3.41	6.588
Hygroscopicity (%)	5.58	6.30	5.02	5.63	7.183
Particles < 45µm (%)	-	-	-	0.00 [(2)]	10.000
Homogeneity Index (-)	-	-	-	0.004742 [(3)]	2.371

[(1)] Cohesion Index average of 10 values (values: 499, 451, 469, 487, 461, 475, 485, 466, 461 and 456)

[(2)] Particle size results

Sieve size	% Retained
1700	34.03
1200	65.47
1000	1.01
850	1.01
Tray	0.48
< 45µm	0.00

[(3)] Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.9: SeDeM parameter values for 2.0 mm doxylamine pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.59	0.59	0.60	0.59	5.930
Tapped Density (g/ml)	0.65	0.67	0.68	0.66	6.639
Inter-particle Porosity (-)	0.16	0.20	0.18	0.18	1.500
Carr's Index (%)	9.41	11.76	10.84	10.67	2.135
Cohesion Index (N)	-	-	-	432.90 (1)	21.645
Hausner Ratio (-)	1.10	1.13	1.12	1.12	6.268
Angle Of Repose (°)	27.83	27.49	27.83	27.72	4.456
Powder Flow (s)	4.70	4.50	4.60	4.60	7.700
Loss on Drying (%)	3.04	3.48	3.51	3.34	6.660
Hygroscopicity (%)	4.64	6.24	5.87	5.58	7.208
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.001422 (3)	0.711

(1) Cohesion Index average of 10 values (values: 373, 422, 458, 428, 469, 456, 478, 489, 409 and 427)

(2) Particle size results

Sieve size	% Retained
2360	8.98
2000	17.71
1700	20.49
1200	46.05
Tray	6.77
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.10: SeDeM parameter values for 2.5 mm doxylamine pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.58	0.58	0.58	0.58	5.814
Tapped Density (g/ml)	0.65	0.63	0.64	0.64	6.411
Inter-particle Porosity (-)	0.18	0.14	0.16	0.16	1.333
Carr's Index (%)	10.47	8.14	9.30	9.30	1.860
Cohesion Index (N)	-	-	-	328.30 (1)	16.415
Hausner Ratio (-)	1.12	1.09	1.10	1.10	6.324
Angle Of Repose (°)	27.10	28.55	26.93	27.52	4.495
Powder Flow (s)	4.60	4.50	4.60	4.57	7.717
Loss on Drying (%)	3.23	3.36	3.84	3.48	6.524
Hygroscopicity (%)	1.94	2.21	2.02	2.06	8.972
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.000505 (3)	0.253

(1) Cohesion Index average of 10 values (values: 289, 279, 321, 354, 283, 354, 352, 348, 398 and 295)

(2) Particle size results

Sieve size	% Retained
2800	2.78
2360	27.35
2000	24.94
1700	20.70
1200	22.32
Tray	1.91
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.11: SeDeM parameter values for 0.5 mm ibuprofen pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.58	0.60	0.60	0.59	5.906
Tapped Density (g/ml)	0.66	0.66	0.66	0.66	6.579
Inter-particle Porosity (-)	0.20	0.16	0.16	0.17	1.444
Carr's Index (%)	11.63	9.52	9.52	10.23	2.045
Cohesion Index (N)	-	-	-	288.50 (1)	14.425
Hausner Ratio (-)	1.13	1.11	1.11	1.11	6.287
Angle Of Repose (°)	17.16	17.68	16.50	17.12	6.577
Powder Flow (s)	3.30	3.30	3.40	3.33	8.333
Loss on Drying (%)	3.51	4.36	4.65	4.17	5.828
Hygroscopicity (%)	0.49	0.39	0.98	0.62	9.690
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.005437 (3)	2.718

(1) Cohesion Index average of 10 values (values: 285, 290, 274, 289, 296, 287, 279, 298, 298 and 289)

(2) Particle size results

Sieve size	% Retained
710	7.58
500	51.09
355	36.51
300	1.91
Tray	2.91
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.12: SeDeM parameter values for 1.0 mm ibuprofen pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.54	0.55	0.54	0.54	5.435
Tapped Density (g/ml)	0.60	0.60	0.60	0.60	6.024
Inter-particle Porosity (-)	0.18	0.16	0.20	0.18	1.500
Carr's Index (%)	9.78	8.79	10.75	9.78	1.955
Cohesion Index (N)	-	-	-	257.00 (1)	12.850
Hausner Ratio (-)	1.11	1.10	1.12	1.11	6.305
Angle Of Repose (°)	20.27	20.27	20.12	20.22	5.956
Powder Flow (s)	4.50	4.60	4.60	4.57	7.717
Loss on Drying (%)	4.05	4.38	4.47	4.30	5.699
Hygroscopicity (%)	0.79	0.79	0.68	0.75	9.623
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.001487 (3)	0.743

(1) Cohesion Index average of 10 values (values: 279, 285, 267, 254, 240, 264, 261, 250, 249 and 221)

(2) Particle size results

Sieve size	% Retained
1200	42.82
1000	6.22
850	23.08
710	19.62
Tray	8.26
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.13: SeDeM parameter values for 1.5 mm ibuprofen pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.53	0.54	0.54	0.54	5.357
Tapped Density (g/ml)	0.60	0.59	0.60	0.59	5.929
Inter-particle Porosity (-)	0.20	0.16	0.18	0.18	1.500
Carr's Index (%)	10.64	8.60	9.68	9.64	1.928
Cohesion Index (N)	-	-	-	273.60 (1)	13.680
Hausner Ratio (-)	1.12	1.09	1.11	1.11	6.311
Angle Of Repose (°)	20.89	20.89	20.75	20.84	5.831
Powder Flow (s)	4.20	4.30	4.20	4.23	7.883
Loss on Drying (%)	3.78	3.00	3.85	3.54	6.458
Hygroscopicity (%)	0.80	0.78	0.79	0.79	9.605
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.005817 (3)	2.909

(1) Cohesion Index average of 10 values (values: 271, 281, 272, 281, 276, 265, 278, 266, 270 and 276)

(2) Particle size results

Sieve size	% Retained
1700	4.48
1200	77.88
1000	3.94
850	7.34
Tray	6.36
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.14: SeDeM parameter values for 2.0 mm ibuprofen pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.53	0.53	0.53	0.53	5.300
Tapped Density (g/ml)	0.58	0.59	0.59	0.59	5.860
Inter-particle Porosity (-)	0.16	0.20	0.18	0.18	1.500
Carr's Index (%)	8.51	10.53	9.57	9.54	1.907
Cohesion Index (N)	-	-	-	260.80 [(1)]	13.040
Hausner Ratio (-)	1.09	1.12	1.11	1.11	6.315
Angle Of Repose (°)	22.11	21.04	21.50	21.55	5.690
Powder Flow (s)	4.80	4.70	4.60	4.70	7.650
Loss on Drying (%)	3.17	3.17	3.06	3.14	6.865
Hygroscopicity (%)	0.89	0.89	0.69	0.82	9.588
Particles < 45µm (%)	-	-	-	0.00 [(2)]	10.000
Homogeneity Index (-)	-	-	-	0.004761 [(3)]	2.381

[(1)] Cohesion Index average of 10 values (values: 265, 568, 576, 252, 254, 227, 270, 268, 264 and 264)

[(2)] Particle size results

Sieve size	% Retained
2360	0.10
2000	3.24
1700	18.98
1200	66.68
Tray	11.00
< 45µm	0.00

[(3)] Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.15: SeDeM parameter values for 2.5 mm ibuprofen pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.51	0.51	0.51	0.51	5.051
Tapped Density (g/ml)	0.56	0.56	0.56	0.56	5.576
Inter-particle Porosity (-)	0.18	0.20	0.18	0.19	1.556
Carr's Index (%)	9.09	10.10	9.09	9.43	1.886
Cohesion Index (N)	-	-	-	232.30 (1)	11.615
Hausner Ratio (-)	1.10	1.11	1.10	1.10	6.320
Angle Of Repose (°)	22.56	23.63	22.56	22.91	5.417
Powder Flow (s)	5.10	5.10	5.00	5.07	7.467
Loss on Drying (%)	3.79	3.92	3.64	3.78	6.217
Hygroscopicity (%)	0.88	0.85	0.78	0.84	9.582
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.000981 (3)	0.491

(1) Cohesion Index average of 10 values (values: 229, 239, 258, 236, 191, 239, 232, 246, 213 and 240)

(2) Particle size results

Sieve size	% Retained
2800	1.55
2360	5.90
2000	17.83
1700	33.37
1200	36.41
Tray	4.94
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.16: SeDeM parameter values for 0.5 mm paracetamol pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.56	0.56	0.57	0.56	5.639
Tapped Density (g/ml)	0.66	0.65	0.65	0.65	6.522
Inter-particle Porosity (-)	0.26	0.24	0.22	0.24	2.000
Carr's Index (%)	14.61	13.48	12.50	13.53	2.706
Cohesion Index (N)	-	-	-	376.50 (1)	18.825
Hausner Ratio (-)	1.17	1.16	1.14	1.16	6.145
Angle Of Repose (°)	21.80	21.50	21.65	21.65	5.670
Powder Flow (s)	3.60	3.80	4.00	3.80	8.100
Loss on Drying (%)	2.59	2.49	3.86	2.98	7.020
Hygroscopicity (%)	1.90	1.00	0.79	1.23	9.385
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.057161 (3)	28.581

(1) Cohesion Index average of 10 values (values: 348, 376, 354, 380, 365, 394, 371, 402, 388 and 387)

(2) Particle size results

Sieve size	% Retained
710	3.27
500	91.81
355	4.46
300	0.18
Tray	0.28
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

TableA.17: SeDeM parameter values for 1.0 mm paracetamol pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.56	0.56	0.56	0.56	5.618
Tapped Density (g/ml)	0.63	0.63	0.63	0.63	6.329
Inter-particle Porosity (-)	0.20	0.20	0.20	0.20	1.667
Carr's Index (%)	11.24	11.24	11.24	11.24	2.247
Cohesion Index (N)	-	-	-	376.50 (1)	18.825
Hausner Ratio (-)	1.13	1.13	1.13	1.13	6.245
Angle Of Repose (°)	21.34	23.47	24.38	23.06	5.388
Powder Flow (s)	3.70	3.70	3.70	3.70	8.150
Loss on Drying (%)	2.78	2.30	2.18	2.42	7.577
Hygroscopicity (%)	1.37	1.39	1.38	1.38	9.310
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.002215 (3)	1.107

(1) Cohesion Index average of 10 values (values: 348, 376, 354, 380, 365, 394, 371, 402, 388 and 387)

(2) Particle size results

Sieve size	% Retained
1200	51.96
1000	10.18
850	16.76
710	11.58
Tray	9.52
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.18: SeDeM parameter values for 1.5 mm paracetamol pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.53	0.53	0.53	0.53	5.319
Tapped Density (g/ml)	0.60	0.60	0.60	0.60	5.952
Inter-particle Porosity (-)	0.20	0.20	0.20	0.20	1.667
Carr's Index (%)	10.64	10.64	10.64	10.64	2.128
Cohesion Index (N)	-	-	-	303.20 (1)	15.160
Hausner Ratio (-)	1.12	1.12	1.12	1.12	6.270
Angle Of Repose (°)	24.04	24.61	24.61	24.42	5.116
Powder Flow (s)	4.30	1.30	4.30	3.30	8.350
Loss on Drying (%)	2.45	2.43	2.32	2.40	7.602
Hygroscopicity (%)	1.48	1.47	1.38	1.44	9.278
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.016910 (3)	8.455

(1) Cohesion Index average of 10 values (values: 292, 297, 283, 350, 304, 279, 334, 312, 279 and 302)

(2) Particle size results

Sieve size	% Retained
1700	23.90
1200	64.80
1000	2.82
850	5.48
Tray	3.00
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.19: SeDeM parameter values for 2.0 mm paracetamol pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.54	0.54	0.54	0.54	5.376
Tapped Density (g/ml)	0.60	0.60	0.60	0.60	6.000
Inter-particle Porosity (-)	0.20	0.18	0.20	0.19	1.611
Carr's Index (%)	10.75	9.68	10.75	10.39	2.079
Cohesion Index (N)	-	-	-	297.30 (1)	14.865
Hausner Ratio (-)	1.12	1.11	1.12	1.12	6.280
Angle Of Repose (°)	23.65	23.40	23.40	23.49	5.303
Powder Flow (s)	4.40	4.30	4.30	4.33	7.833
Loss on Drying (%)	2.24	2.43	2.24	2.31	7.695
Hygroscopicity (%)	1.49	1.50	1.50	1.50	9.252
Particles < 45µm (%)	-	-	-	0.00 (2)	10.000
Homogeneity Index (-)	-	-	-	0.002779 (3)	1.390

(1) Cohesion Index average of 10 values (values: 308, 279, 313, 315, 278, 293, 338, 316, 262 and 271)

(2) Particle size results

Sieve size	% Retained
2360	0.06
2000	2.80
1700	41.68
1200	53.94
Tray	1.52
< 45µm	0.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.20: SeDeM parameter values for 2.5 mm paracetamol pellets

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.51	0.51	0.50	0.50	5.034
Tapped Density (g/ml)	0.56	0.56	0.57	0.56	5.639
Inter-particle Porosity (-)	0.20	0.20	0.24	0.21	1.778
Carr's Index (%)	10.10	10.10	12.00	10.73	2.147
Cohesion Index (N)	-	-	-	277.10 [(1)]	13.855
Hausner Ratio (-)	1.11	1.11	1.14	1.12	6.265
Angle Of Repose (°)	28.02	26.93	27.11	27.35	4.529
Powder Flow (s)	5.40	5.30	5.30	5.33	7.333
Loss on Drying (%)	2.36	2.27	2.38	2.34	7.661
Hygroscopicity (%)	1.59	1.28	1.65	1.51	9.247
Particles < 45µm (%)	-	-	-	0.00 [(2)]	10.000
Homogeneity Index (-)	-	-	-	0.001942 [(3)]	0.971

[(1)] Cohesion Index average of 10 values (values: 267, 267, 265, 268, 283, 298, 275, 295, 267 and 286)

[(2)] Particle size results

Sieve size	% Retained
2800	4.54
2360	23.12
2000	47.32
1700	17.26
1200	6.64
Tray	1.12
< 45µm	0.00

[(3)] Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.21: SeDeM parameter values for Avicel® PH 200 (excipient)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.38	0.37	0.38	0.37	3.738
Tapped Density (g/ml)	0.44	0.44	0.44	0.44	4.395
Inter-particle Porosity (-)	0.40	0.40	0.40	0.40	3.333
Carr's Index (%)	15.00	14.85	15.00	14.95	2.990
Cohesion Index (N)	-	-	-	500.00 (1)	25.000
Hausner Ratio (-)	1.18	1.17	1.18	1.18	6.081
Angle Of Repose (°)	20.96	20.96	20.69	20.87	5.827
Powder Flow (s)	8.10	7.80	7.80	7.90	6.050
Loss on Drying (%)	3.78	3.96	4.34	4.03	5.974
Hygroscopicity (%)	7.92	7.21	5.31	6.81	6.593
Particles < 45µm (%)	-	-	-	8.00 (2)	8.400
Homogeneity Index (-)	-	-	-	0.000913 (3)	0.456

(1) Cohesion Index average of 10 values (values: above maximum capacity of hardness tester values)

(2) Particle size results

Sieve size	% Retained
355	3.14
212	36.21
106	35.85
45	16.80
Tray	8.00
< 45µm	8.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.22: SeDeM parameter values for Cellactose® 80 (excipient)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.45	0.44	0.45	0.45	4.451
Tapped Density (g/ml)	0.54	0.54	0.54	0.54	5.396
Inter-particle Porosity (-)	0.38	0.40	0.40	0.39	3.278
Carr's Index (%)	16.96	17.70	17.86	17.51	3.501
Cohesion Index (N)	-	-	-	372.70 (1)	18.635
Hausner Ratio (-)	1.20	1.22	1.22	1.21	5.959
Angle Of Repose (°)	23.09	22.44	22.97	22.83	5.433
Powder Flow (s)	7.30	7.50	7.70	7.50	6.250
Loss on Drying (%)	5.11	5.11	4.98	5.07	4.933
Hygroscopicity (%)	7.83	8.74	7.08	7.88	6.058
Particles < 45µm (%)	-	-	-	17.18 (2)	6.564
Homogeneity Index (-)	-	-	-	0.006414 (3)	3.207

(1) Cohesion Index average of 10 values (376, 389, 386, 341, 350, 398, 328, 379, 364 and 416)

(2) Particle size results

Sieve size	% Retained
355	0.63
212	27.71
106	44.20
45	10.28
Tray	17.18
< 45µm	17.18

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.23: SeDeM parameter values for Kollidon® VA 64 (excipient)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.34	0.34	0.34	0.34	3.398
Tapped Density (g/ml)	0.43	0.44	0.43	0.43	4.339
Inter-particle Porosity (-)	0.63	0.66	0.63	0.64	5.317
Carr's Index (%)	21.36	22.33	21.36	21.68	4.337
Cohesion Index (N)	-	-	-	346.10 (1)	17.305
Hausner Ratio (-)	1.27	1.29	1.27	1.28	5.744
Angle Of Repose (°)	21.92	22.04	21.92	21.96	5.608
Powder Flow (s)	13.60	12.20	13.80	13.20	3.400
Loss on Drying (%)	1.70	1.58	1.55	1.61	8.392
Hygroscopicity (%)	17.48	12.38	14.71	14.86	2.572
Particles < 45µm (%)	-	-	-	19.64 (2)	6.072
Homogeneity Index (-)	-	-	-	0.006652 (3)	3.326

(1) Cohesion Index average of 10 values (345, 320, 359, 335, 334, 344, 352, 358, 356 and 358)

(2) Particle size results

Sieve size	% Retained
355	0.96
212	7.98
106	32.70
45	38.72
Tray	19.64
< 45µm	19.64

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.24: SeDeM parameter values for MicroceLac® 200 (excipient)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.50	0.50	0.50	0.50	4.967
Tapped Density (g/ml)	0.57	0.57	0.57	0.57	5.704
Inter-particle Porosity (-)	0.26	0.28	0.24	0.26	2.167
Carr's Index (%)	12.87	13.86	12.00	12.91	2.582
Cohesion Index (N)	-	-	-	434.00 (1)	21.700
Hausner Ratio (-)	1.15	1.16	1.14	1.15	6.172
Angle Of Repose (°)	24.51	25.53	24.51	24.85	5.030
Powder Flow (s)	7.10	7.30	7.50	7.30	6.350
Loss on Drying (%)	4.17	4.89	4.55	4.54	5.463
Hygroscopicity (%)	3.83	3.12	3.32	3.42	8.288
Particles < 45µm (%)	-	-	-	8.44 (2)	8.312
Homogeneity Index (-)	-	-	-	0.008596 (3)	4.298

(1) Cohesion Index average of 10 values (497, 418, 420, 425, 410, 448, 417, 435, 435 and 435)

(2) Particle size results

Sieve size	% Retained
355	0.66
212	24.48
106	50.04
45	16.39
Tray	8.44
< 45µm	8.44

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.25: SeDeM parameter values for Tablettose® 80 (excipient)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.60	0.61	0.60	0.60	6.049
Tapped Density (g/ml)	0.76	0.63	0.76	0.71	7.134
Inter-particle Porosity (-)	0.34	0.04	0.34	0.24	2.000
Carr's Index (%)	20.48	2.44	20.48	14.47	2.894
Cohesion Index (N)	-	-	-	326.70 (1)	16.335
Hausner Ratio (-)	1.26	1.03	1.26	1.18	6.066
Angle Of Repose (°)	30.43	31.30	30.63	30.78	3.843
Powder Flow (s)	5.20	5.80	5.40	5.47	7.267
Loss on Drying (%)	4.27	4.40	4.02	4.23	5.772
Hygroscopicity (%)	26.55	22.88	20.00	23.14	0.000
Particles < 45µm (%)	-	-	-	13.10 (2)	7.380
Homogeneity Index (-)	-	-	-	0.003745 (3)	1.873

(1) Cohesion Index average of 10 values (315, 358, 334, 315, 314, 354, 330, 318, 309 and 320)

(2) Particle size results

Sieve size	% Retained
355	10.25
212	27.92
106	31.44
45	17.28
Tray	13.10
< 45µm	13.10

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.26: SeDeM parameter values for 0.5 mm MicroceLac® 200 with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.55	0.55	0.55	0.55	5.495
Tapped Density (g/ml)	0.64	0.64	0.64	0.64	6.410
Inter-particle Porosity (-)	0.26	0.26	0.26	0.26	2.167
Carr's Index (%)	14.29	14.29	14.29	14.29	2.857
Cohesion Index (N)	-	-	-	500.00 (1)	25.000
Hausner Ratio (-)	1.17	1.17	1.17	1.17	6.111
Angle Of Repose (°)	21.67	21.94	21.94	21.85	5.630
Powder Flow (s)	5.60	5.70	5.60	5.63	7.183
Loss on Drying (%)	2.73	2.80	2.46	2.66	7.338
Hygroscopicity (%)	7.77	5.71	6.06	6.51	6.743
Particles < 45µm (%)	-	-	-	1.49 (2)	9.702
Homogeneity Index (-)	-	-	-	0.001382 (3)	0.691

(1) Cohesion Index average of 10 values (values: above maximum capacity of hardness tester)

(2) Particle size results

Sieve size	% Retained
710	1.56
500	32.02
355	23.10
300	6.53
212	5.37
106	20.39
45	9.54
Tray	1.49

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.27: SeDeM parameter values for 1.0 mm MicroceLac® 200 with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.58	0.59	0.58	0.58	5.837
Tapped Density (g/ml)	0.69	0.70	0.69	0.70	6.977
Inter-particle Porosity (-)	0.28	0.28	0.28	0.28	2.333
Carr's Index (%)	16.28	16.47	16.28	16.34	3.269
Cohesion Index (N)	-	-	-	422.20 (1)	21.1
Hausner Ratio (-)	1.19	1.20	1.19	1.20	6.015
Angle Of Repose (°)	21.09	17.10	18.43	18.88	6.225
Powder Flow (s)	5.30	4.80	4.70	4.93	7.533
Loss on Drying (%)	1.79	1.74	1.78	1.77	8.229
Hygroscopicity (%)	3.54	2.83	2.35	2.91	8.547
Particles < 45µm (%)	-	-	-	1.00 (2)	9.800
Homogeneity Index (-)	-	-	-	0.001724 (3)	0.862

(1) Cohesion Index average of 10 values (values: 492, 415, 422,413, 418, 418, 405, 412, 421 and 469)

(2) Particle size results

Sieve size	% Retained
1200	10.28
1000	6.12
850	23.58
710	21.75
355	11.67
212	0.00
106	15.46
45	10.14
Tray	1.00

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.28: SeDeM parameter values for 1.5 mm MicroceLac® 200 with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.63	0.62	0.63	0.63	6.251
Tapped Density (g/ml)	0.72	0.71	0.71	0.72	7.177
Inter-particle Porosity (-)	0.20	0.22	0.20	0.21	1.722
Carr's Index (%)	12.66	13.58	12.50	12.91	2.583
Cohesion Index (N)	-	-	-	486.80 (1)	24.340
Hausner Ratio (-)	1.14	1.16	1.14	1.15	6.172
Angle Of Repose (°)	25.11	24.04	24.21	24.46	5.109
Powder Flow (s)	5.10	4.90	5.30	5.10	7.450
Loss on Drying (%)	4.36	3.41	3.46	3.74	6.258
Hygroscopicity (%)	4.20	3.19	3.66	3.68	8.158
Particles < 45µm (%)	-	-	-	1.59 (2)	9.682
Homogeneity Index (-)	-	-	-	0.001267 (3)	0.634

(1) Cohesion Index average of 10 values (values: 488, 475, 480, 495, 486, 499, 487, 483, 486 and 489)

(2) Particle size results

Sieve size	% Retained
1700	1.36
1200	54.93
1000	4.71
850	10.15
355	4.71
212	1.39
106	14.16
45	7.00
Tray	1.59

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.29: SeDeM parameter values for 2.0 mm MicroceLac® 200 with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.66	0.66	0.67	0.66	6.608
Tapped Density (g/ml)	0.74	0.72	0.72	0.73	7.282
Inter-particle Porosity (-)	0.16	0.14	0.12	0.14	1.167
Carr's Index (%)	10.53	9.21	8.00	9.25	1.849
Cohesion Index (N)	-	-	-	447.60 (1)	22.380
Hausner Ratio (-)	1.12	1.10	1.09	1.10	6.327
Angle Of Repose (°)	21.66	20.78	21.07	21.17	5.766
Powder Flow (s)	4.40	4.20	4.60	4.40	7.800
Loss on Drying (%)	2.69	2.88	3.06	2.87	7.127
Hygroscopicity (%)	4.13	3.88	5.77	4.59	7.703
Particles < 45µm (%)	-	-	-	3.71 (2)	9.258
Homogeneity Index (-)	-	-	-	0.001527 (3)	0.763

(1) Cohesion Index average of 10 values (values: 457, 443, 458, 465, 452, 466, 406, 453, 447 and 429)

(2) Particle size results

Sieve size	% Retained
2360	0.00
2000	0.00
1700	0.33
1200	63.68
355	9.77
212	1.36
106	14.04
45	7.12
Tray	3.71

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.30: SeDeM parameter values for 2.5 mm MicroceLac® 200 with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.63	0.63	0.63	0.63	6.276
Tapped Density (g/ml)	0.72	0.74	0.74	0.73	7.317
Inter-particle Porosity (-)	0.20	0.24	0.24	0.23	1.889
Carr's Index (%)	12.66	15.00	15.00	14.22	2.844
Cohesion Index (N)	-	-	-	475.30 (1)	23.765
Hausner Ratio (-)	1.14	1.18	1.18	1.17	6.113
Angle Of Repose (°)	24.12	23.88	23.72	23.91	5.218
Powder Flow (s)	5.00	4.80	5.00	4.93	7.533
Loss on Drying (%)	1.45	1.66	1.63	1.58	8.420
Hygroscopicity (%)	5.04	3.91	4.00	4.32	7.842
Particles < 45µm (%)	-	-	-	1.94 (2)	9.612
Homogeneity Index (-)	-	-	-	0.001031 (3)	0.516

(1) Cohesion Index average of 10 values (values: 476, 475, 478, 475, 487, 490, 438, 475, 473 and 486)

(2) Particle size results

Sieve size	% Retained
2800	0.00
2360	0.54
2000	4.19
1700	20.67
1200	46.67
355	2.95
212	1.57
106	14.07
45	7.40
Tray	1.94

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.31: SeDeM parameter values for 0.5 mm doxylamine with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.66	0.65	0.66	0.66	6.550
Tapped Density (g/ml)	0.75	0.76	0.75	0.75	7.500
Inter-particle Porosity (-)	0.18	0.22	0.18	0.19	1.611
Carr's Index (%)	11.84	14.29	11.84	12.66	2.531
Cohesion Index (N)	-	-	-	463.10 (1)	23.155
Hausner Ratio (-)	1.13	1.17	1.13	1.15	6.183
Angle Of Repose (°)	18.80	19.78	18.80	19.13	6.174
Powder Flow (s)	3.50	3.50	3.50	3.50	8.250
Loss on Drying (%)	3.16	2.95	3.14	3.08	6.919
Hygroscopicity (%)	10.52	10.17	10.57	10.42	4.790
Particles < 45µm (%)	-	-	-	0.42 (2)	9.916
Homogeneity Index (-)	-	-	-	0.004063 (3)	2.032

(1) Cohesion Index average of 10 values (values: 438, 458, 427, 484, 479, 458, 479, 462, 474 and 472)

(2) Particle size results

Sieve size	% Retained
710	2.04
500	47.29
355	41.94
300	2.08
212	0.62
106	3.31
45	2.31
Tray	0.42

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.32: SeDeM parameter values for 1.0 mm doxylamine with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.67	0.67	0.67	0.67	6.667
Tapped Density (g/ml)	0.78	0.79	0.78	0.79	7.854
Inter-particle Porosity (-)	0.22	0.24	0.22	0.23	1.889
Carr's Index (%)	14.67	16.00	14.67	15.11	3.022
Cohesion Index (N)	-	-	-	360.60 (1)	18.030
Hausner Ratio (-)	1.17	1.19	1.17	1.18	6.073
Angle Of Repose (°)	23.47	23.30	22.71	23.16	5.368
Powder Flow (s)	4.00	4.10	4.10	4.07	7.967
Loss on Drying (%)	1.34	1.45	1.79	1.53	8.474
Hygroscopicity (%)	4.70	5.28	5.15	5.04	7.478
Particles < 45µm (%)	-	-	-	4.64 (2)	9.072
Homogeneity Index (-)	-	-	-	0.003641 (3)	1.820

(1) Cohesion Index average of 10 values (values: 345, 358, 351, 362, 359, 370, 361, 358, 374 and 368)

(2) Particle size results

Sieve size	% Retained
1200	70.46
1000	7.80
850	9.24
710	3.19
355	0.56
212	0.36
106	3.38
45	0.38
Tray	4.64

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.33: SeDeM parameter values for 1.5 mm doxylamine with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.66	0.65	0.66	0.66	6.550
Tapped Density (g/ml)	0.79	0.77	0.79	0.79	7.855
Inter-particle Porosity (-)	0.26	0.24	0.26	0.25	2.111
Carr's Index (%)	17.11	15.58	17.11	16.60	3.320
Cohesion Index (N)	-	-	-	346.90 (1)	17.345
Hausner Ratio (-)	1.21	1.18	1.21	1.20	6.003
Angle Of Repose (°)	24.66	40.16	42.09	35.63	2.873
Powder Flow (s)	5.40	5.20	5.10	5.23	7.383
Loss on Drying (%)	2.39	2.34	2.35	2.36	7.641
Hygroscopicity (%)	8.40	7.53	7.97	7.97	6.017
Particles < 45µm (%)	-	-	-	2.05 (2)	9.590
Homogeneity Index (-)	-	-	-	0.001511 (3)	0.756

(1) Cohesion Index average of 10 values (values: 349, 359, 341, 339, 342, 351, 359, 349, 342 and 338)

(2) Particle size results

Sieve size	% Retained
1700	14.42
1200	58.39
1000	1.33
850	1.43
355	0.44
212	1.21
106	11.19
45	9.54
Tray	2.05

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.34: SeDeM parameter values for 2.0 mm doxylamine with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.69	0.66	0.67	0.67	6.714
Tapped Density (g/ml)	0.83	0.82	0.83	0.83	8.288
Inter-particle Porosity (-)	0.25	0.30	0.30	0.28	2.361
Carr's Index (%)	17.24	19.74	20.00	18.99	3.799
Cohesion Index (N)	-	-	-	299.60 (1)	14.980
Hausner Ratio (-)	1.21	1.25	1.25	1.23	5.884
Angle Of Repose (°)	23.09	23.88	23.70	23.55	5.289
Powder Flow (s)	4.80	4.80	4.80	4.80	7.600
Loss on Drying (%)	1.18	1.02	1.01	1.07	8.930
Hygroscopicity (%)	7.86	8.62	8.71	8.40	5.802
Particles < 45µm (%)	-	-	-	4.41 (2)	9.118
Homogeneity Index (-)	-	-	-	0.000611 (3)	0.306

(1) Cohesion Index average of 10 values (values: 285, 312, 288, 283, 294, 304, 295, 312, 299 and 324)

(2) Particle size results

Sieve size	% Retained
2360	7.01
2000	14.43
1700	15.91
1200	34.63
355	6.99
212	1.09
106	10.05
45	5.48
Tray	4.41

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.35: SeDeM parameter values for 2.5 mm doxylamine with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.64	0.64	0.64	0.64	6.410
Tapped Density (g/ml)	0.79	0.79	0.79	0.79	7.937
Inter-particle Porosity (-)	0.30	0.30	0.30	0.30	2.500
Carr's Index (%)	19.23	19.23	19.23	19.23	3.846
Cohesion Index (N)	-	-	-	235.20 (1)	11.760
Hausner Ratio (-)	1.24	1.24	1.24	1.24	5.873
Angle Of Repose (°)	24.78	23.88	24.78	24.48	5.105
Powder Flow (s)	4.70	4.70	4.70	4.70	7.650
Loss on Drying (%)	1.50	1.05	1.10	1.22	8.784
Hygroscopicity (%)	7.59	8.39	7.69	7.89	6.055
Particles < 45µm (%)	-	-	-	2.55 (2)	9.490
Homogeneity Index (-)	-	-	-	0.000419 (3)	0.210

(1) Cohesion Index average of 10 values (values: 224, 229, 238, 245, 328, 248, 241, 235, 233 and 221)

(2) Particle size results

Sieve size	% Retained
2800	0.86
2360	11.50
2000	14.59
1700	21.00
1200	25.01
355	1.74
212	1.34
106	14.25
45	7.17
Tray	2.55

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.36: SeDeM parameter values for 0.5 mm ibuprofen with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.55	0.54	0.54	0.55	5.455
Tapped Density (g/ml)	0.68	0.68	0.68	0.68	6.757
Inter-particle Porosity (-)	0.34	0.36	0.36	0.35	2.944
Carr's Index (%)	18.68	19.57	19.57	19.27	3.854
Cohesion Index (N)	-	-	-	388.90 (1)	19.445
Hausner Ratio (-)	1.23	1.24	1.24	1.24	5.871
Angle Of Repose (°)	22.99	24.78	24.04	23.94	5.213
Powder Flow (s)	5.60	5.60	5.50	5.57	7.217
Loss on Drying (%)	2.56	2.01	2.27	2.28	7.719
Hygroscopicity (%)	7.69	6.16	7.49	7.11	6.443
Particles < 45µm (%)	-	-	-	0.39 (2)	9.922
Homogeneity Index (-)	-	-	-	0.000277 (3)	0.139

(1) Cohesion Index average of 10 values (values: 376, 395, 387, 395, 374, 395, 384, 397, 399 and 387)

(2) Particle size results

Sieve size	% Retained
710	8.46
500	44.69
355	25.37
300	6.47
212	2.42
106	9.72
45	2.47
Tray	0.39

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.37: SeDeM parameter values for 1.0 mmi ibuprofen with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.56	0.57	0.56	0.56	5.639
Tapped Density (g/ml)	0.67	0.69	0.68	0.68	6.773
Inter-particle Porosity (-)	0.28	0.31	0.30	0.30	2.472
Carr's Index (%)	15.73	17.61	16.85	16.73	3.347
Cohesion Index (N)	-	-	-	353.20 (1)	17.660
Hausner Ratio (-)	1.19	1.21	1.20	1.20	5.996
Angle Of Repose (°)	22.80	22.95	22.80	22.85	5.431
Powder Flow (s)	4.40	4.60	4.50	4.50	7.750
Loss on Drying (%)	1.49	1.76	1.72	1.66	8.345
Hygroscopicity (%)	2.61	2.12	2.92	2.55	8.725
Particles < 45µm (%)	-	-	-	2.99 (2)	9.402
Homogeneity Index (-)	-	-	-	0.000626 (3)	0.313

(1) Cohesion Index average of 10 values (values: 376, 367, 330, 345, 353, 355, 333, 342, 344 and 387)

(2) Particle size results

Sieve size	% Retained
1200	30.74
1000	8.94
850	17.95
710	16.82
355	5.08
212	0.76
106	9.07
45	7.64
Tray	2.99

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.38: SeDeM parameter values for 1.5 mm ibuprofen with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.56	0.57	0.57	0.57	5.661
Tapped Density (g/ml)	0.68	0.68	0.68	0.68	6.849
Inter-particle Porosity (-)	0.32	0.30	0.30	0.31	2.556
Carr's Index (%)	17.98	17.05	17.05	17.36	3.471
Cohesion Index (N)	-	-	-	373.90 (1)	18.695
Hausner Ratio (-)	1.22	1.21	1.21	1.21	5.967
Angle Of Repose (°)	23.25	23.56	23.40	23.41	5.319
Powder Flow (s)	4.60	4.80	4.70	4.70	7.650
Loss on Drying (%)	3.22	2.16	2.00	2.46	7.537
Hygroscopicity (%)	2.58	3.43	2.30	2.77	8.615
Particles < 45µm (%)	-	-	-	1.36 (2)	9.728
Homogeneity Index (-)	-	-	-	0.001509 (3)	0.754

(1) Cohesion Index average of 10 values (values: 361, 357, 382, 345, 382, 378, 406, 386, 378 and 364)

(2) Particle size results

Sieve size	% Retained
1700	3.12
1200	58.68
1000	5.97
850	6.57
355	4.38
212	0.90
106	11.20
45	8.00
Tray	1.36

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.39: SeDeM parameter values for 2.0 mm ibuprofen with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.54	0.54	0.54	0.54	5.376
Tapped Density (g/ml)	0.67	0.67	0.67	0.67	6.667
Inter-particle Porosity (-)	0.36	0.36	0.36	0.36	3.000
Carr's Index (%)	19.35	19.35	19.35	19.35	3.871
Cohesion Index (N)	-	-	-	353.60 (1)	17.680
Hausner Ratio (-)	1.24	1.24	1.24	1.24	5.867
Angle Of Repose (°)	23.50	22.80	23.65	23.32	5.337
Powder Flow (s)	4.80	4.80	4.80	4.80	7.600
Loss on Drying (%)	1.65	1.71	1.89	1.75	8.252
Hygroscopicity (%)	3.77	5.23	4.80	4.60	7.700
Particles < 45µm (%)	-	-	-	1.79 (2)	9.642
Homogeneity Index (-)	-	-	-	0.001090 (3)	0.545

(1) Cohesion Index average of 10 values (values: 363, 354, 361, 327, 362, 362, 333, 330, 379 and 365)

(2) Particle size results

Sieve size	% Retained
2360	0.00
2000	1.63
1700	18.31
1200	48.76
355	8.13
212	1.09
106	12.97
45	7.33
Tray	1.79

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.40: SeDeM parameter values for 2.5 mm ibuprofen with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.56	0.56	0.56	0.56	5.556
Tapped Density (g/ml)	0.67	0.67	0.67	0.67	6.667
Inter-particle Porosity (-)	0.30	0.30	0.30	0.30	2.500
Carr's Index (%)	16.67	16.67	16.67	16.67	3.333
Cohesion Index (N)	-	-	-	358.80 (1)	17.940
Hausner Ratio (-)	1.20	1.20	1.20	1.20	6.000
Angle Of Repose (°)	23.35	23.89	23.89	23.71	5.259
Powder Flow (s)	5.00	5.10	4.80	4.97	7.517
Loss on Drying (%)	1.91	1.75	1.50	1.72	8.282
Hygroscopicity (%)	6.44	7.69	5.83	6.65	6.673
Particles < 45µm (%)	-	-	-	4.36 (2)	9.128
Homogeneity Index (-)	-	-	-	0.000461 (3)	0.231

(1) Cohesion Index average of 10 values (values: 377, 324, 401, 360, 375, 337, 403, 339, 329 and 343)

(2) Particle size results

Sieve size	% Retained
2800	1.92
2360	5.79
2000	13.79
1700	27.90
1200	26.55
355	4.07
212	1.12
106	10.18
45	4.33
Tray	4.36

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.41: SeDeM parameter values for 0.5 mm paracetamol with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.56	0.56	0.56	0.56	5.618
Tapped Density (g/ml)	0.63	0.62	0.63	0.62	6.224
Inter-particle Porosity (-)	0.18	0.16	0.18	0.17	1.444
Carr's Index (%)	10.11	8.99	10.11	9.74	1.948
Cohesion Index (N)	-	-	-	500.00 (1)	25.000
Hausner Ratio (-)	1.11	1.10	1.11	1.11	6.307
Angle Of Repose (°)	20.11	21.09	21.09	20.77	5.847
Powder Flow (s)	4.10	3.90	3.90	3.97	8.017
Loss on Drying (%)	3.84	3.15	3.44	3.48	6.521
Hygroscopicity (%)	4.49	4.91	4.10	4.50	7.750
Particles < 45µm (%)	-	-	-	0.02 (2)	9.996
Homogeneity Index (-)	-	-	-	0.013287 (3)	6.643

(1) Cohesion Index average of 10 values (values: above maximum capacity of hardness tester)

(2) Particle size results

Sieve size	% Retained
710	9.66
500	76.00
355	9.31
300	0.95
212	0.70
106	1.20
45	0.02
Tray	2.10

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.42: SeDeM parameter values for 1.0 mm paracetamol with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.59	0.59	0.59	0.59	5.882
Tapped Density (g/ml)	0.69	0.61	0.69	0.67	6.662
Inter-particle Porosity (-)	0.26	0.06	0.26	0.19	1.611
Carr's Index (%)	15.29	3.53	15.29	11.37	2.275
Cohesion Index (N)	-	-	-	451.20 (1)	22.560
Hausner Ratio (-)	1.18	1.04	1.18	1.13	6.225
Angle Of Repose (°)	22.50	21.94	22.09	22.18	5.564
Powder Flow (s)	3.70	3.80	3.90	3.80	8.100
Loss on Drying (%)	2.23	2.35	2.22	2.26	7.736
Hygroscopicity (%)	6.19	6.83	5.70	6.24	6.880
Particles < 45µm (%)	-	-	-	4.55 (2)	9.090
Homogeneity Index (-)	-	-	-	0.000600 (3)	0.300

(1) Cohesion Index average of 10 values (values: 412, 470, 490, 485, 433, 476, 493, 470, 358 and 425)

(2) Particle size results

Sieve size	% Retained
1200	28.78
1000	9.96
850	19.05
710	13.94
355	13.61
212	1.06
106	7.07
45	1.99
Tray	4.55

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.43: SeDeM parameter values for 1.5 mm paracetamol with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.57	0.59	0.59	0.58	5.837
Tapped Density (g/ml)	0.68	0.68	0.70	0.69	6.914
Inter-particle Porosity (-)	0.28	0.24	0.28	0.27	2.222
Carr's Index (%)	16.09	14.12	16.47	15.56	3.112
Cohesion Index (N)	-	-	-	427.20 (1)	21.360
Hausner Ratio (-)	1.19	1.16	1.20	1.18	6.052
Angle Of Repose (°)	22.95	22.68	23.25	22.96	5.408
Powder Flow (s)	4.00	4.00	4.10	4.03	7.983
Loss on Drying (%)	2.44	2.48	2.04	2.32	7.676
Hygroscopicity (%)	7.45	7.26	6.50	7.07	6.465
Particles < 45µm (%)	-	-	-	1.33 (2)	9.734
Homogeneity Index (-)	-	-	-	0.002771 (3)	1.386

(1) Cohesion Index average of 10 values (values: 446, 450, 438, 423, 428, 378, 439, 397, 451 and 422)

(2) Particle size results

Sieve size	% Retained
1700	18.49
1200	53.59
1000	4.25
850	6.04
355	2.12
212	1.16
106	8.43
45	4.58
Tray	1.33

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.44: SeDeM parameter values for 2.0 mm paracetamol with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.58	0.60	0.59	0.59	5.883
Tapped Density (g/ml)	0.71	0.71	0.70	0.71	7.109
Inter-particle Porosity (-)	0.32	0.28	0.28	0.29	2.444
Carr's Index (%)	18.60	16.67	16.47	17.25	3.449
Cohesion Index (N)	-	-	-	488.40 (1)	24.420
Hausner Ratio (-)	1.23	1.20	1.20	1.21	5.971
Angle Of Repose (°)	21.66	23.30	23.40	22.79	5.442
Powder Flow (s)	3.90	3.90	3.90	3.90	8.050
Loss on Drying (%)	2.07	2.16	2.22	2.15	7.847
Hygroscopicity (%)	5.82	6.59	6.51	6.31	6.847
Particles < 45µm (%)	-	-	-	1.50 (2)	9.700
Homogeneity Index (-)	-	-	-	0.001487 (3)	0.743

(1) Cohesion Index average of 10 values (values: 489, 498, 487, 469, 489, 487, 498, 485, 493 and 489)

(2) Particle size results

Sieve size	% Retained
2360	0.07
2000	1.86
1700	24.68
1200	53.64
355	2.36
212	0.73
106	8.95
45	6.22
Tray	1.50

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.45: SeDeM parameter values for 2.5 mm paracetamol with Kollidon® VA 64 pellets (intermediate blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.57	0.58	0.58	0.58	5.770
Tapped Density (g/ml)	0.68	0.68	0.68	0.68	6.788
Inter-particle Porosity (-)	0.30	0.24	0.24	0.26	2.167
Carr's Index (%)	17.05	13.95	13.95	14.98	2.997
Cohesion Index (N)	-	-	-	419.40 (1)	20.970
Hausner Ratio (-)	1.21	1.16	1.16	1.18	6.078
Angle Of Repose (°)	24.61	24.78	24.28	24.56	5.089
Powder Flow (s)	4.40	4.30	4.40	4.37	7.817
Loss on Drying (%)	2.19	2.68	2.38	2.42	7.583
Hygroscopicity (%)	3.93	2.73	4.85	3.84	8.082
Particles < 45µm (%)	-	-	-	1.43 (2)	9.714
Homogeneity Index (-)	-	-	-	0.000849 (3)	0.424

(1) Cohesion Index average of 10 values (values: 405, 418, 438, 438, 377, 425, 438, 424, 437 and 394)

(2) Particle size results

Sieve size	% Retained
2800	3.96
2360	18.58
2000	40.16
1700	18.62
1200	5.78
355	0.17
212	0.47
106	5.55
45	5.29
Tray	1.43

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.46: SeDeM parameter values for 0.5 mm MicroceLac® 200 pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.55	0.56	0.56	0.55	5.535
Tapped Density (g/ml)	0.68	0.68	0.68	0.68	6.757
Inter-particle Porosity (-)	0.34	0.32	0.32	0.33	2.722
Carr's Index (%)	18.68	17.78	17.78	18.08	3.616
Cohesion Index (N)	-	-	-	184.10 (1)	9.205
Hausner Ratio (-)	1.23	1.22	1.22	1.22	5.931
Angle Of Repose (°)	25.16	24.12	24.12	24.47	5.107
Powder Flow (s)	11.70	11.90	11.90	11.83	4.083
Loss on Drying (%)	4.06	3.07	3.08	3.40	6.595
Hygroscopicity (%)	8.45	7.35	8.17	7.99	6.005
Particles < 45µm (%)	-	-	-	8.76 (2)	8.248
Homogeneity Index (-)	-	-	-	0.001128 (3)	0.564

(1) Cohesion Index average of 10 values (values: 186, 179, 175, 201, 174, 165, 175, 207, 175 and 204)

(2) Particle size results

Sieve size	% Retained
710	1.13
500	33.20
355	18.98
300	3.60
212	2.83
106	17.82
45	13.69
Tray	8.76

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.47: SeDeM parameter values for 1.0 mm MicroceLac® 200 pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.61	0.60	0.60	0.60	6.049
Tapped Density (g/ml)	0.71	0.71	0.71	0.71	7.143
Inter-particle Porosity (-)	0.24	0.26	0.26	0.25	2.111
Carr's Index (%)	14.63	15.66	15.66	15.32	3.064
Cohesion Index (N)	-	-	-	247.50 (1)	12.375
Hausner Ratio (-)	1.17	1.19	1.19	1.18	6.063
Angle Of Repose (°)	25.33	26.39	25.50	25.74	4.853
Powder Flow (s)	10.50	10.10	10.20	10.27	4.867
Loss on Drying (%)	2.96	2.80	3.01	2.92	7.079
Hygroscopicity (%)	7.84	7.59	6.97	7.47	6.267
Particles < 45µm (%)	-	-	-	11.35 (2)	7.730
Homogeneity Index (-)	-	-	-	0.000479 (3)	0.240

(1) Cohesion Index average of 10 values (values: 250, 249, 240, 242, 245, 253, 248, 250, 251 and 247)

(2) Particle size results

Sieve size	% Retained
1200	6.57
1000	5.66
850	16.74
710	18.54
355	11.72
212	1.32
106	14.94
45	13.15
Tray	11.35

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.48: SeDeM parameter values for 1.5 mm MicroceLac® 200 pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.63	0.63	0.63	0.63	6.250
Tapped Density (g/ml)	0.74	0.75	0.75	0.74	7.426
Inter-particle Porosity (-)	0.24	0.26	0.26	0.25	2.111
Carr's Index (%)	15.00	16.25	16.25	15.83	3.167
Cohesion Index (N)	-	-	-	267.00 (1)	13.350
Hausner Ratio (-)	1.18	1.19	1.19	1.19	6.039
Angle Of Repose (°)	25.64	24.04	25.46	25.05	4.990
Powder Flow (s)	8.70	7.60	7.40	7.90	6.050
Loss on Drying (%)	2.53	2.98	2.97	2.83	7.174
Hygroscopicity (%)	6.75	6.13	6.75	6.54	6.728
Particles < 45µm (%)	-	-	-	7.50 (2)	8.500
Homogeneity Index (-)	-	-	-	0.000588 (3)	0.294

(1) Cohesion Index average of 10 values (values: 264, 250, 248, 267, 280, 283, 274, 268, 249 and 287)

(2) Particle size results

Sieve size	% Retained
1700	0.80
1200	38.17
1000	6.00
850	10.60
355	5.43
212	1.57
106	16.53
45	13.40
Tray	7.50

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.49: SeDeM parameter values for 2.0 mm MicroceLac® 200 pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.60	0.60	0.60	0.60	6.024
Tapped Density (g/ml)	0.71	0.71	0.71	0.71	7.143
Inter-particle Porosity (-)	0.26	0.26	0.26	0.26	2.167
Carr's Index (%)	15.66	15.66	15.66	15.66	3.133
Cohesion Index (N)	-	-	-	286.70 (1)	14.335
Hausner Ratio (-)	1.19	1.19	1.19	1.19	6.048
Angle Of Repose (°)	23.35	25.50	23.81	24.22	5.157
Powder Flow (s)	8.10	8.00	8.10	8.07	5.967
Loss on Drying (%)	2.21	2.62	2.71	2.51	7.490
Hygroscopicity (%)	6.21	7.08	7.27	6.85	6.573
Particles < 45µm (%)	-	-	-	6.81 (2)	8.638
Homogeneity Index (-)	-	-	-	0.001094 (3)	0.547

(1) Cohesion Index average of 10 values (values: 293, 285, 285, 334, 294, 255, 278, 268, 288 and 287)

(2) Particle size results

Sieve size	% Retained
2360	0.33
2000	0.20
1700	0.37
1200	57.36
355	6.01
212	1.56
106	19.43
45	7.94
Tray	6.81

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.50: SeDeM parameter values for 2.5 mm MicroceLac® 200 pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.63	0.63	0.63	0.63	6.250
Tapped Density (g/ml)	0.76	0.76	0.76	0.76	7.576
Inter-particle Porosity (-)	0.28	0.28	0.28	0.28	2.333
Carr's Index (%)	17.50	17.50	17.50	17.50	3.500
Cohesion Index (N)	-	-	-	262.40 (1)	13.120
Hausner Ratio (-)	1.21	1.21	1.21	1.21	5.960
Angle Of Repose (°)	24.38	24.21	24.38	24.32	5.136
Powder Flow (s)	8.80	7.40	7.10	7.77	6.117
Loss on Drying (%)	2.21	2.62	2.71	2.51	7.490
Hygroscopicity (%)	6.21	7.08	7.27	6.85	6.573
Particles < 45µm (%)	-	-	-	6.31 (2)	8.738
Homogeneity Index (-)	-	-	-	0.000659 (3)	0.329

(1) Cohesion Index average of 10 values (values: 285, 268, 275, 294, 245, 266, 248, 258, 236 and 249)

(2) Particle size results

Sieve size	% Retained
2800	0.00
2360	0.23
2000	3.59
1700	19.57
1200	39.22
355	2.06
212	1.63
106	14.32
45	13.06
Tray	6.31

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.51: SeDeM parameter values for 0.5 mm doxylamine pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.71	0.72	0.71	0.72	7.177
Tapped Density (g/ml)	0.83	0.83	0.83	0.83	8.333
Inter-particle Porosity (-)	0.20	0.18	0.20	0.19	1.611
Carr's Index (%)	14.29	13.04	14.29	13.87	2.774
Cohesion Index (N)	-	-	-	177.80 (1)	8.890
Hausner Ratio (-)	1.17	1.15	1.17	1.16	6.130
Angle Of Repose (°)	25.25	26.19	25.25	25.56	4.888
Powder Flow (s)	4.10	4.00	3.90	4.00	8.000
Loss on Drying (%)	5.03	5.93	5.14	5.37	4.635
Hygroscopicity (%)	5.61	7.77	5.00	6.13	6.937
Particles < 45µm (%)	-	-	-	5.90 (2)	8.820
Homogeneity Index (-)	-	-	-	0.000271 (3)	0.136

(1) Cohesion Index average of 10 values (values: 132, 157, 139, 252, 138, 148, 248, 267, 259 and 238)

(2) Particle size results

Sieve size	% Retained
710	2.77
500	42.77
355	39.57
300	1.85
212	0.49
106	3.23
45	3.43
Tray	5.90

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.52: SeDeM parameter values for 1.0 mm doxylamine pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.72	0.71	0.72	0.72	7.212
Tapped Density (g/ml)	0.83	0.83	0.83	0.83	8.333
Inter-particle Porosity (-)	0.18	0.20	0.18	0.19	1.556
Carr's Index (%)	13.04	14.29	13.04	13.46	2.692
Cohesion Index (N)	-	-	-	208.50 (1)	10.425
Hausner Ratio (-)	1.15	1.17	1.15	1.16	6.148
Angle Of Repose (°)	25.11	25.29	24.38	24.93	5.015
Powder Flow (s)	4.90	4.80	4.90	4.87	7.567
Loss on Drying (%)	3.20	2.28	2.52	2.67	7.333
Hygroscopicity (%)	5.00	6.56	6.31	5.96	7.022
Particles < 45µm (%)	-	-	-	6.97 (2)	8.606
Homogeneity Index (-)	-	-	-	0.001697 (3)	0.849

(1) Cohesion Index average of 10 values (values: 187, 193, 207, 209, 198, 252, 213, 208, 207 and 211)

(2) Particle size results

Sieve size	% Retained
1200	60.16
1000	7.99
850	9.60
710	4.37
355	2.04
212	0.43
106	3.71
45	4.73
Tray	6.97

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.53: SeDeM parameter values for 1.5 mm doxylamine pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.65	0.66	0.65	0.65	6.522
Tapped Density (g/ml)	0.81	0.83	0.81	0.82	8.154
Inter-particle Porosity (-)	0.30	0.32	0.30	0.31	2.556
Carr's Index (%)	19.48	21.05	19.48	20.00	4.001
Cohesion Index (N)	-	-	-	246.70 (1)	12.335
Hausner Ratio (-)	1.24	1.27	1.24	1.25	5.833
Angle Of Repose (°)	28.61	28.81	29.34	28.92	4.216
Powder Flow (s)	10.20	11.30	10.40	10.63	4.683
Loss on Drying (%)	1.96	1.69	1.78	1.81	8.187
Hygroscopicity (%)	10.42	10.00	10.78	10.40	4.800
Particles < 45µm (%)	-	-	-	8.17 (2)	8.366
Homogeneity Index (-)	-	-	-	0.000888 (3)	0.444

(1) Cohesion Index average of 10 values (values: 255, 252, 249, 252, 231, 246, 251, 248, 246 and 237)

(2) Particle size results

Sieve size	% Retained
1700	16.81
1200	47.02
1000	1.17
850	0.94
355	0.30
212	0.54
106	10.88
45	14.17
Tray	8.17

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.54: SeDeM parameter values for 2.0 mm doxylamine pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.69	0.69	0.69	0.69	6.944
Tapped Density (g/ml)	0.86	0.85	0.86	0.86	8.572
Inter-particle Porosity (-)	0.28	0.26	0.28	0.27	2.278
Carr's Index (%)	19.44	18.06	19.44	18.98	3.796
Cohesion Index (N)	-	-	-	184.60 (1)	9.230
Hausner Ratio (-)	1.24	1.22	1.24	1.23	5.885
Angle Of Repose (°)	30.89	30.38	31.11	30.79	3.841
Powder Flow (s)	7.30	7.80	8.60	7.90	6.050
Loss on Drying (%)	3.24	3.06	2.46	2.92	7.076
Hygroscopicity (%)	7.80	8.26	6.25	7.44	6.282
Particles < 45µm (%)	-	-	-	9.24 (2)	8.152
Homogeneity Index (-)	-	-	-	0.000485 (3)	0.243

(1) Cohesion Index average of 10 values (values: 192, 186, 194, 162, 179, 196, 199, 176, 188 and 174)

(2) Particle size results

Sieve size	% Retained
2360	6.08
2000	10.75
1700	11.39
1200	30.97
355	14.75
212	0.74
106	8.53
45	7.56
Tray	9.24

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.55: SeDeM parameter values for 2.5 mm doxylamine pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.66	0.66	0.65	0.66	6.550
Tapped Density (g/ml)	0.79	0.79	0.81	0.80	7.979
Inter-particle Porosity (-)	0.26	0.26	0.30	0.27	2.278
Carr's Index (%)	17.11	17.11	19.48	17.90	3.579
Cohesion Index (N)	-	-	-	269.40 [(1)]	13.470
Hausner Ratio (-)	1.21	1.21	1.24	1.22	5.939
Angle Of Repose (°)	29.95	29.95	29.01	29.64	4.072
Powder Flow (s)	9.70	9.90	10.40	10.00	5.000
Loss on Drying (%)	1.90	1.26	1.93	1.70	8.302
Hygroscopicity (%)	8.08	7.14	7.08	7.43	6.283
Particles < 45µm (%)	-	-	-	13.07 [(2)]	7.386
Homogeneity Index (-)	-	-	-	0.000251 [(3)]	0.126

[(1)] Cohesion Index average of 10 values (values: 283, 252, 249, 237, 250, 318, 297, 237, 281 and 290)

[(2)] Particle size results

Sieve size	% Retained
2800	0.92
2360	13.76
2000	14.22
1700	14.85
1200	20.30
355	2.18
212	0.92
106	10.17
45	9.60
Tray	13.07

[(3)] Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.56: SeDeM parameter values for 0.5 mm ibuprofen pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.59	0.59	0.59	0.59	5.882
Tapped Density (g/ml)	0.71	0.71	0.71	0.71	7.143
Inter-particle Porosity (-)	0.30	0.30	0.30	0.30	2.500
Carr's Index (%)	17.65	17.65	17.65	17.65	3.529
Cohesion Index (N)	-	-	-	171.10 (1)	8.555
Hausner Ratio (-)	1.21	1.21	1.21	1.21	5.952
Angle Of Repose (°)	22.25	22.83	0.00	15.03	6.994
Powder Flow (s)	6.40	6.10	6.50	6.33	6.833
Loss on Drying (%)	3.53	3.13	2.72	3.13	6.873
Hygroscopicity (%)	3.17	3.27	3.22	3.22	8.390
Particles < 45µm (%)	-	-	-	7.88 (2)	8.424
Homogeneity Index (-)	-	-	-	0.001462 (3)	0.731

(1) Cohesion Index average of 10 values (values: 142, 196, 179, 146, 150, 169, 165, 181, 163 and 220)

(2) Particle size results

Sieve size	% Retained
710	4.82
500	34.11
355	23.11
300	2.79
212	2.66
106	12.53
45	12.10
Tray	7.88

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.57: SeDeM parameter values for 1.0 mm ibuprofen pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.57	0.57	0.58	0.58	5.769
Tapped Density (g/ml)	0.69	0.69	0.69	0.69	6.944
Inter-particle Porosity (-)	0.30	0.30	0.28	0.29	2.444
Carr's Index (%)	17.24	17.24	16.28	16.92	3.384
Cohesion Index (N)	-	-	-	220.90 (1)	11.045
Hausner Ratio (-)	1.21	1.21	1.19	1.20	5.988
Angle Of Repose (°)	24.78	23.56	24.78	24.37	5.126
Powder Flow (s)	5.50	5.50	5.80	5.60	7.200
Loss on Drying (%)	2.71	2.25	2.27	2.41	7.592
Hygroscopicity (%)	1.34	2.44	1.34	1.71	9.147
Particles < 45µm (%)	-	-	-	11.70 (2)	7.660
Homogeneity Index (-)	-	-	-	0.000645 (3)	0.323

(1) Cohesion Index average of 10 values (values: 211, 236, 224, 236, 217, 225, 217, 227, 232 and 184)

(2) Particle size results

Sieve size	% Retained
1200	34.39
1000	7.85
850	12.32
710	13.25
355	4.61
212	1.41
106	10.36
45	4.10
Tray	11.70

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.58: SeDeM parameter values for 1.5 mm ibuprofen pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.58	0.59	0.59	0.59	5.860
Tapped Density (g/ml)	0.71	0.71	0.71	0.71	7.143
Inter-particle Porosity (-)	0.32	0.30	0.30	0.31	2.556
Carr's Index (%)	18.60	17.65	17.65	17.97	3.593
Cohesion Index (N)	-	-	-	196.20 (1)	9.810
Hausner Ratio (-)	1.23	1.21	1.21	1.22	5.937
Angle Of Repose (°)	22.53	23.30	22.99	22.94	5.412
Powder Flow (s)	5.70	5.30	5.50	5.50	7.250
Loss on Drying (%)	6.37	5.62	4.11	5.36	4.635
Hygroscopicity (%)	1.59	1.62	1.93	1.71	9.143
Particles < 45µm (%)	-	-	-	12.06 (2)	7.588
Homogeneity Index (-)	-	-	-	0.000977 (3)	0.489

(1) Cohesion Index average of 10 values (values: 199, 198, 193, 205, 203, 192, 195, 187, 193 and 197)

(2) Particle size results

Sieve size	% Retained
1700	2.62
1200	49.73
1000	4.98
850	7.41
355	6.21
212	1.59
106	14.65
45	0.73
Tray	12.06

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.29: SeDeM parameter values for 2.0 mm ibuprofen pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.59	0.58	0.58	0.58	5.837
Tapped Density (g/ml)	0.71	0.71	0.71	0.71	7.143
Inter-particle Porosity (-)	0.30	0.32	0.32	0.31	2.611
Carr's Index (%)	17.65	18.60	18.60	18.29	3.657
Cohesion Index (N)	-	-	-	213.10 (1)	10.655
Hausner Ratio (-)	1.21	1.23	1.23	1.22	5.921
Angle Of Repose (°)	22.10	22.25	22.10	22.15	5.570
Powder Flow (s)	7.00	7.00	6.70	6.90	6.550
Loss on Drying (%)	2.78	2.32	2.38	2.49	7.508
Hygroscopicity (%)	3.40	3.98	4.28	3.89	8.057
Particles < 45µm (%)	-	-	-	6.58 (2)	8.684
Homogeneity Index (-)	-	-	-	0.000688 (3)	0.344

(1) Cohesion Index average of 10 values (values: 217, 208, 212, 216, 197, 235, 215, 214, 203 and 214)

(2) Particle size results

Sieve size	% Retained
2360	0.17
2000	0.63
1700	5.92
1200	42.51
355	14.08
212	1.72
106	14.61
45	13.79
Tray	6.58

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.60: SeDeM parameter values for 2.5 mm ibuprofen pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.57	0.60	0.59	0.59	5.861
Tapped Density (g/ml)	0.71	0.71	0.71	0.71	7.143
Inter-particle Porosity (-)	0.34	0.28	0.30	0.31	2.556
Carr's Index (%)	19.54	16.67	17.65	17.95	3.590
Cohesion Index (N)	-	-	-	222.20 (1)	11.110
Hausner Ratio (-)	1.24	1.20	1.21	1.22	5.937
Angle Of Repose (°)	24.55	22.83	23.63	23.67	5.266
Powder Flow (s)	6.40	6.70	6.70	6.60	6.700
Loss on Drying (%)	2.04	2.08	2.03	2.05	7.949
Hygroscopicity (%)	0.20	0.42	0.34	0.32	9.840
Particles < 45µm (%)	-	-	-	7.51 (2)	8.498
Homogeneity Index (-)	-	-	-	0.000365 (3)	0.182

(1) Cohesion Index average of 10 values (values: 210, 227, 246, 228, 200, 223, 215, 221, 238 and 214)

(2) Particle size results

Sieve size	% Retained
2800	0.36
2360	2.05
2000	8.24
1700	21.32
1200	25.89
355	4.30
212	1.92
106	16.45
45	11.95
Tray	7.51

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.61: SeDeM parameter values for 0.5 mm paracetamol pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.63	0.62	0.63	0.62	6.224
Tapped Density (g/ml)	0.70	0.70	0.70	0.70	7.042
Inter-particle Porosity (-)	0.18	0.20	0.18	0.19	1.556
Carr's Index (%)	11.25	12.35	11.25	11.62	2.323
Cohesion Index (N)	-	-	-	85.30 (1)	4.265
Hausner Ratio (-)	1.13	1.14	1.13	1.13	6.228
Angle Of Repose (°)	24.12	22.83	22.99	23.31	5.337
Powder Flow (s)	3.90	3.80	3.90	3.87	8.067
Loss on Drying (%)	3.72	3.12	3.02	3.29	6.712
Hygroscopicity (%)	1.14	1.91	1.67	1.57	9.213
Particles < 45µm (%)	-	-	-	3.50 (2)	9.300
Homogeneity Index (-)	-	-	-	0.006683 (3)	3.341

(1) Cohesion Index average of 10 values (values: 87, 87, 90, 78, 90, 79, 81, 85, 84 and 92)

(2) Particle size results

Sieve size	% Retained
710	9.17
500	66.72
355	11.39
300	0.97
212	0.90
106	3.20
45	4.17
Tray	3.50

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.62: SeDeM parameter values for 1.0 mm paracetamol pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.61	0.63	0.62	0.62	6.173
Tapped Density (g/ml)	0.74	0.74	0.74	0.74	7.353
Inter-particle Porosity (-)	0.28	0.24	0.26	0.26	2.167
Carr's Index (%)	17.07	15.00	16.05	16.04	3.208
Cohesion Index (N)	-	-	-	156.50 (1)	7.825
Hausner Ratio (-)	1.21	1.18	1.19	1.19	6.029
Angle Of Repose (°)	23.88	23.96	23.79	23.88	5.224
Powder Flow (s)	4.90	4.90	5.20	5.00	7.500
Loss on Drying (%)	2.40	2.21	2.00	2.20	7.796
Hygroscopicity (%)	8.14	7.60	8.54	8.09	5.953
Particles < 45µm (%)	-	-	-	3.01 (2)	9.398
Homogeneity Index (-)	-	-	-	0.002783 (3)	1.392

(1) Cohesion Index average of 10 values (values: 169, 135, 160, 169, 138, 154, 172, 163, 149 and 156)

(2) Particle size results

Sieve size	% Retained
1200	12.28
1000	4.37
850	57.81
710	6.13
355	4.78
212	0.66
106	6.00
45	4.98
Tray	3.01

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.63: SeDeM parameter values for 1.5 mm paracetamol pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.60	0.60	0.60	0.60	6.000
Tapped Density (g/ml)	0.72	0.72	0.72	0.72	7.246
Inter-particle Porosity (-)	0.30	0.28	0.28	0.29	2.389
Carr's Index (%)	17.86	16.87	16.87	17.20	3.439
Cohesion Index (N)	-	-	-	232.20 (1)	11.610
Hausner Ratio (-)	1.22	1.20	1.20	1.21	5.974
Angle Of Repose (°)	24.04	24.38	23.30	23.91	5.218
Powder Flow (s)	6.00	5.20	5.50	5.57	7.217
Loss on Drying (%)	2.26	2.15	2.23	2.21	7.787
Hygroscopicity (%)	5.15	5.88	5.46	5.50	7.252
Particles < 45µm (%)	-	-	-	5.54 (2)	8.892
Homogeneity Index (-)	-	-	-	0.001043 (3)	0.522

(1) Cohesion Index average of 10 values (values: 268, 280, 191, 207, 218, 218, 197, 274, 253 and 215)

(2) Particle size results

Sieve size	% Retained
1700	10.31
1200	41.19
1000	5.04
850	6.84
355	2.74
212	1.40
106	16.48
45	10.47
Tray	5.54

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.64: SeDeM parameter values for 2.0 mm paracetamol pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.59	0.60	0.72	0.64	6.384
Tapped Density (g/ml)	0.72	0.72	0.72	0.72	7.246
Inter-particle Porosity (-)	0.32	0.28	0.00	0.20	1.667
Carr's Index (%)	18.82	16.87	0.00	11.90	2.379
Cohesion Index (N)	-	-	-	221.70 (1)	11.085
Hausner Ratio (-)	1.23	1.20	1.00	1.14	6.184
Angle Of Repose (°)	26.38	25.11	25.46	25.65	4.869
Powder Flow (s)	6.30	6.30	6.20	6.27	6.867
Loss on Drying (%)	3.53	2.23	2.28	2.68	7.317
Hygroscopicity (%)	5.67	4.96	5.54	5.39	7.305
Particles < 45µm (%)	-	-	-	6.44 (2)	8.712
Homogeneity Index (-)	-	-	-	0.000883 (3)	0.441

(1) Cohesion Index average of 10 values (values: 184, 243, 206, 261, 211, 214, 205, 217, 253 and 223)

(2) Particle size results

Sieve size	% Retained
2360	0.13
2000	0.80
1700	17.06
1200	45.84
355	6.31
212	1.17
106	12.82
45	9.42
Tray	6.44

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Table A.65: SeDeM parameter values for 2.5 mm paracetamol pellets (final blend)

SeDeM Parameter (unit)	Value 1	Value 2	Value 3	Average of 3 values	SeDeM Parameter tests values (v)
Bulk density (g/ml)	0.60	0.72	0.60	0.64	6.384
Tapped Density (g/ml)	0.72	0.72	0.72	0.72	7.246
Inter-particle Porosity (-)	0.30	0.00	0.30	0.20	1.667
Carr's Index (%)	17.86	0.00	17.86	11.90	2.381
Cohesion Index (N)	-	-	-	196.40 (1)	9.820
Hausner Ratio (-)	1.22	1.00	1.22	1.14	6.184
Angle Of Repose (°)	28.02	26.39	25.16	26.53	4.695
Powder Flow (s)	5.20	5.00	5.00	5.07	7.467
Loss on Drying (%)	2.11	2.02	2.00	2.04	7.955
Hygroscopicity (%)	4.25	4.48	4.23	4.32	7.840
Particles < 45µm (%)	-	-	-	8.39 (2)	8.322
Homogeneity Index (-)	-	-	-	0.000360 (3)	0.180

(1) Cohesion Index average of 10 values (values: 212, 191, 205, 193, 174, 185, 215, 192, 196 and 201)

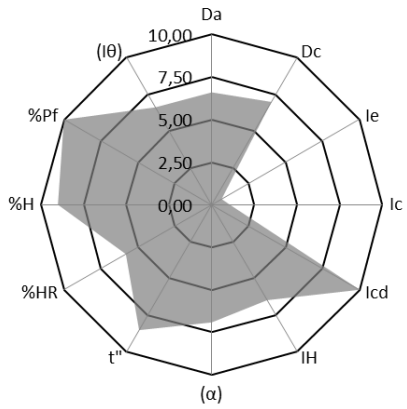
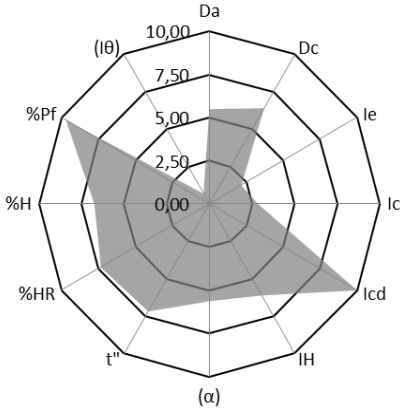
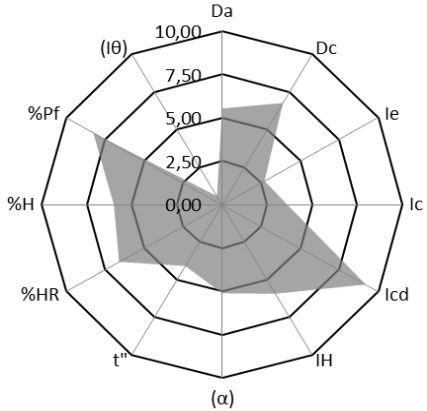
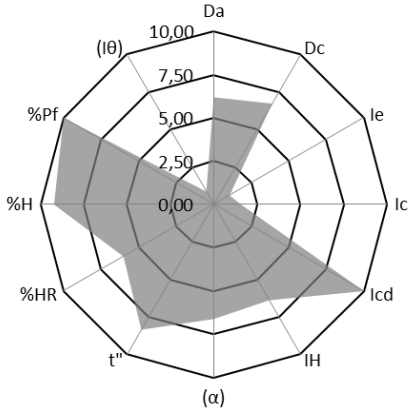
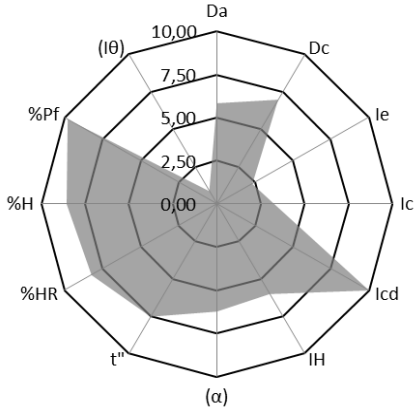
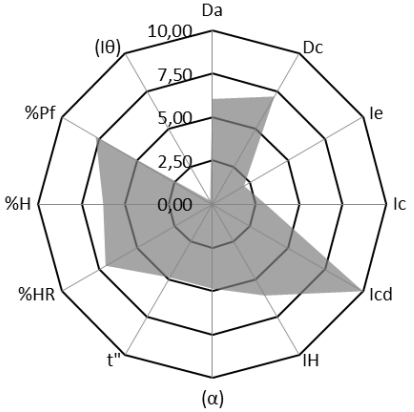
(2) Particle size results

Sieve size	% Retained
2800	1.96
2360	11.04
2000	30.15
1700	16.62
1200	8.16
355	0.70
212	1.36
106	10.58
45	11.04
Tray	8.39

(3) Calculated by using the equation (as described in Chapter 4):

$$I\Theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Figure A.1: SeDeM diagrams of the MicroceLac® 200 pellets, pellet formulation after addition of excipient (intermediate blend) and pellet formulation after addition of all excipients (final blend)

	Pellet formulation	**Intermediate blend (pellet formulation after addition of excipient (Kollidon® VA 64))**	**Final blend (compressed in MUPS tablet) (containing pellets, Kollidon® VA 64, Aerosil, Ac-di-Sol, Magnesium stearate and Talc)**
MicroceLac® 200 (0.5 mm)			
MicroceLac® 200 (1.0 mm)			

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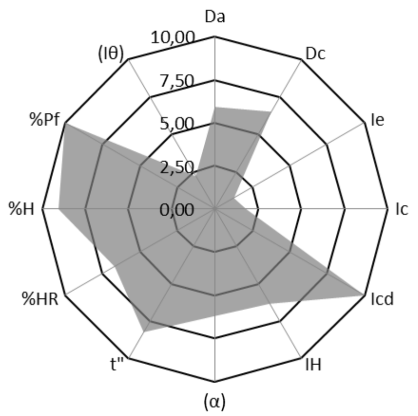
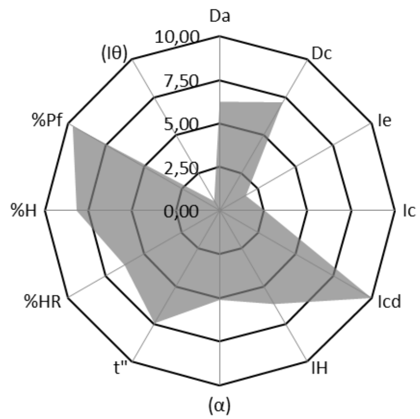
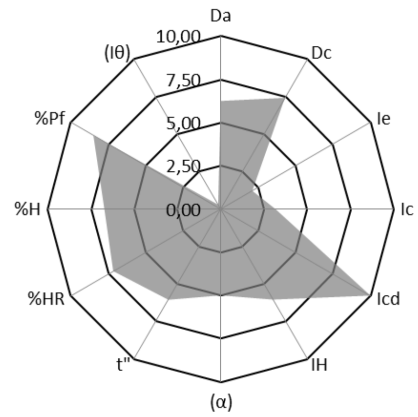
<td>  </td>
<td>  </td>
<td>  </td>
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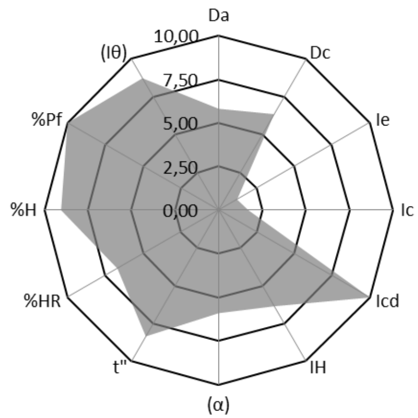
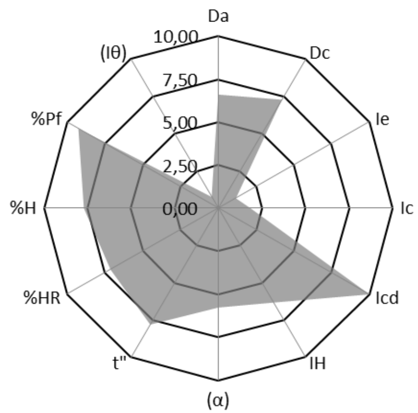
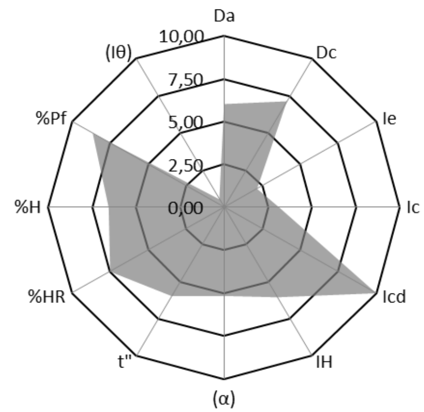
<td>  </td>
<td>  </td>
<td>  </td>
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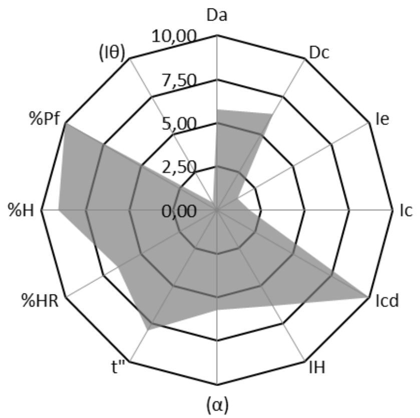
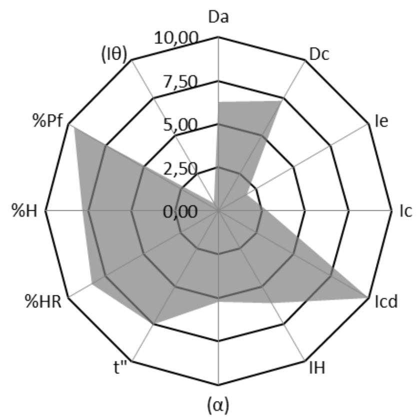
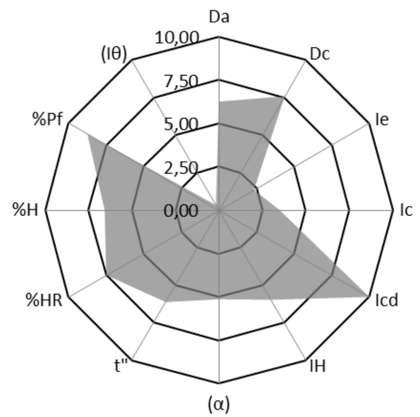
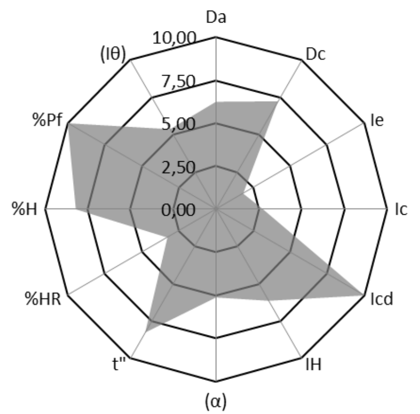
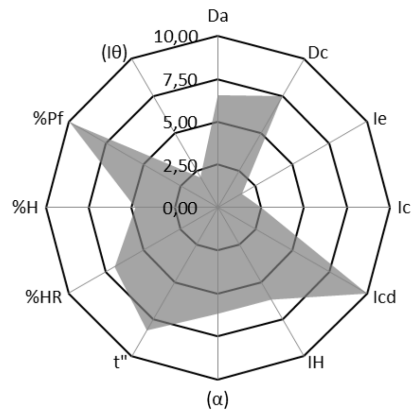
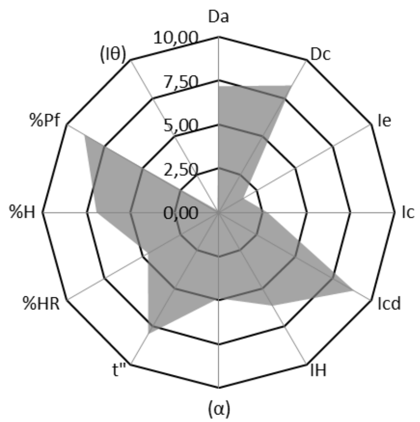
MicroceLac® 200 (2.5 mm)			

Figure A.2: SeDeM diagrams of the doxylamine pellets, pellet formulation after addition of excipient (intermediate blend) and pellet formulation after addition of all excipients (final blend)

	Pellet formulation	**Intermediate blend (pellet formulation after addition of excipient (Kollidon® VA 64))**	**Final blend (compressed in MUPS tablet) (containing pellets, Kollidon® VA 64, Aerosil, Ac-di-Sol, Magnesium stearate and Talc)**
Doxylamine (0.5 mm)			

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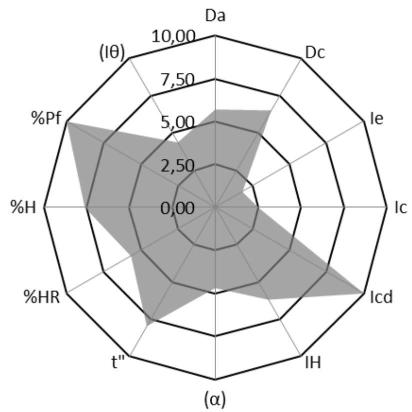
<td> 
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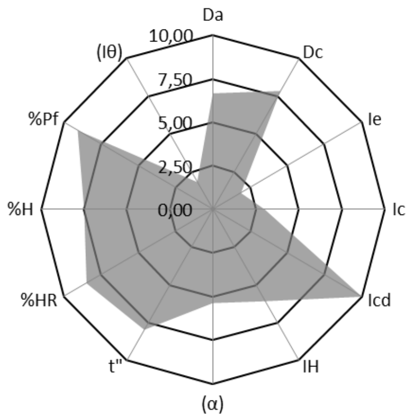
<td> 
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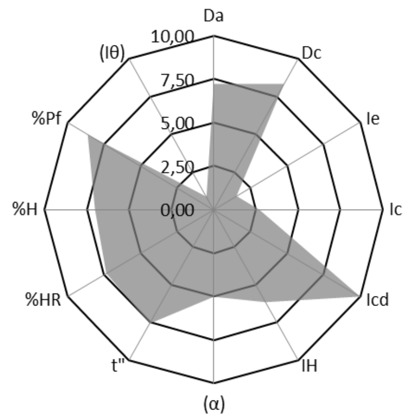
<td> 
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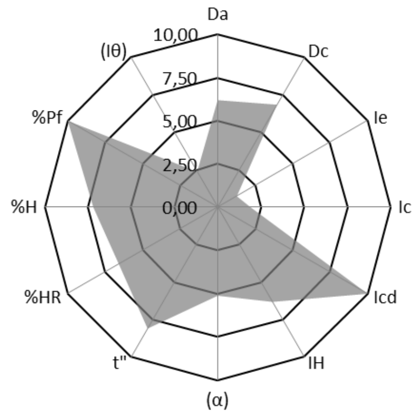
<td> 
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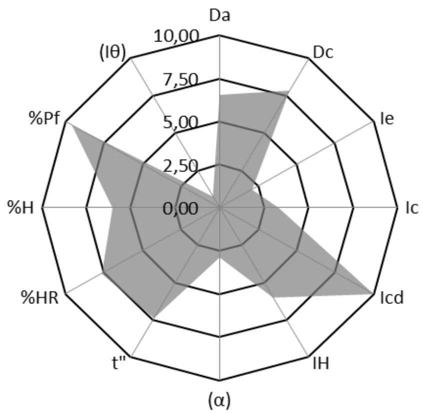
<td> 
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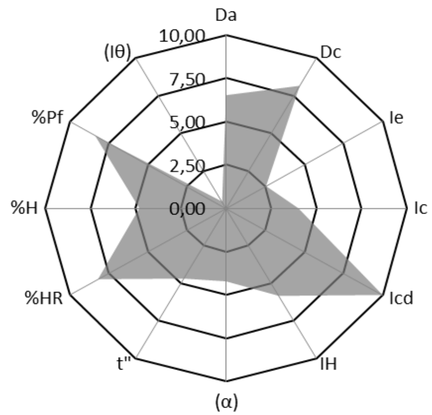
<td> 
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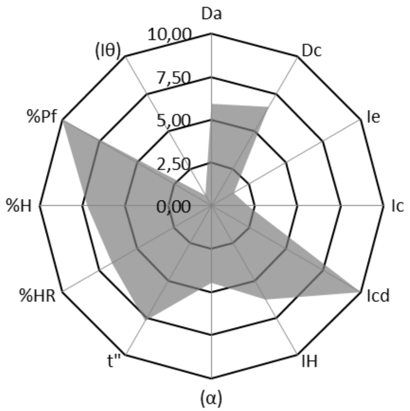
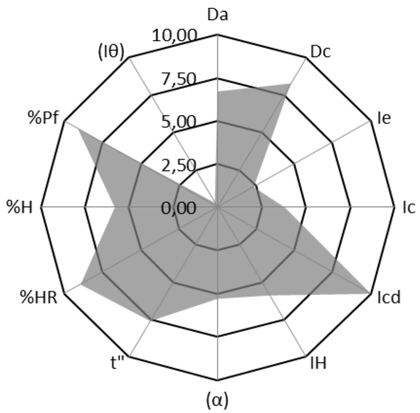
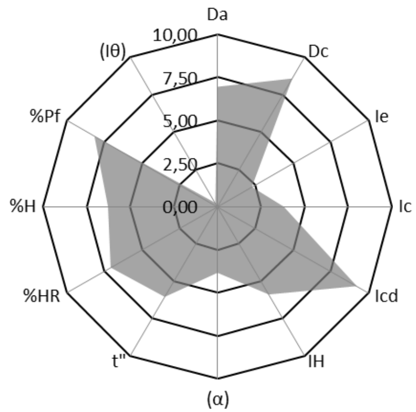
<td>  </td>
<td>  </td>
<td>  </td>
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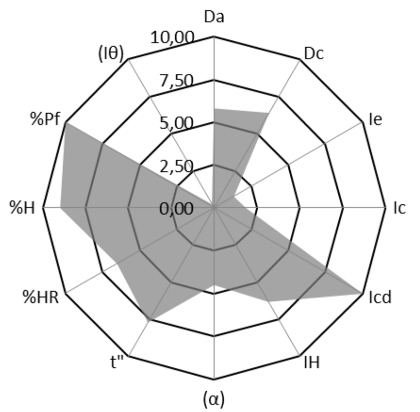
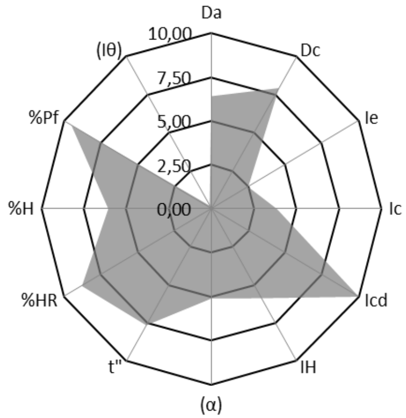
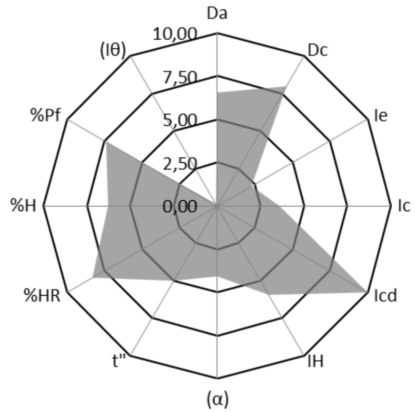
<td>  </td>
<td>  </td>
<td>  </td>
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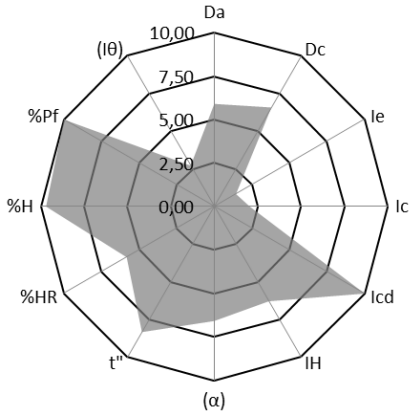
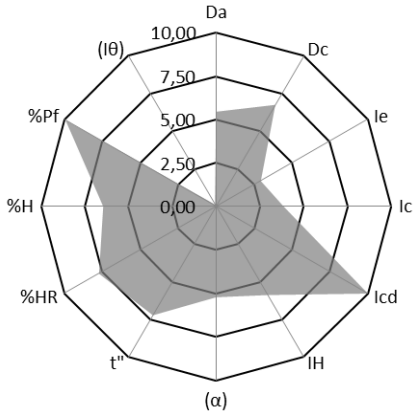
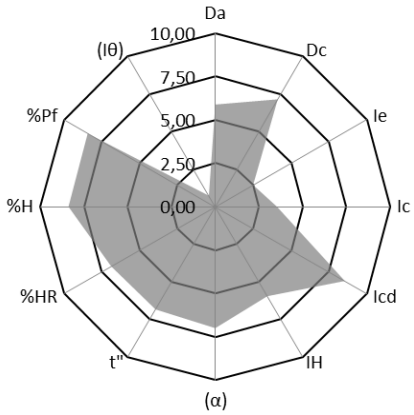
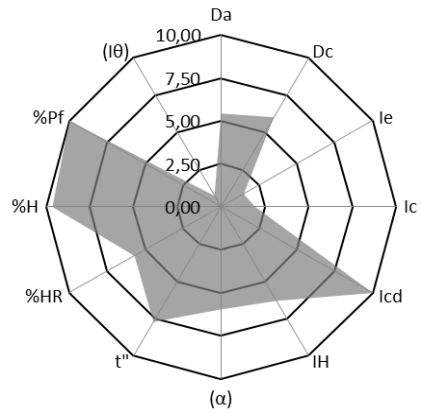
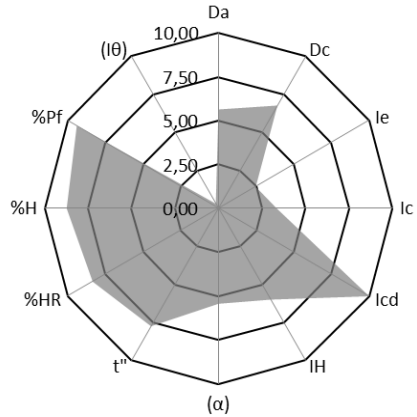
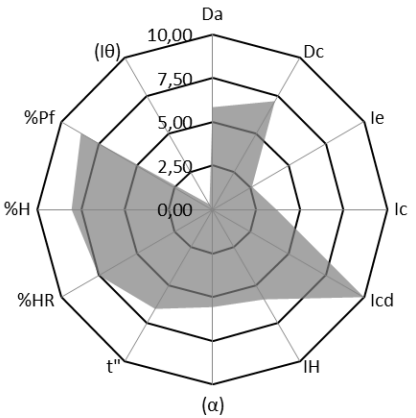
Figure A.3: SeDeM diagrams of the ibuprofen pellets, pellet formulation after addition of excipient (intermediate blend) and pellet formulation after addition of all excipients (final blend)

	Pellet formulation	**Pellet formulation after addition of excipient (Kollidon® VA 64)**	**Final blend (compressed in MUPS tablet) (containing pellets, Kollidon® VA 64, Aerosil, Ac-di-Sol, Magnesium stearate and Talc)**
Ibuprofen (0.5 mm)			
Ibuprofen (1.0 mm)			

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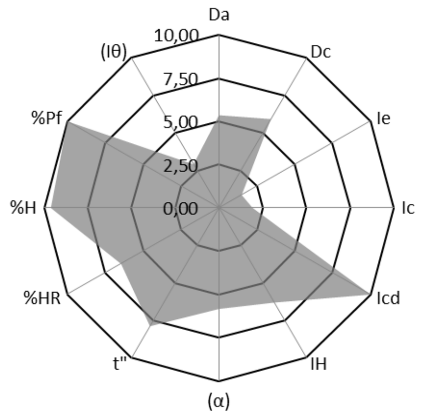
<td> 
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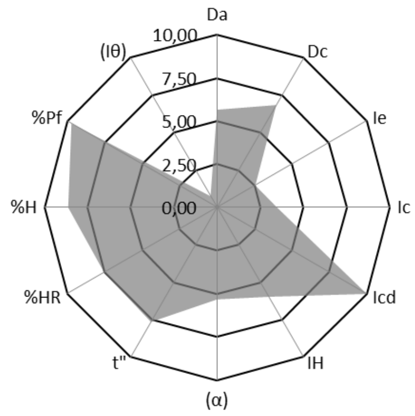
<td> 
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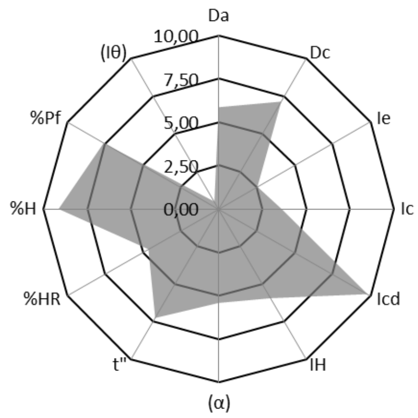
<td> 
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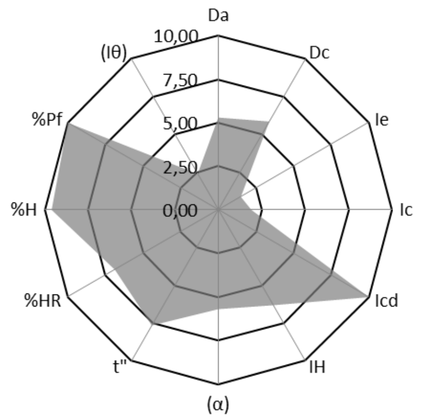
<td> 
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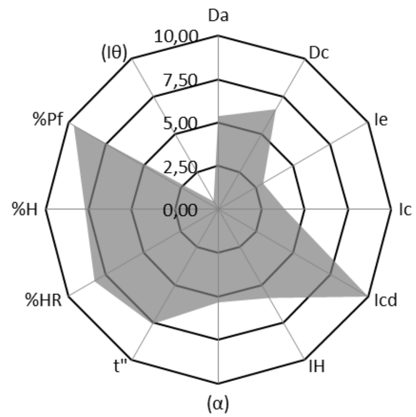
<td> 
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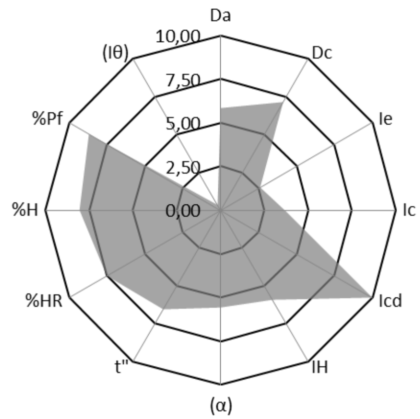
<td> 
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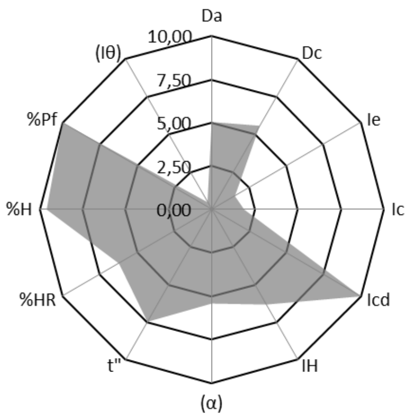
<td> 
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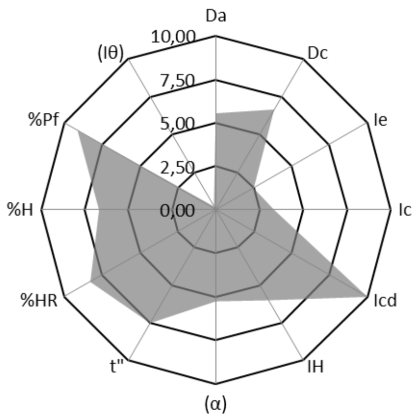
<td> 
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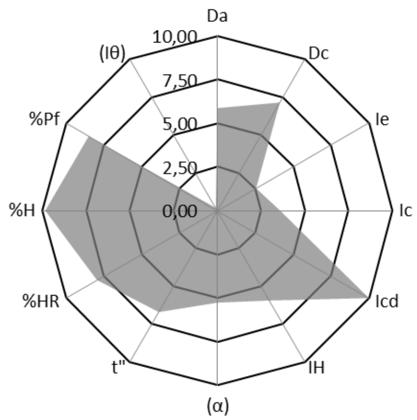
<td> 
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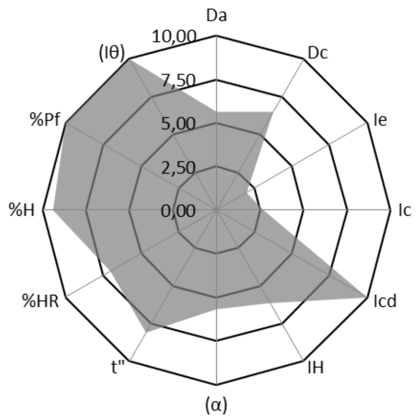
Figure A.4: SeDeM diagrams of the paracetamol pellets, pellet formulation after addition of excipient (intermediate blend) and pellet formulation after addition of all excipients (final blend)

<table>
<tr><th></th><th>Pellet formulation</th><th>Intermediate blend (pellet formulation after addition of excipient (Kollidon® VA 64))</th><th>Final blend (compressed in MUPS tablet) (containing pellets, Kollidon® VA 64, Aerosil, Ac-di-Sol, Magnesium stearate and Talc)</th></tr>
<tr><td>Paracetamol
(0.5 mm)</td>
<td> 
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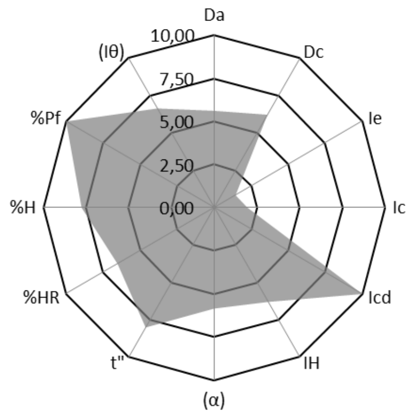
<td> 
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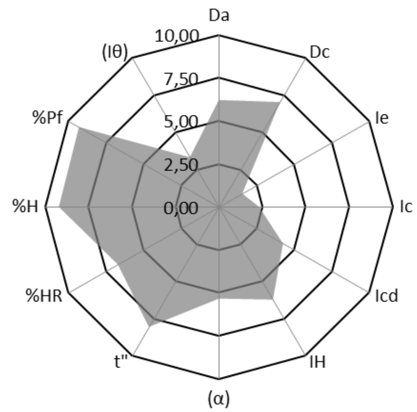
<td> 
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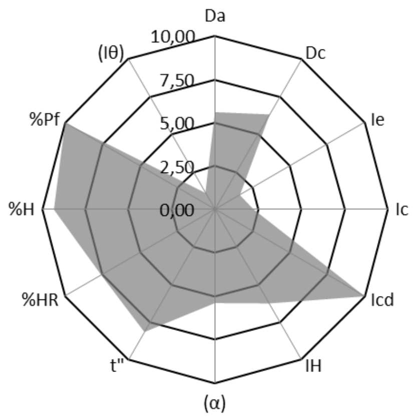
<td> 
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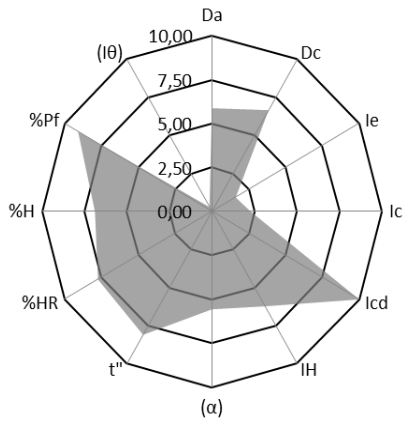
<td> 
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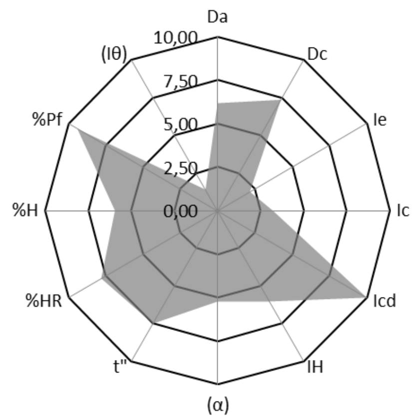
<td> 
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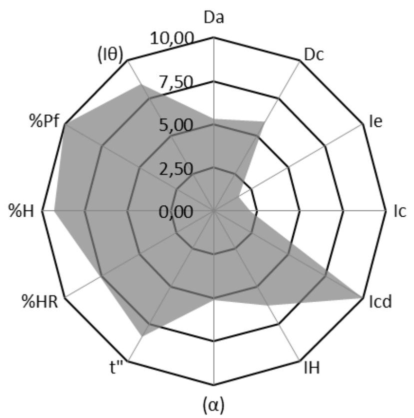
<td> 
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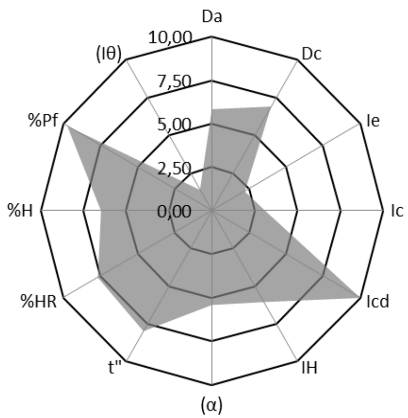
<td> 
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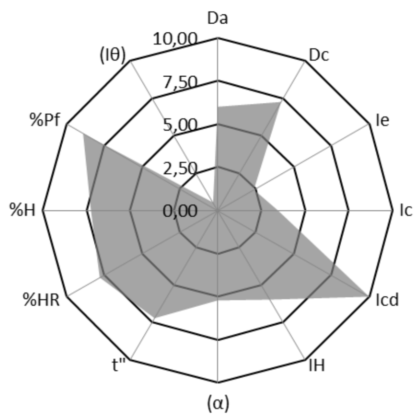
<td> 
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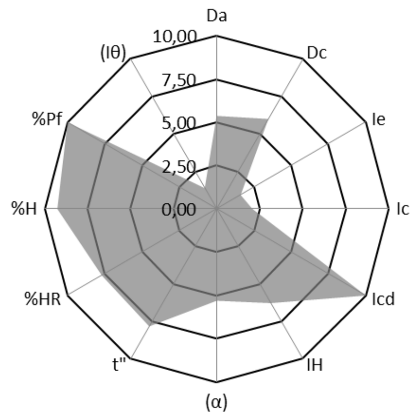
<td> 
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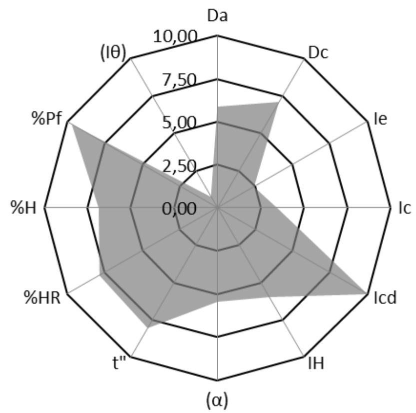
<td> 
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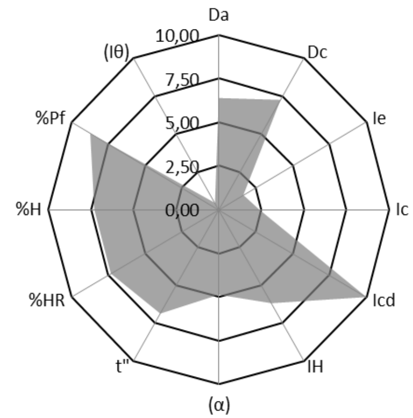
<td> 
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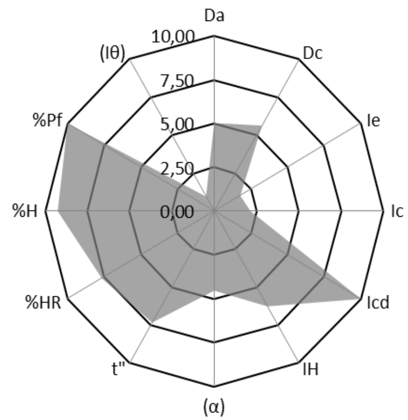
<td> 
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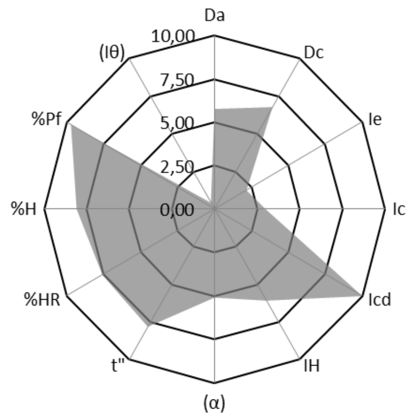
<td> 
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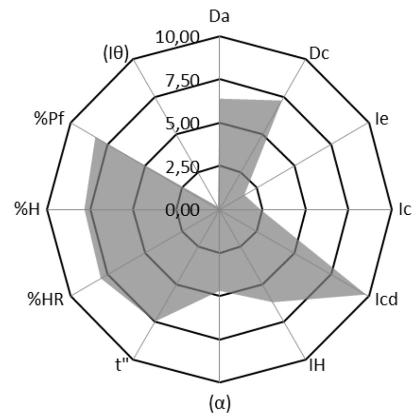
<td> 
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Table A.66: Final blend formulation for MicroceLac® 200 MUPS tablets

Materials	Amount (mg) per formulation				
	0.5 mm	**1.0 mm**	**1.5 mm**	**2.0 mm**	**2.5 mm**
Pellets					
MicroceLac® 200	241.75	272.74	292.76	284.92	295.47
MUPS tablet					
Pellets	241.75	272.74	292.76	284.92	295.47
Kollidon® VA 64	170.00	139.01	118.99	126.83	116.28
Talc	10.62	10.62	10.62	10.62	10.62
Aerosil 200	0.63	0.63	0.63	0.63	0.63
Mg stearate	4.50	4.50	4.50	4.50	4.50
Ac-Di-Sol	22.50	22.50	22.50	22.50	22.50
Tablet mass (mg)	***450.00***	***450.00***	***450.00***	***450.00***	***450.00***

Table A.67: Final blend formulation doxylamine MUPS tablets

Materials	Amount (mg) per formulation				
	0.5 mm	**1.0 mm**	**1.5 mm**	**2.0 mm**	**2.5 mm**
Pellets					
MicroceLac® 200	94.41	90.14	73.87	79.38	74.21
Doxylamine	283.23	270.43	221.60	238.14	222.63
MUPS tablet					
Pellets	377.64	360.57	295.47	317.52	296.84
Kollidon® VA 64	34.11	51.18	116.28	94.23	114.91
Talc	10.62	10.62	10.62	10.62	10.62
Aerosil 200	0.63	0.63	0.63	0.63	0.63
Mg stearate	4.50	4.50	4.50	4.50	4.50
Ac-Di-Sol	22.50	22.50	22.50	22.50	22.50
Tablet mass (mg)	***450.00***	***450.00***	***450.00***	***450.00***	***450.00***

Table A.68: Final blend formulation ibuprofen MUPS tablets

Materials	Amount (mg) per formulation				
	0.5 mm	**1.0 mm**	**1.5 mm**	**2.0 mm**	**2.5 mm**
Pellets					
MicroceLac® 200	77.83	77.46	77.07	76.71	77.07
Ibuprofen	233.48	232.37	231.22	230.12	231.22
MUPS tablet					
Pellets	311.31	309.83	308.30	306.83	308.30
Kollidon® VA 64	100.43	101.94	103.43	104.92	103.43
Talc	10.62	10.62	10.62	10.62	10.62
Aerosil 200	0.63	0.63	0.63	0.63	0.63
Mg stearate	4.50	4.50	4.50	4.50	4.50
Ac-Di-Sol	22.50	22.50	22.50	22.50	22.50
Tablet mass (mg)	***450.00***	***450.00***	***450.00***	***450.00***	***450.00***

Table A.69: Final blend formulation paracetamol MUPS tablets

Materials	Amount (mg) per formulation				
	0.5 mm	**1.0 mm**	**1.5 mm**	**2.0 mm**	**2.5 mm**
Pellets					
MicroceLac® 200	96.69	83.53	81.82	80.18	83.53
Paracetamol	290.08	250.59	245.46	240.55	250.59
MUPS tablet					
Pellets	386.78	334.13	327.29	320.73	334.13
Kollidon® VA 64	24.96	77.61	84.46	91.04	77.61
Talc	10.62	10.62	10.62	10.62	10.62
Aerosil 200	0.63	0.63	0.63	0.63	0.63
Mg stearate	4.50	4.50	4.50	4.50	4.50
Ac-Di-Sol	22.50	22.50	22.50	22.50	22.50
Tablet mass (mg)	***450.00***	***450.00***	***450.00***	***450.00***	***450.00***

Appendix B: Validation of analytical methods

B.1 Introduction

The drug content of the individual MUPS tablets (content uniformity) were analytically determined by means of an High Performance Liquid Chromatography (HPLC) method and the release rate of the drug from the MUPS tablets (dissolution) were analytically determined by means of an Ultraviolet (UV) spectrophotometric method. The analytical tests were performed in accordance to chapters 905 and 711 of the United States Pharmacopeia (USP, 2015).

B.2 Validation

B.2.1 HPLC validation parameters

The content uniformity of all three the model drug MUPS tablet formulations were analytically determined by HPLC analysis in accordance to the USP (2015) monographs for the respective tablet products. The methods were verified in house for linearity and precision (repeatability and intermediate precision).

B.2.1.1 Linearity

The linearity of an analytical procedure is its ability to elicit test results that are directly proportional to the concentration of the analyte in samples within a given range (USP, 2015). The linearity of the model drugs were determined by performing linear regression analysis on the plot of the peak areas versus concentration of the standards (prepared as described in Appendix C) on three concentrations covering a range of about 50–120% of the expected concentration. This plot should give a straight line ($r^2 \geq 0.99$) as described by the following linear equation (Eq. B.1):

$$y = mx + c \qquad \text{Eq. B.1}$$

where:

y	=	peak area of the analyte
m	=	slope
x	=	concentration of the analyte
c	=	y intercept

The standard solutions, for each model drug respectively, (as described in Appendix C) were injected 6 times at each concentration level and the peak areas of model drugs were integrated from the chromatograms, plotted on standard curves and the regression values were calculated.

Linearity results of doxylamine

Table B.1: Linearity results of doxylamine standard solutions

Concentration (mg/ml)	Peak area Injection 1	Peak area Injection 2	Peak area Injection 3	Peak area Injection 4	Peak area Injection 5	Peak area Injection 6	Mean peak area	% RSD
6	2446432	2446652	2445718	2451751	2450828	2452416	2448966	0.123
10	4067551	4076643	4077239	4067540	4072829	4073958	4072626	0.105
12	4829489	4826714	4835860	4831240	4830734	4827766	4830300	0.067

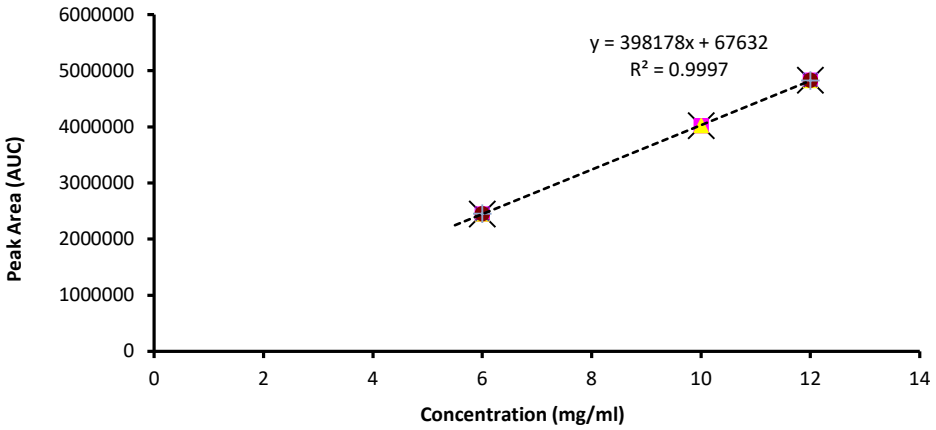


Figure B.1: Linear regression graph for doxylamine

The regression value of (r^2 = 0.9997) obtained for doxylamine from the linear regression curve (Figure B.1) indicates a high degree of linearity.

Linearity results of ibuprofen

Table B.2: Linearity results of ibuprofen standard solutions

Concentration (mg/ml)	Peak area Injection 1	Peak area Injection 2	Peak area Injection 3	Peak area Injection 4	Peak area Injection 5	Peak area Injection 6	Mean peak area	% RSD
8	2434941	2436678	2401883	2428212	2441237	2404140	2424515	0.709
12	3255703	3279011	3262167	3289246	3273568	3274115	3272301	0.360
16	4293800	4364483	4295595	4310836	4310410	4289285	4310734	0.645

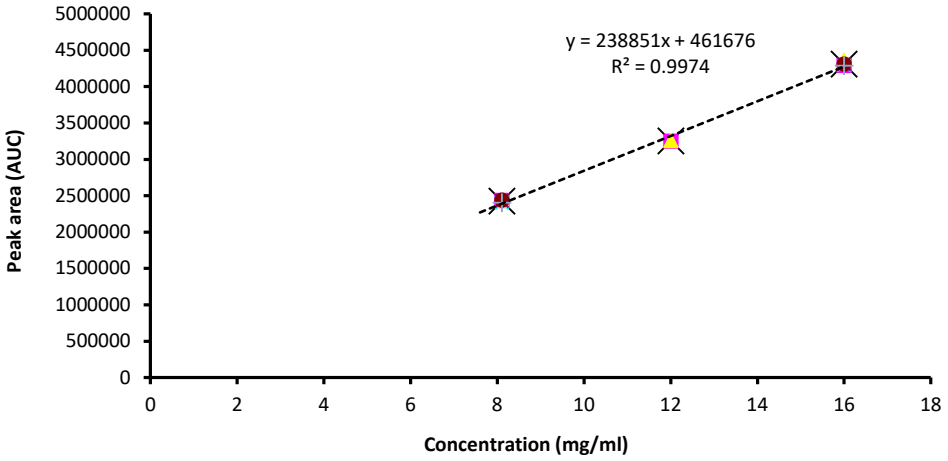


Figure B.2: Linear regression graph for ibuprofen

The regression value of (r^2 = 0.9974) obtained for ibuprofen from the linear regression curve (Figure B.2) indicates a high degree of linearity.

Linearity results of paracetamol

Table B.3: Linearity results of paracetamol standard solutions

Concentration (mg/ml)	Peak area Injection 1	Peak area Injection 2	Peak area Injection 3	Peak area Injection 4	Peak area Injection 5	Peak area Injection 6	Mean peak area	% RSD
5	249600	248525	248815	250254	248423	248469	249014	0.301
10	512830	517931	511853	516427	512503	517890	514905	0.548
15	748843	748061	748242	750136	749288	759982	750758	0.610

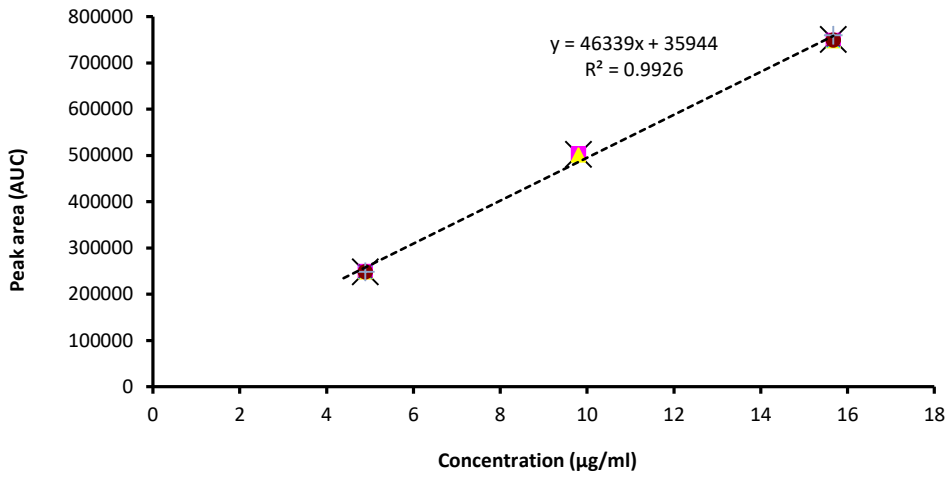


Figure B.3: Linear regression graph for paracetamol

The regression value of (r^2 = 0.9926) obtained for paracetamol from the linear regression curve (Figure B.3) indicates a high degree of linearity.

B.2.1.2 Precision

Precision of an analytical procedure is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample. The precision of an analytical procedure is usually expressed as the standard deviation or relative standard deviation (% RSD) of a series of measurements (USP, 2015). Precision is determined by means of repeatability and intermediate precision.

B.2.1.2.1 Repeatability

In order to evaluate the repeatability of the analytical method all of the standard solutions were injected 6 times. The peak areas (as reflected in Table B.1–B.3 respectively) and retention times (reflected in Table B.4–B.6 respectively) of the 6 repetitions were recorded and evaluated in terms of the % RSD. The % RSD for 6 samplings of the same standard should be less than 2.0% in order for repeatability to be proven.

Repeatability results of doxylamine

Table B.4: Retention time results of doxylamine standard solution (10 mg/ml)

	Injection number 1	Injection number 2	Injection number 3	Injection number 4	Injection number 5	Injection number 6	Mean	% RSD
Retention time (min)	11.157	11.167	11.173	11.180	11.187	11.197	11.177	0.128

The % RSD obtained for the 6 samplings of the doxylamine standard solution was below 2.0%, thus indicating acceptable repeatability.

Repeatability results of ibuprofen

Table B.5: Retention time results of ibuprofen standard solution (12 mg/ml)

	Injection number 1	Injection number 2	Injection number 3	Injection number 4	Injection number 5	Injection number 6	Mean	% RSD
Retention time (min)	5.270	5.267	5.267	5.263	5.260	5.257	5.264	0.093

The % RSD obtained for the 6 samplings of the ibuprofen standard solution was below 2.0%, thus indicating acceptable repeatability.

Repeatability results of paracetamol

Table B.6: Retention time results of paracetamol standard solution (10 µg/ml)

	Injection number 1	Injection number 2	Injection number 3	Injection number 4	Injection number 5	Injection number 6	Mean	% RSD
Retention time (min)	4.880	4.880	4.883	4.880	4.883	4.880	4.881	0.032

The % RSD obtained for the 6 samplings of the paracetamol standard solution was below 2.0%, thus indicating acceptable repeatability.

B.2.1.2.2 Intermediate precision

In order to evaluate the intermediate precision of the peak areas and retention times of one of the standard solutions were injected in duplicate after every 10 sample injections.

Intermediate precision results of doxylamine

Table B.7: Intermediate precision results of doxylamine standard solution (10 mg/ml)

	Retention time (min)	Peak area
Injection number 1	10.810	4036896
Injection number 2	10.813	4034773
Injection number 3	10.880	4046903
Injection number 4	10.890	4050012
Injection number 5	10.987	4064104
Injection number 6	10.993	4072145
Injection number 7	11.067	4060142
Injection number 8	11.073	4059081
Injection number 9	11.157	4067551
Injection number 10	11.167	4076643
Mean	10.984	**4056825**
% RSD	1.204	**0.352**

Intermediate precision results of ibuprofen

Table B.8: Intermediate precision results of ibuprofen standard solution (12 mg/ml)

	Retention time (min)	Peak area
Injection number 1	5.390	3254891
Injection number 2	5.387	3236676
Injection number 3	5.350	3276278
Injection number 4	5.350	3276050
Injection number 5	5.317	3265561
Injection number 6	5.317	3249931
Injection number 7	5.300	3250367
Injection number 8	5.297	3257261
Injection number 9	5.270	3255703
Injection number 10	5.267	3279011
Mean	5.325	**3260173**
% RSD	0.822	**0.422**

Intermediate precision results of paracetamol

Table B.9: Intermediate precision results of paracetamol standard solution (12 mg/ml)

	Retention time (min)	Peak area
Injection number 1	4.860	510639
Injection number 2	4.867	517281
Injection number 3	4.880	512414
Injection number 4	4.877	514691
Injection number 5	4.880	517890
Injection number 6	4.873	508441
Injection number 7	4.873	518265
Injection number 8	4.877	509122
Injection number 9	4.880	512830
Injection number 10	4.880	517931
Mean	4.875	**513950**
% RSD	0.137	**0.739**

*B.*2.2 UV spectrophotometric validation parameters

The drug release (dissolution) of all three the model drug MUPS tablet formulations were analytically determined by UV spectrophotometric analysis in accordance to the USP (2015) monographs for the respective tablet products. The methods were verified in house for linearity, recovery and precision (repeatability).

B.2.2.1 Linearity

The linearity of an analytical procedure is its ability to elicit test results that are directly proportional to the concentration of the analyte in samples within a given range (USP, 2015). The linearity was established by preparing solutions of the drug, ranging in concentration from below the lowest expected concentration to above the highest concentration during dissolution testing of the MUPS tablets containing the three model drugs respectively. The standard solutions, for each model drug respectively, (as described in Appendix C) were analysed in triplicate at each concentration level, the absorbance values of the model drugs were plotted on standard curves and the regression values were calculated. Typically a square of the correlation coefficient ($r^2 \geq 0.99$) demonstrated linearity.

Linearity results of doxylamine

Table B.10: Linearity results of doxylamine standard solutions

Concentration (µg/ml)	Absorbance value				
	Measurement 1	Measurement 2	Measurement 3	Average	% RSD
2	0.0479	0.0482	0.0485	0.0482	0.622
5	0.1230	0.1233	0.1235	0.1233	0.204
10	0.2467	0.2473	0.2472	0.2471	0.130
20	0.4863	0.4852	0.4852	0.4856	0.131
30	0.7306	0.7314	0.7323	0.7314	0.116
40	0.9705	0.9716	0.9716	0.9712	0.065
50	1.1844	1.1870	1.1870	1.1861	0.127
60	1.4545	1.4545	1.4545	1.4545	0.000
70	1.6857	1.6884	1.6884	1.6875	0.092
100	2.3951	2.4082	2.3951	2.3995	0.315
120	2.8341	2.7992	2.8341	2.8225	0.714

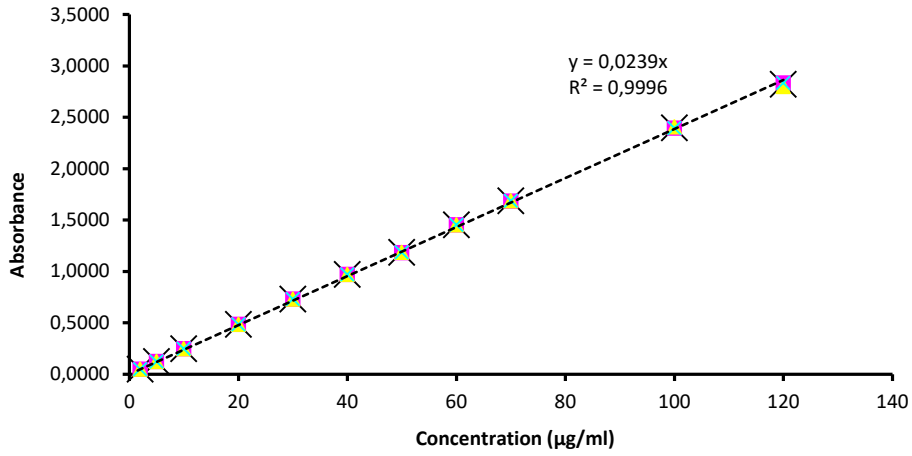


Figure B.4: Linear regression graph for doxylamine

The regression value of (r^2 = 0.9996) obtained for doxylamine from the linear regression curve (Figure B.4) indicates a high degree of linearity.

Linearity results of ibuprofen

Table B.11: Linearity results of ibuprofen standard solutions

Concentration (µg/ml)	Absorbance value				
	Measurement 1	Measurement 2	Measurement 3	Average	% RSD
2	0.0405	0.0415	0.0420	0.0413	1.848
5	0.1250	0.1245	0.1255	0.1250	0.400
10	0.2289	0.2294	0.2244	0.2276	1.210
20	0.4817	0.4817	0.4975	0.4870	1.873
30	0.6878	0.6914	0.6959	0.6917	0.587
40	0.9414	0.9414	0.9583	0.9470	1.030
50	1.1775	1.1758	1.1735	1.1756	0.171
60	1.3887	1.3795	1.3795	1.3826	0.384
70	1.6558	1.6487	1.6558	1.6534	0.248
100	2.3591	2.3591	2.3591	2.3591	0.000
120	2.7092	2.7092	2.7092	2.7092	0.000

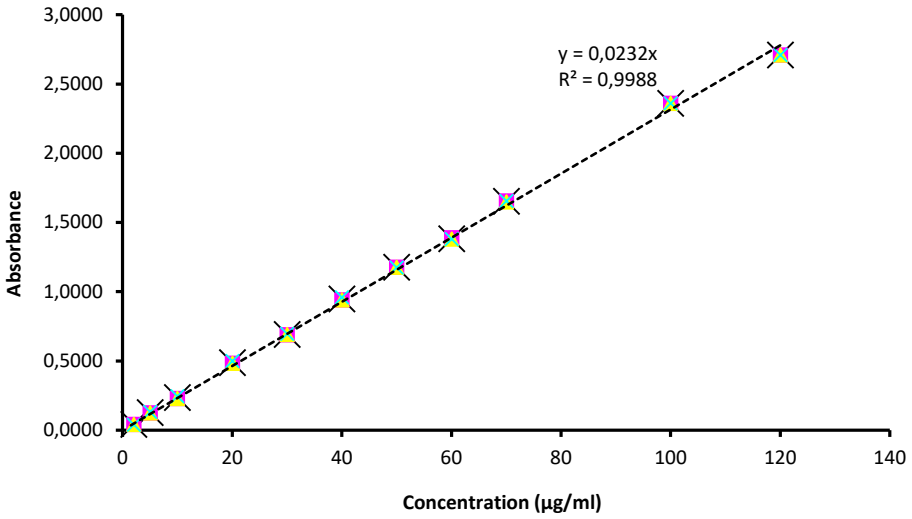


Figure B.5: Linear regression graph for ibuprofen

The regression value of (r^2 = 0.9988) obtained for ibuprofen from the linear regression curve (Figure B.5) indicates a high degree of linearity.

Linearity results of paracetamol

Table B.12: Linearity results of paracetamol standard solutions

Concentration (µg/ml)	Absorbance value				
	Measurement 1	Measurement 2	Measurement 3	Average	% RSD
2	0.0739	0.0723	0.0719	0.0727	1.456
5	0.1310	0.1302	0.1307	0.1306	0.309
10	0.2371	0.2374	0.2373	0.2373	0.064
20	0.4469	0.4468	0.4467	0.4468	0.022
30	0.6570	0.6573	0.6580	0.6574	0.078
40	0.8878	0.8876	0.8878	0.8877	0.013
50	1.1359	1.1359	1.1351	1.1356	0.041
60	1.2981	1.2981	1.2993	1.2985	0.053
70	1.5476	1.5476	1.5476	1.5476	0.000
100	2.1351	2.1351	2.1351	2.1351	0.000
120	2.6833	2.6833	2.6587	2.6751	0.531

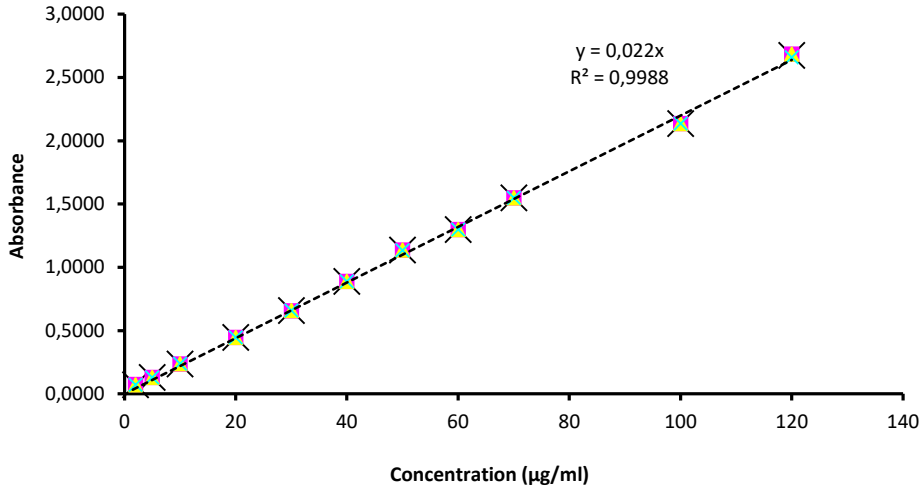


Figure B.6: Linear regression graph for paracetamol

The regression value of (r^2 = 0.9988) obtained for paracetamol from the linear regression curve (Figure B.6) indicates a high degree of linearity.

B.2.2.2 Recovery

The accuracy/recovery of an analytical procedure is the closeness of test results obtained by that procedure to the true value (USP, 2015). Recovery was established by preparing multiple samples containing the drug and any other constituents present in the dosage form ranging in concentration from below the lowest expected concentration to above the highest concentration during release. The measured recovery should typically be 95% to 105% of the amount added.

Recovery results of doxylamine

Table B.13: Recovery results of doxylamine standard solutions

Prepared concentration (µg/ml)	Absorbance value	Measured concentration (µg/ml)	% Recovery	Average % Recovery	% RSD
1.96	0.0441	1.88	96.09		
1.96	0.0443	1.89	96.52		
1.96	0.0459	1.96	100.01	**97.54**	0.0010
4.90	0.1116	4.77	97.26		
4.90	0.1140	4.87	99.35		
4.90	0.1140	4.87	99.35	**98.66**	0.0014
49.0	1.1142	47.62	97.10		
49.0	1.1163	47.71	97.29		
49.0	1.1142	47.62	97.10	**97.17**	0.0013
73.55	1.6755	71.60	97.35		
73.55	1.6730	71.50	97.20		
73.55	1.6781	71.71	97.50	**97.35**	0.0026
98.07	2.2241	95.05	96.92		
98.07	2.2254	95.10	96.97		
98.07	2.2241	95.05	96.92	**96.94**	0.0008
122.59	2.7992	119.62	97.58		
122.59	2.7992	119.62	97.58		
122.59	2.7993	119.63	97.59	**97.58**	0.0001

The recovery obtained for doxylamine was between 95% and 105% of the amount added, thus indicating acceptable recovery.

Recovery results of ibuprofen

Table B.14: Recovery results of ibuprofen standard solutions

Prepared concentration (µg/ml)	Absorbance value	Measured concentration (µg/ml)	% Recovery	Average % Recovery	% RSD
2.01	0.0455	2.07	102.93		
2.01	0.0455	2.07	102.93		
2.01	0.0431	1.96	97.50	**101.12**	0.0014
5.03	0.1085	4.93	98.17		
5.03	0.1105	5.02	99.98		
5.03	0.1189	5.40	107.59	**101.91**	0.0054
50.24	1.1059	50.27	100.07		
50.24	1.1059	50.27	100.07		
50.24	1.1087	50.40	100.32	**100.15**	0.0016
75.35	1.6558	75.26	99.88		
75.35	1.6558	75.26	99.88		
75.35	1.6985	77.20	102.46	**100.74**	0.0225
100.47	2.2028	100.13	99.66		
100.47	2.2823	103.74	103.26		
100.47	2.3028	104.67	104.18	**102.37**	0.0516
125.59	2.8341	128.82	102.58		
125.59	2.8341	128.82	102.58		
125.59	2.8341	128.82	102.58	**102.58**	0

The recovery obtained for ibuprofen was between 95% and 105% of the amount added, thus indicating acceptable recovery.

Recovery results of paracetamol

Table B.15: Recovery results of paracetamol standard solutions

Prepared concentration (µg/ml)	Absorbance value	Measured concentration (µg/ml)	% Recovery	Average % Recovery	% RSD
2.00	0.0453	2.06	102.95		
2.00	0.0444	2.02	100.91		
2.00	0.0441	2.00	100.23	**101.36**	0.0006
5.00	0.1069	4.86	97.18		
5.00	0.1069	4.86	97.18		
5.00	0.1068	4.85	97.09	**97.15**	0.0001
50.00	1.0519	47.81	95.63		
50.00	1.0531	47.87	95.74		
50.00	1.0514	47.79	95.58	**95.65**	0.0009
75.00	1.5846	72.03	96.04		
75.00	1.5908	72.31	96.41		
75.00	1.5887	72.21	96.28	**96.24**	0.0033
100.00	2.0976	95.35	95.35		
100.00	2.0976	95.35	95.35		
100.00	2.0941	95.19	95.19	**95.29**	0.0021
125.00	2.6380	119.67	95.74		
125.00	2.6380	119.67	95.74		
125.00	2.6380	119.67	95.74	**95.74**	0

The recovery obtained for paracetamol was between 95% and 105% of the amount added, thus indicating acceptable recovery.

B.2.2.3 Precision

Precision of an analytical procedure is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample. The precision of an analytical procedure is usually expressed as the standard deviation or relative standard deviation (% RSD) of a series of measurements (USP, 2015). Repeatability was measured by calculating the % RSD of the multiple spectrophotometric sampling for each standard solution, or from the accuracy or linearity data (refer to Table B.10–B.12). The % RSD for 3 samplings of the same standard should be less than 2.0% in order for repeatability to be proven.

Repeatability results of doxylamine

As reflected in Table B.10 the % RSD obtained for the 3 samplings of the doxylamine standard solutions were below 2.0%, thus indicating acceptable repeatability.

Repeatability results of ibuprofen

As reflected in Table B.11 the % RSD obtained for the 3 samplings of the ibuprofen standard solutions were below 2.0%, thus indicating acceptable repeatability.

Repeatability results of paracetamol

As reflected in Table B.12 the % RSD obtained for the 3 samplings of the ibuprofen standard solutions were below 2.0%, thus indicating acceptable repeatability.

B.3 References

USP ***see*** UNITED STATES PHARMACOPEIA

UNITED STATES PHARMACOPEIA AND NATIONAL FORMULARY (USP 39-NF 34). 2015 Rockville, MD: United States Pharmacopeial Convention.

Appendix C: Evaluation of MUPS tablet formulations

C.1 Introduction

One placebo pellet formulation and three pellet formulations containing API were formulated as described in the articles "Development of multiple-unit pellet system tablets by employing the SeDeM expert diagram system I: pellets with different sizes" (Chapter 4) and "Development of multiple-unit pellet system tablets by employing the SeDeM Expert Diagram System II: pellets containing different active pharmaceutical ingredients (Chapter 5).

The SeDeM EDS was applied to the pellet formulations to identify the most appropriate excipient and the smallest possible quantity thereof to yield formulations suitable for compression into MUPS tablets. The pellets formulations were then compressed to yield MUPS tablets. The MUPS tablets were evaluated in terms of uniformity of mass, hardness, friability, disintegration, content uniformity and dissolution.

C.2 Methods

C.2.1 Uniformity of mass

The uniformity of mass of MUPS tablets was determined as described in the BP (2015). A number of tablets (20 tablets per formulation) was selected randomly and weighed individually. The average mass of the 20 tablets was calculated. The uniformity of mass complies with the acceptance criteria if not more than 2 of the individual masses deviate from the average mass by more than 5% and none deviates by more than 10%.

C.2.2 Hardness

No specific criterion for crushing strength of tablets is given in the USP or the BP. The crushing strength was assessed by randomly selecting ten MUPS tablets and analysing them on an Erweka TBH 425 TD hardness tester (Erweka, Germany) unit.

C.2.3 Friability

The friability of the tablets was assessed as described in chapter 1216 of the USP (2015) by taking a sample of whole tablets corresponding as near as possible to 650 mg. The tablets were accurately weighed and placed into the drum of an Erweka TAR 220 friabilitor (Erweka, Germany). The friabilitor was turned on at 25 revolutions per minute for 4 min. The MUPS tablets were removed, dusted and

weighed once more. Equation C.1 was used to determine percentage of friability. A mean weight loss (% friability) of not more than 1.0% is acceptable:

$$\text{Friability (\%)} = \frac{\text{Initial tablet weight - Weight after friability}}{\text{Initial tablet weight}} \times 100 \qquad \text{Eq. C.1}$$

C.2.4 Disintegration

Disintegration of the different MUPS tablet formulations was determined in accordance to chapter 701 of the USP (2015). Six tablets from each formulation were placed within an Erweka ZT 123 tablet disintegration unit (Erweka, Germany), with distilled water and a thermostat that regulates the water temperature to between 36.5°C and 37.5°C. The tablet disintegration time was measured and disintegration is deemed complete when there are no tablet or pellet fragments left on the sieve.

C.2.5 Content uniformity

Content uniformity of all three the model drug MUPS tablet formulations were determined in accordance to chapter 905 of the USP (2015) (refer to Appendix B for the method validation). The requirements for dosage uniformity are met if the acceptance value of 10 dosage units is less than or equal to L1% (L1% = 15.0 unless otherwise specified).

C.2.5.1 Doxylamine

Content uniformity analysis as performed on 10 doxylamine MUPS tablets using the method as described in the USP (2015).

Analytical instrument: The HPLC analysis of doxylamine was performed by using a Hitachi Chromaster chromatographic system. The system consists of a 5410 UV detector, an auto-sampler (5260) with a sample temperature controller and a solvent delivery module (5160).

Column: A Phenomenex Luna C_8, 4.6 x 150 mm column was used during the analysis.

Mobile phase: The mobile phase consisted of 340 mg of monobasic potassium phosphate, 150 mg of triethylamine hydrochloride and 150 mg of sodium lauryl sulphate dissolved in 63 ml of water and made up to 100 ml with acetonitrile

Flow rate: 1.5 ml/min

Injection volume: 10 µl

Detection: UV at 262 nm

Run time: 15 min

Retention time: Approximately 11 min

Solvent: 0.1 M hydrochloric acid

Standard solution preparation

The standard doxylamine solutions were prepared as follows:

- Approximately 60 mg doxylamine was accurately weighed, transferred to a 100 ml volumetric flask and made up to volume with 0.1 M hydrochloric acid to obtain a 6 mg/ml doxylamine solution
- Approximately 100 mg doxylamine was accurately weighed, transferred to a 100 ml volumetric flask and made up to volume with 0.1 M hydrochloric acid to obtain a 10 mg/ml doxylamine solution
- Approximately 120 mg doxylamine was accurately weighed, transferred to a 100 ml volumetric flask and made up to volume with 0.1 M hydrochloric acid to obtain a 12 mg/ml doxylamine solution

These solutions were injected six times to obtain the linear regression graph for doxylamine.

Sample preparation

The tablet samples were prepared as follows:

- Ten individual tablets were accurately weighed. The tablets were each placed in a 100 ml volumetric flask and made up to volume with 0.1 M hydrochloric acid. Approximately 2 ml of this solution was filtrated through a 0.45 µm filter and transferred to HPLC vials.

The concentrations of these sample solutions fell within the concentration range used for linearity.

C.2.5.2 Ibuprofen

Content uniformity analysis as performed on 10 ibuprofen MUPS tablets using the method as described in the USP (2015).

Analytical instrument: The HPLC analysis of ibuprofen was performed by using a Hitachi Chromaster chromatographic system. The system consists of a 5410 UV

detector, an auto-sampler (5260) with a sample temperature controller and a solvent delivery module (5160).

Column: A Phenomenex Luna C_{18}, 4.6 x 250 mm column was used during the analysis.

Mobile phase: The mobile phase consisted of 4.0 g of chloroacetic acid which was dissolved in 400 ml water. The pH was adjusted with ammonium hydroxide to a pH of 3.0. 600 ml of acetonitrile was then added to the solution

Flow rate: 2 ml/min

Injection volume: standard solutions: 10 µl and sample solutions: 50 µl

Detection: UV at 254 nm

Run time: 12 min

Retention time: Approximately 5 min

Solvent: Mobile phase

Standard solution preparation

The standard ibuprofen solutions were prepared as follows:

- Approximately 80 mg ibuprofen was accurately weighed, transferred to a 10 ml volumetric flask and made up to volume with mobile phase to obtain a 8 mg/ml ibuprofen solution
- Approximately 120 mg ibuprofen was accurately weighed, transferred to a 10 ml volumetric flask and made up to volume with mobile phase to obtain a 12 mg/ml ibuprofen solution
- Approximately 160 mg ibuprofen was accurately weighed, transferred to a 10 ml volumetric flask and made up to volume with mobile phase to obtain a 16 mg/ml ibuprofen solution

These solutions were injected six times to obtain the linear regression graph for ibuprofen.

Sample preparation

The tablet samples were prepared as follows:

- Ten individual tablets were accurately weighed. The tablets were each placed in a 50 ml erlenmeyer flask, 30 ml of mobile phase was accurately added to dissolve the tablets.

Approximately 2 ml of this solution was filtrated through a 0.45 µm filter and transferred to HPLC vials.

The concentrations of these sample solutions fell within the concentration range used for linearity.

C.2.5.3 Paracetamol

Content uniformity analysis was performed on 10 paracetamol MUPS tablets using the method as described in the USP (2015).

Analytical instrument: The HPLC analysis of paracetamol was performed by using a Hitachi Chromaster chromatographic system. The system consists of a 5410 UV detector, an auto-sampler (5260) with a sample temperature controller and a solvent delivery module (5160).

Column: A Phenomenex Luna C_{18}, 4.6 x 250 mm column was used during the analysis.

Mobile phase: The mobile phase consisted of methanol and water (1:3)

Flow rate: 1.5 ml/min

Injection volume: 20 µl

Detection: UV at 243 nm

Run time: 10 min

Retention time: Approximately 5 min

Solvent: Methanol and water (1:3)

Standard solution preparation

The standard paracetamol solutions were prepared as follows:

- Approximately 50 mg paracetamol was accurately weighed, transferred to a 100 ml volumetric flask and made up to volume with mobile phase.
- A volume of 1 ml of the 0.5 mg/ml paracetamol solution was diluted to 100 ml with mobile phase to obtain a 5 µg/ml paracetamol solution
- A volume of 2 ml of the 0.5 mg/ml paracetamol solution was diluted to 100 ml with mobile phase to obtain a 10 µg/ml paracetamol solution

- A volume of 3 ml of the 0.5 mg/ml paracetamol solution was diluted to 100 ml with mobile phase to obtain a 15 µg/ml paracetamol solution

These solutions were injected six times to obtain the linear regression graph for paracetamol.

Sample preparation

The tablet samples were prepared as follows:

- Ten individual tablets were accurately weighed. The tablets were each placed in a 100 ml volumetric flask, dissolved in approximately 75 ml mobile phase and made up to volume with mobile phase. Approximately 2 ml of this solution was filtrated through a 0.45 µm filter and transferred to HPLC vials
- 1 ml of the filtered solution was transferred to a 100 ml volumetric flask and made up to volume with mobile phase.

The concentrations of these sample solutions fell within the concentration range used for linearity.

C.2.6 Dissolution

Tablet dissolution of all three the model drug MUPS tablet formulations were determined in accordance to the USP (2015) (refer to Appendix B for the method validation). Dissolution medium was replaced after each sampling.

C.2.6.1 Doxylamine

Tablet dissolution was performed on 3 doxylamine MUPS tablets using the method as described in the USP (2015) (USP type II apparatus).

Dissolution apparatus: The tablet dissolution was performed using a Distek Model 2500 dissolution bath (Distek, New Jersey) complying with a USP type II apparatus, a Distek Evolution 4300 Dissolution Sampler (Distek, New Jersey) and Distek Syringe Pump (Distek, New Jersey).

Paddle speed: 50 rpm

Dissolution medium: 0.01 N hydrochloric acid

Medium volume: 900 ml

Sample volume: 7 ml

Sample intervals: 5; 15; 30; 45; 60; 90; 120 and 150 min

UV Detection: Samples were analysed by UV-spectrophotometry using a UV 1700 PharmacSpec Spectrophotometer (Shimadzu Corporation, Kyoto, Japan).

Absorbance: UV at 262 nm

Standard solution preparation

The standard doxylamine solutions were prepared as follows:

- Approximately 50 mg doxylamine was accurately weighed, transferred to a 100 ml volumetric flask, dissolved in 10 ml water and made up to volume with 0.01 N hydrochloric acid
- A volume of 1 ml of the 0.5 mg/ml doxylamine solution was diluted to 100 ml with 0.01 N hydrochloric acid to obtain a 5 µg/ml doxylamine solution
- A volume of 2 ml of the 0.5 mg/ml doxylamine solution was diluted to 50 ml with 0.01 N hydrochloric acid to obtain a 20 µg/ml doxylamine solution
- A volume of 5 ml of the 0.5 mg/ml doxylamine solution was diluted to 50 ml with 0.01 N hydrochloric acid to obtain a 50 µg/ml doxylamine solution
- A volume of 7 ml of the 0.5 mg/ml doxylamine solution was diluted to 50 ml with 0.01 N hydrochloric acid to obtain a 70 µg/ml doxylamine solution
- A volume of 10 ml of the 0.5 mg/ml doxylamine solution was diluted to 50 ml with 0.01 N hydrochloric acid to obtain a 100 µg/ml doxylamine solution
- A volume of 12 ml of the 0.5 mg/ml doxylamine solution was diluted to 50 ml with 0.01 N hydrochloric acid to obtain a 120 µg/ml doxylamine solution

These solutions were analysed in triplicate to obtain the linear regression graph for doxylamine.

C.2.6.2 Ibuprofen

Tablet dissolution was performed on 3 ibuprofen MUPS tablets using the method as described in the USP (2015) (USP type II apparatus).

Dissolution apparatus: The tablet dissolution was performed using a Distek Model 2500 dissolution bath (Distek, New Jersey) complying with a USP type II apparatus, a Distek Evolution 4300 Dissolution Sampler (Distek, New Jersey) and Distek Syringe Pump (Distek, New Jersey).

Paddle speed: 50 rpm

Dissolution medium: phosphate buffer (pH 7.2)

Medium volume: 900 ml

Sample volume: 7 ml

Sample intervals: 5; 15; 30; 45; 60; 90; 120 and 150 min

UV Detection: Samples were analysed by UV-spectrophotometry using a UV 1700 PharmacSpec Spectrophotometer (Shimadzu Corporation, Kyoto, Japan).

Absorbance: UV at 221 nm

Standard solution preparation

The standard ibuprofen solutions were prepared as follows:

- Approximately 50 mg ibuprofen was accurately weighed, transferred to a 100 ml volumetric flask, dissolved in 10 ml ethanol and made up to volume with phosphate buffer (pH 7.2).
- A volume of 1 ml of the 0.5 mg/ml ibuprofen solution was diluted to 100 ml with phosphate buffer (pH 7.2) to obtain a 5 µg/ml ibuprofen solution
- A volume of 2 ml of the 0.5 mg/ml ibuprofen solution was diluted to 50 ml with phosphate buffer (pH 7.2) to obtain a 20 µg/ml ibuprofen solution
- A volume of 5 ml of the 0.5 mg/ml ibuprofen solution was diluted to 50 ml with phosphate buffer (pH 7.2) to obtain a 50 µg/ml ibuprofen solution
- A volume of 7 ml of the 0.5 mg/ml ibuprofen solution was diluted to 50 ml with phosphate buffer (pH 7.2) to obtain a 70 µg/ml ibuprofen solution
- A volume of 10 ml of the 0.5 mg/ml ibuprofen solution was diluted to 50 ml with phosphate buffer (pH 7.2) to obtain a 100 µg/ml ibuprofen solution
- A volume of 12 ml of the 0.5 mg/ml ibuprofen solution was diluted to 50 ml with phosphate buffer (pH 7.2) to obtain a 120 µg/ml ibuprofen solution

These solutions were analysed in triplicate to obtain the linear regression graph for ibuprofen.

C.2.6.3 Paracetamol

Tablet dissolution was performed on 3 paracetamol MUPS tablets using the method as described in the USP (2015) (USP type II apparatus).

Dissolution apparatus: The tablet dissolution was performed using a Distek Model 2500 dissolution bath (Distek, New Jersey) complying with a USP type II

apparatus, a Distek Evolution 4300 Dissolution Sampler (Distek, New Jersey) and Distek Syringe Pump (Distek, New Jersey).

Paddle speed: 50 rpm

Dissolution medium: phosphate buffer (pH 5.8)

Medium volume: 900 ml

Sample volume: 7 ml

Sample intervals: 5; 15; 30; 45; 60; 90; 120 and 150 min

UV Detection: Samples were analysed by UV-spectrophotometry using a UV 1700 PharmacSpec Spectrophotometer (Shimadzu Corporation, Kyoto, Japan).

Absorbance: UV at 243 nm

Standard solution preparation

The standard paracetamol solutions were prepared as follows:

- Approximately 50 mg paracetamol was accurately weighed, transferred to a 100 ml volumetric flask, dissolved in 10 ml ethanol and made up to volume with phosphate buffer (pH 5.8).
- A volume of 1 ml of the 0.5 mg/ml paracetamol solution was diluted to 100 ml with phosphate buffer (pH 5.8) to obtain a 5 µg/ml paracetamol solution
- A volume of 2 ml of the 0.5 mg/ml paracetamol solution was diluted to 50 ml with phosphate buffer (pH 5.8) to obtain a 20 µg/ml paracetamol solution
- A volume of 5 ml of the 0.5 mg/ml paracetamol solution was diluted to 50 ml with phosphate buffer (pH 5.8) to obtain a 50 µg/ml paracetamol solution
- A volume of 7 ml of the 0.5 mg/ml paracetamol solution was diluted to 50 ml with phosphate buffer (pH 5.8) to obtain a 70 µg/ml paracetamol solution
- A volume of 10 ml of the 0.5 mg/ml paracetamol solution was diluted to 50 ml with phosphate buffer (pH 5.8) to obtain a 100 µg/ml paracetamol solution
- A volume of 12 ml of the 0.5 mg/ml paracetamol solution was diluted to 50 ml with phosphate buffer (pH 5.8) to obtain a 120 µg/ml paracetamol solution

These solutions were analysed in triplicate to obtain the linear regression graph for paracetamol.

C.3 Results

C.3.1 Uniformity of mass

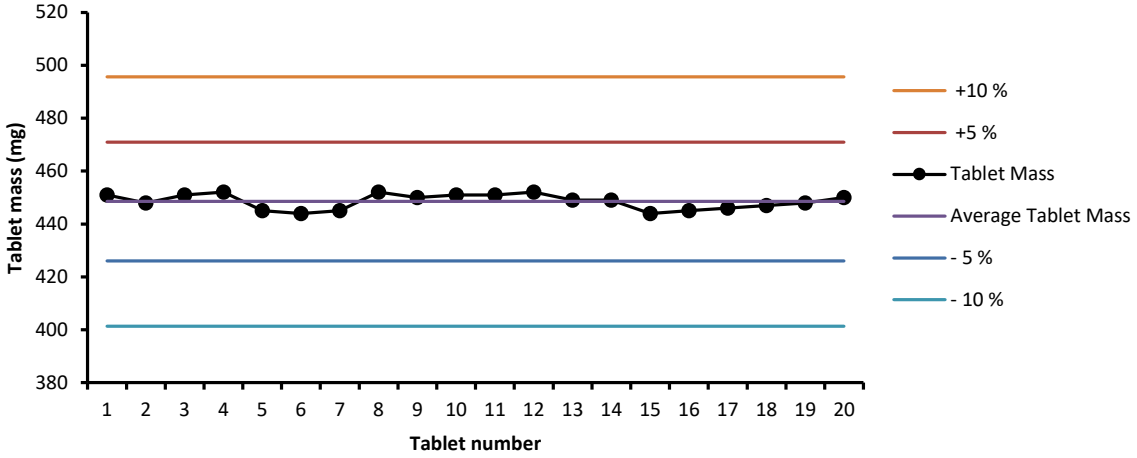
The individual tablet mass and average tablet masses of the various MUPS tablet formulation are presented in Tables C.1–C.4.

Table C.1: Tablet mass variation of the MicroceLac® 200 MUPS tablet formulations

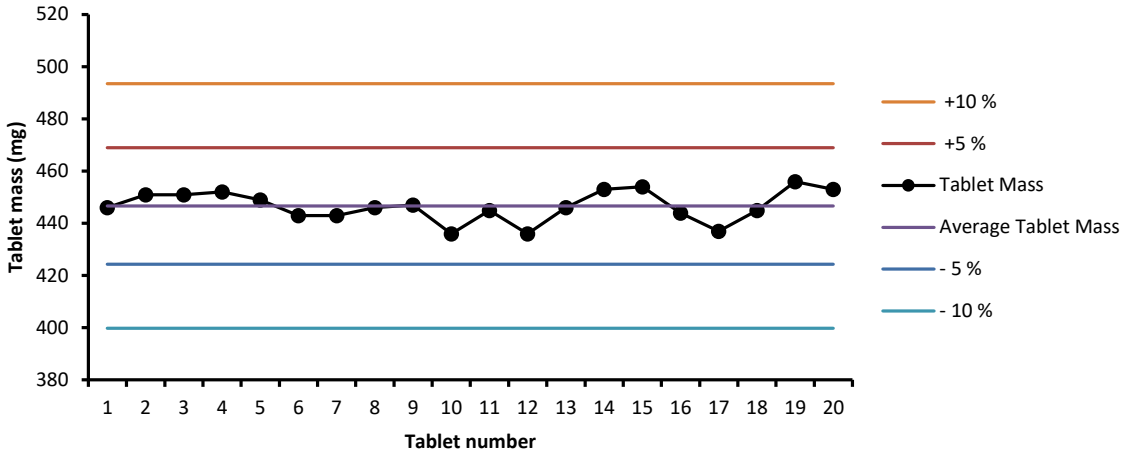
	MicroceLac® 200 MUPS tablets Tablet mass (mg)				
Tablet number	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
1	451	446	457	458	447
2	448	451	440	449	452
3	451	451	445	460	446
4	452	452	445	454	435
5	445	449	446	452	446
6	444	443	446	446	445
7	445	443	452	444	444
8	452	446	444	446	447
9	450	447	447	451	440
10	451	436	445	458	449
11	451	445	445	449	459
12	452	436	449	442	442
13	449	446	442	456	443
14	449	453	444	456	443
15	444	454	446	450	445
16	445	444	450	446	446
17	446	437	441	448	448
18	447	445	451	451	449
19	448	456	445	454	434
20	450	453	441	443	451
Average	***448.50***	***446.65***	***446.05***	***450.65***	***445.55***
Std Dev	*2.84*	*5.87*	*4.12*	*5.29*	*5.58*
% RSD	*0.63*	*1.31*	*0.92*	*1.17*	*1.25*

The individual tablet masses of the various MUPS tablet formulation are graphically presented in Figures C.1–C.4.

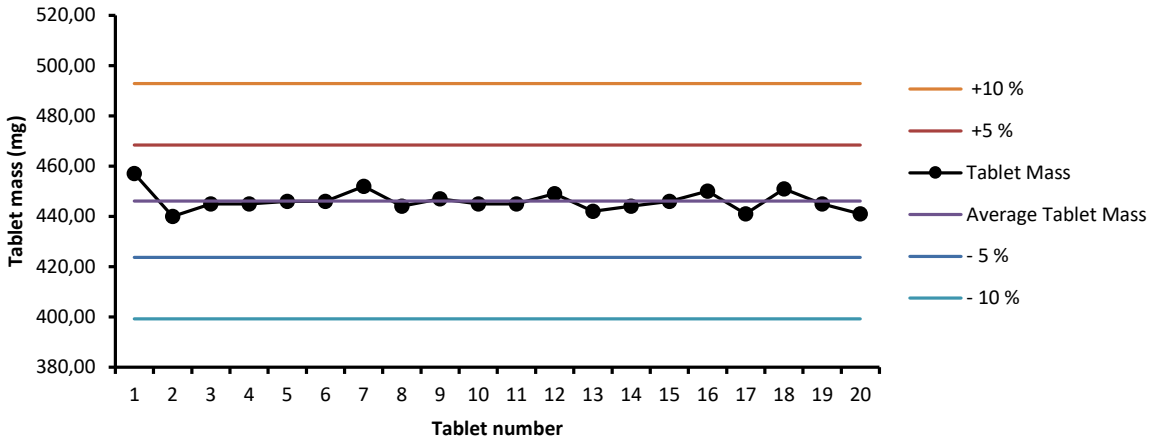
a)


520
500
480
460
440
420
400
380
Tablet mass (mg)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Tablet number
+10 %
+5 %
Tablet Mass
Average Tablet Mass
- 5 %
- 10 %

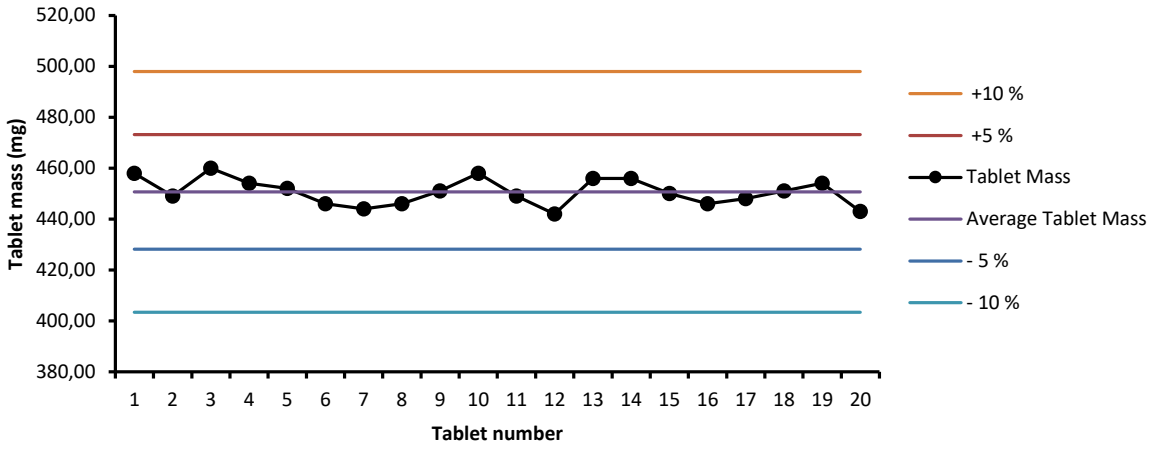
b)


520
500
480
460
440
420
400
380
Tablet mass (mg)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Tablet number
+10 %
+5 %
Tablet Mass
Average Tablet Mass
- 5 %
- 10 %

c)


520,00
500,00
480,00
460,00
440,00
420,00
400,00
380,00
Tablet mass (mg)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Tablet number
+10 %
+5 %
Tablet Mass
Average Tablet Mass
- 5 %
- 10 %

d)



e)

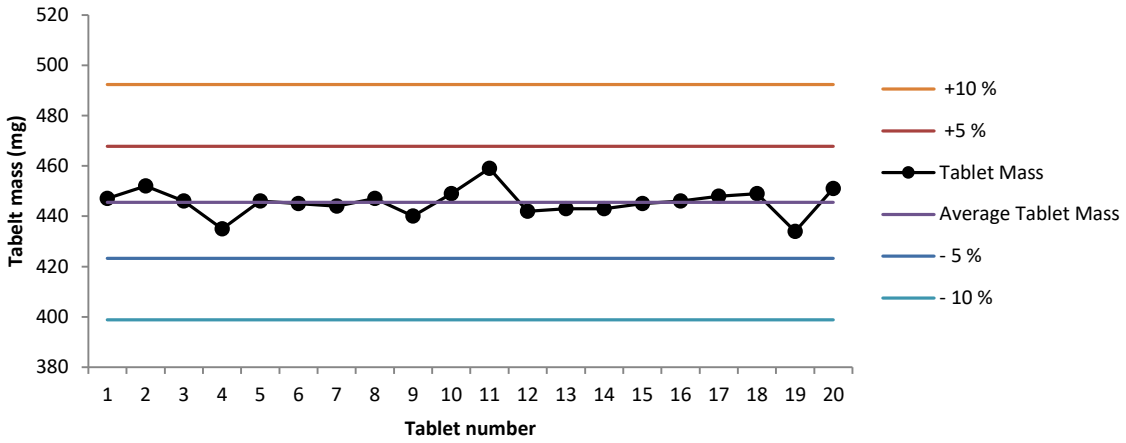


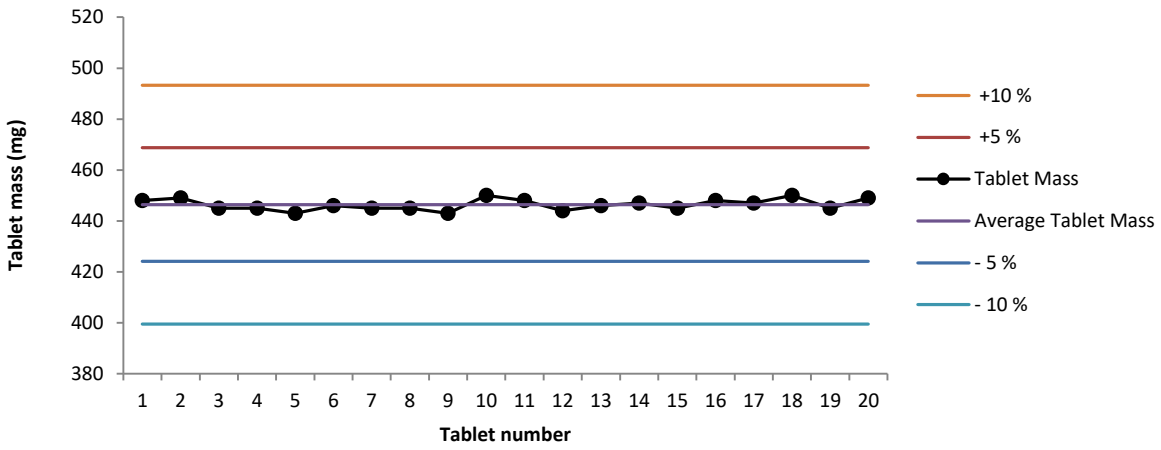
Figure C.1: Uniformity of mass of the MicroceLac® 200 MUPS tablets containing a) 0.5 mm; b) 1,0 mm; c) 1,5 mm; d) 2,0 mm and e) 2,5 mm pellets

The various MicroceLac® 200 MUPS tablet formulations all complied with the uniformity of mass specifications as specified in the BP (2015).

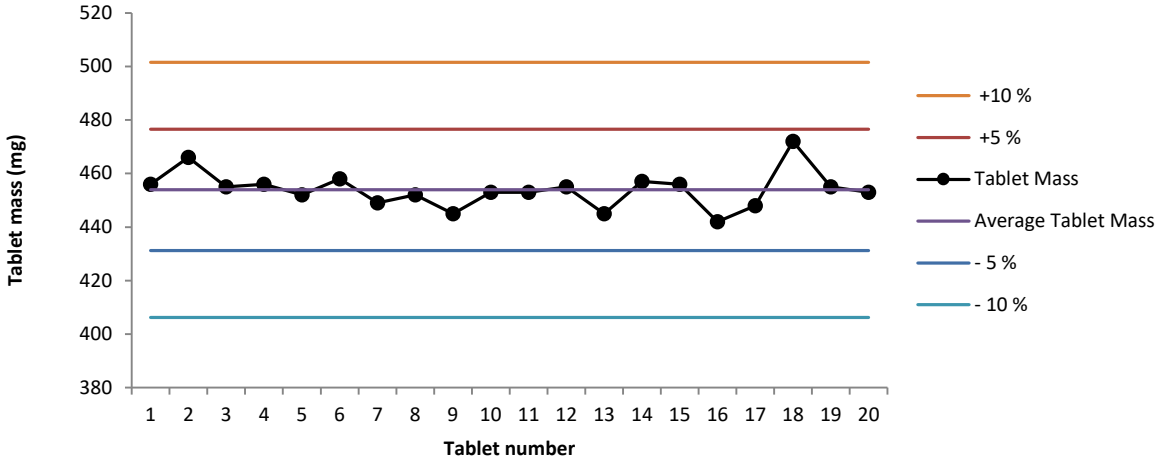
Table C.2: Tablet mass variation of the doxylamine MUPS tablet formulations

Tablet number	Doxylamine MUPS tablets Tablet mass (mg)				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
1	448	456	447	442	438
2	449	466	450	444	456
3	445	455	435	479	425
4	445	456	443	455	429
5	443	452	452	453	430
6	446	458	445	457	441
7	445	449	435	438	431
8	445	452	436	441	462
9	443	445	446	460	439
10	450	453	447	450	436
11	448	453	452	452	436
12	444	455	438	436	436
13	446	445	443	456	438
14	447	457	450	436	435
15	445	456	451	442	445
16	448	442	448	453	447
17	447	448	449	450	444
18	450	472	445	457	427
19	445	455	440	451	439
20	449	453	435	450	444
Average	***446.40***	***453.90***	***444.35***	***450.10***	***438.90***
Std Dev	*2.16*	*6.83*	*5.95*	*10.01*	*9.18*
% RSD	*0.48*	*1.50*	*1.34*	*2.22*	*2.09*

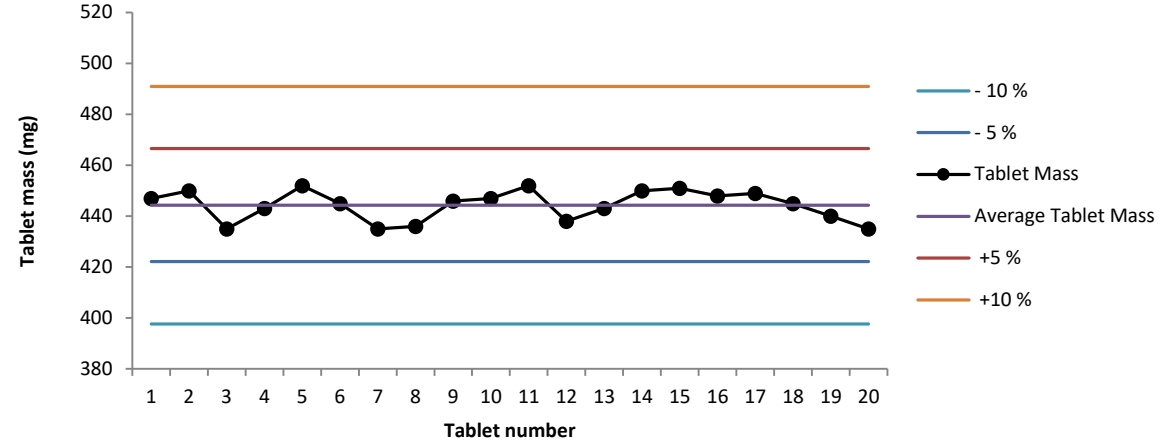
a)



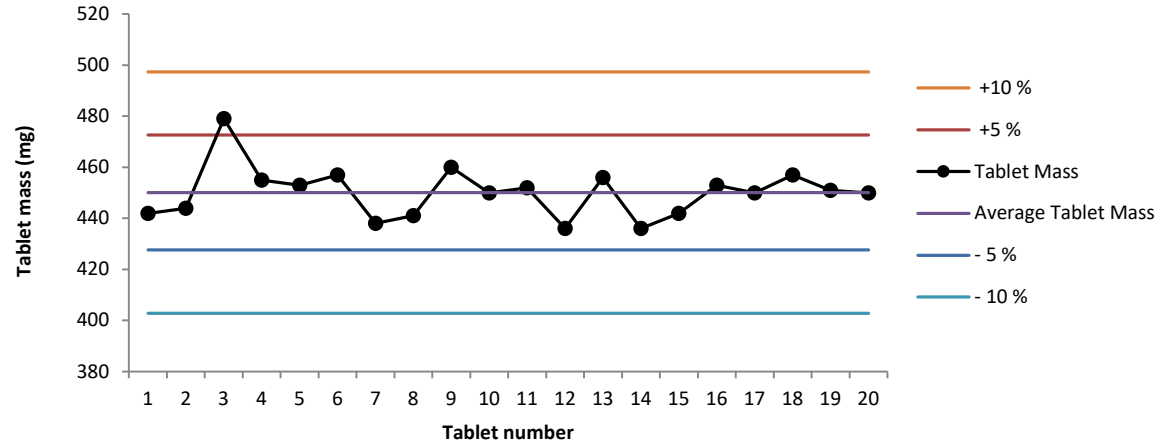
b)


Tablet mass (mg)
520
500
480
460
440
420
400
380
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Tablet number
+10 %
+5 %
Tablet Mass
Average Tablet Mass
- 5 %
- 10 %

c)


Tablet mass (mg)
520
500
480
460
440
420
400
380
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Tablet number
- 10 %
- 5 %
Tablet Mass
Average Tablet Mass
+5 %
+10 %

d)


Tablet mass (mg)
520
500
480
460
440
420
400
380
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Tablet number
+10 %
+5 %
Tablet Mass
Average Tablet Mass
- 5 %
- 10 %

e)

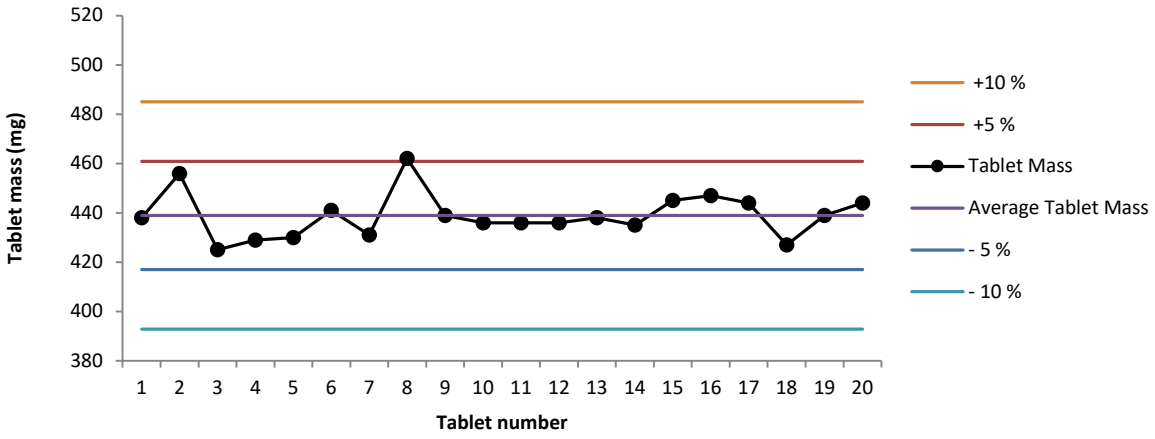


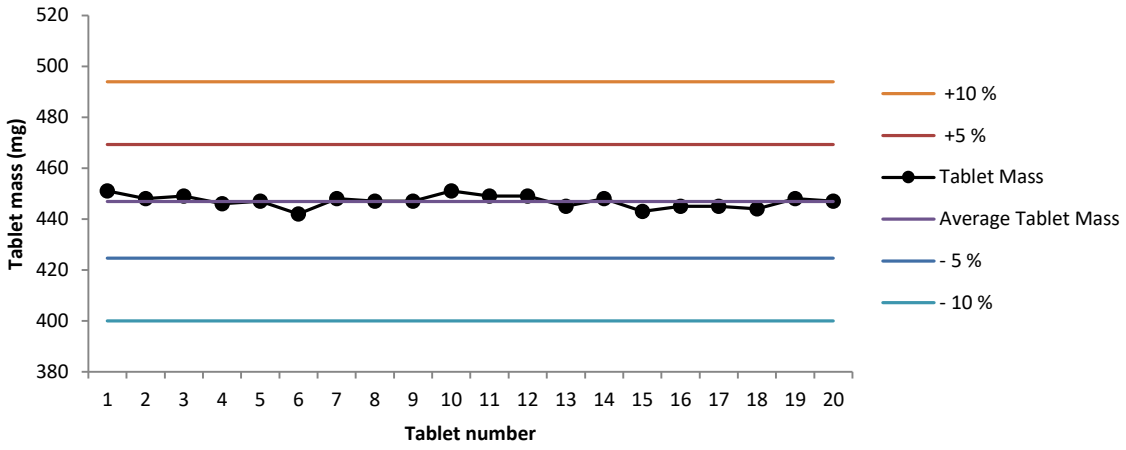
Figure C.2: Uniformity of mass of the doxylamine MUPS tablets containing a) 0.5 mm; b) 1,0 mm; c) 1,5 mm; d) 2,0 mm and e) 2,5 mm pellets

The various doxylamine MUPS tablet formulations all complied with the uniformity of mass specifications as specified in the BP (2015).

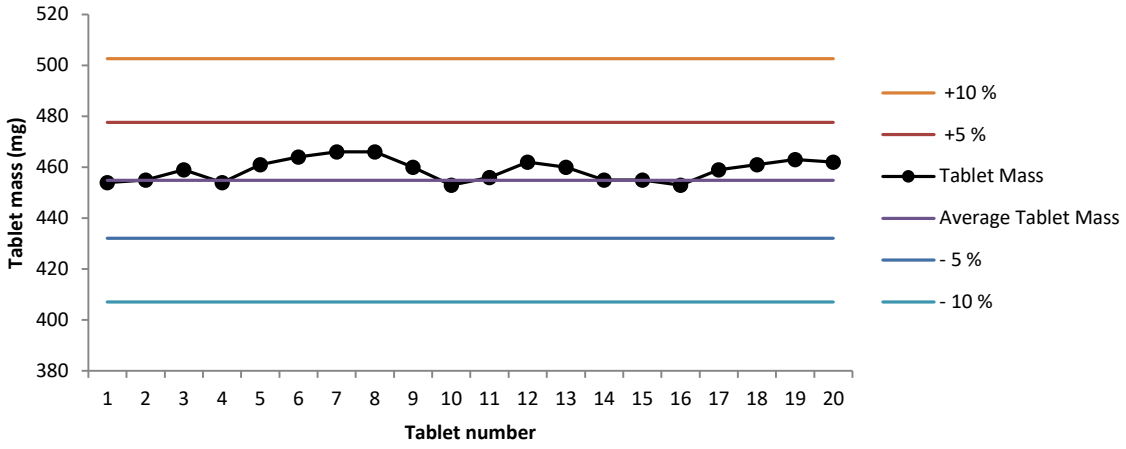
Table C.3: Tablet mass variation of the ibuprofen MUPS tablet formulations

	Ibuprofen MUPS tablets Tablet mass (mg)				
Tablet number	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
1	451	448	467	444	434
2	448	464	455	446	458
3	449	447	458	436	440
4	446	450	454	441	454
5	447	459	464	450	457
6	442	454	444	445	439
7	448	450	462	446	451
8	447	457	462	446	452
9	447	456	449	435	466
10	451	451	450	439	458
11	449	465	459	442	452
12	449	464	470	452	451
13	445	454	454	447	483
14	448	448	463	443	487
15	443	449	468	440	461
16	445	453	453	445	459
17	445	456	465	440	486
18	444	464	447	447	452
19	448	453	470	449	457
20	447	455	469	445	445
Average	***446.95***	***454.85***	***459.15***	***443.90***	***457.10***
Std Dev	*2.42*	*5.80*	*8.06*	*4.44*	*14.44*
% RSD	*0.54*	*1.27*	*1.76*	*1.00*	*3.16*

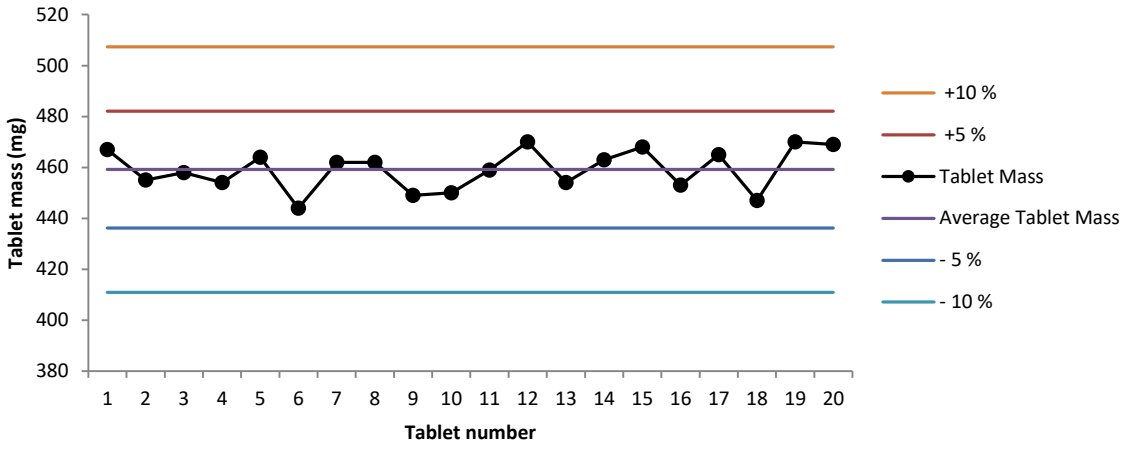
a)


520
500
480
460
440
420
400
380
Tablet mass (mg)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Tablet number
+10 %
+5 %
Tablet Mass
Average Tablet Mass
- 5 %
- 10 %

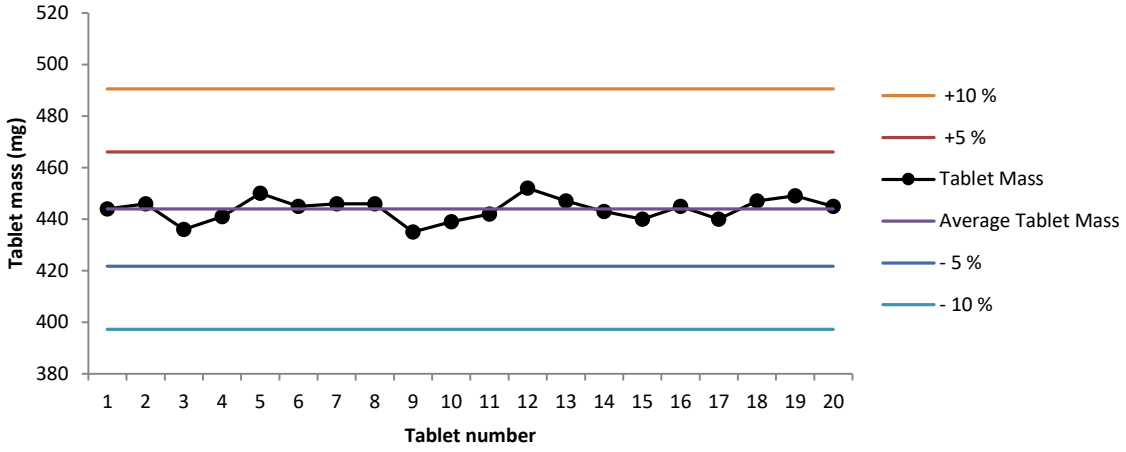
b)


520
500
480
460
440
420
400
380
Tablet mass (mg)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Tablet number
+10 %
+5 %
Tablet Mass
Average Tablet Mass
- 5 %
- 10 %

c)


520
500
480
460
440
420
400
380
Tablet mass (mg)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Tablet number
+10 %
+5 %
Tablet Mass
Average Tablet Mass
- 5 %
- 10 %

d)



e)

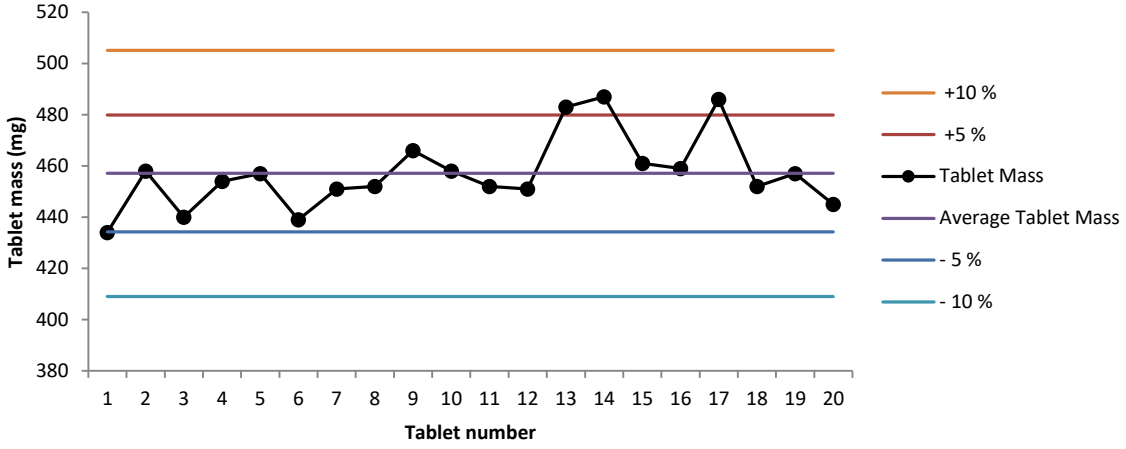


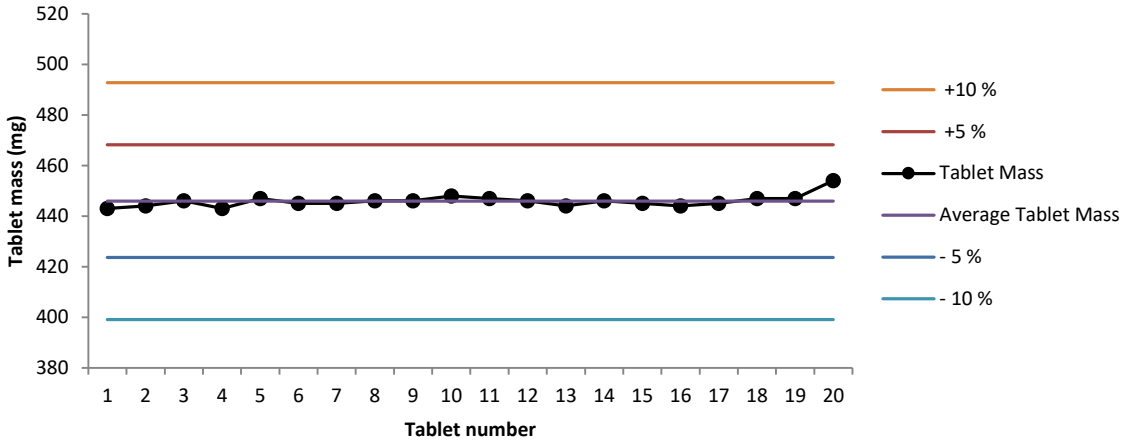
Figure C.3: Uniformity of mass of the ibuprofen MUPS tablets containing a) 0.5 mm; b) 1,0 mm; c) 1,5 mm; d) 2,0 mm and e) 2,5 mm pellets

The various ibuprofen MUPS tablet formulations all complied with the uniformity of mass specifications as specified in the BP (2015) except for the 2.5 mm ibuprofen MUPS tablet formulation which had four tablets with individual masses that deviated more than 5% from the average tablet mass.

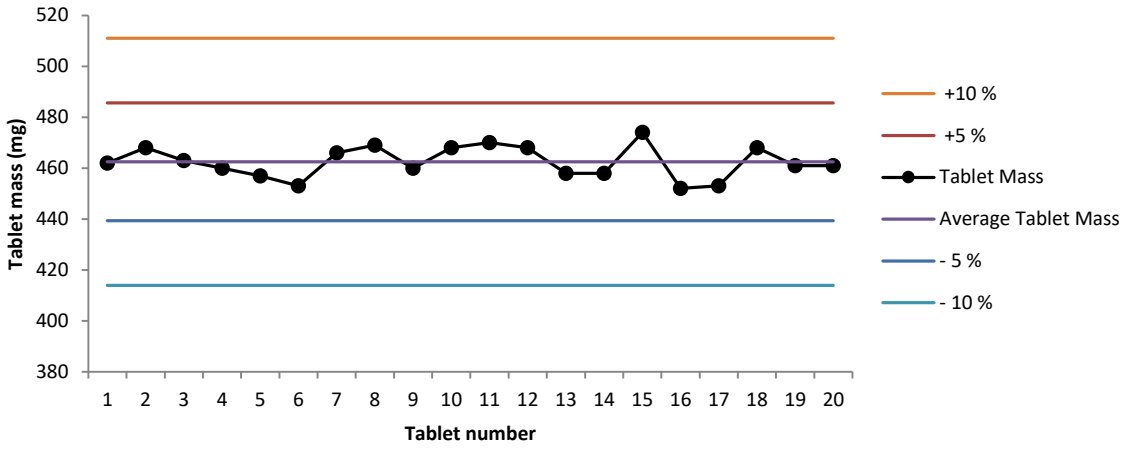
Table C.4: Tablet mass variation of the paracetamol MUPS tablet formulations

Tablet number	Paracetamol MUPS tablets Tablet mass (mg)				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
1	443	462	464	449	464
2	444	468	460	449	455
3	446	463	464	468	441
4	443	460	452	440	469
5	447	457	466	456	474
6	445	453	464	450	456
7	445	466	463	447	466
8	446	469	452	441	461
9	446	460	446	447	450
10	448	468	461	453	454
11	447	470	436	444	472
12	446	468	452	454	452
13	444	458	456	448	500
14	446	458	450	467	463
15	445	474	460	445	461
16	444	452	454	451	455
17	445	453	455	435	453
18	447	468	462	439	450
19	447	461	455	465	471
20	454	461	452	454	442
Average	***445.90***	***462.45***	***456.20***	***450.10***	***460.45***
Std Dev	*2.36*	*6.25*	*7.40*	*8.97*	*13.18*
% RSD	*0.53*	*1.35*	*1.62*	*1.99*	*2.86*

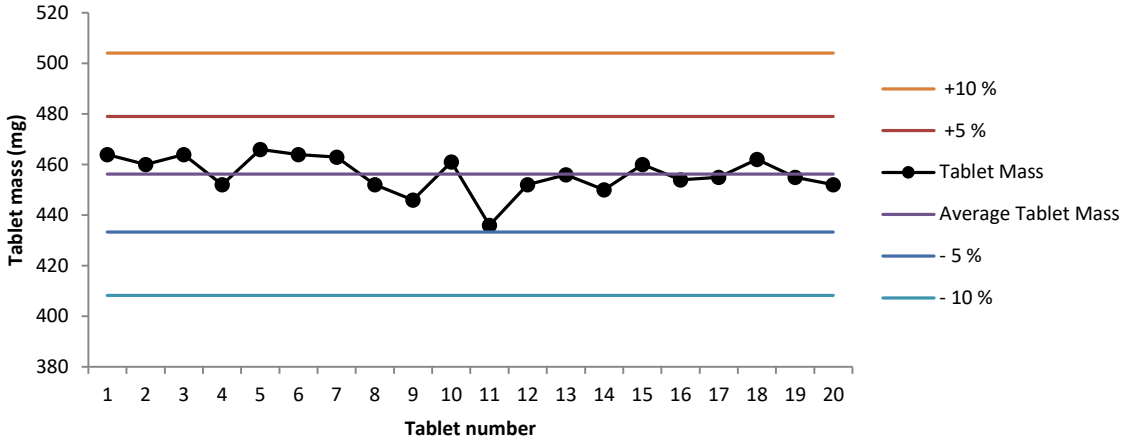
a)



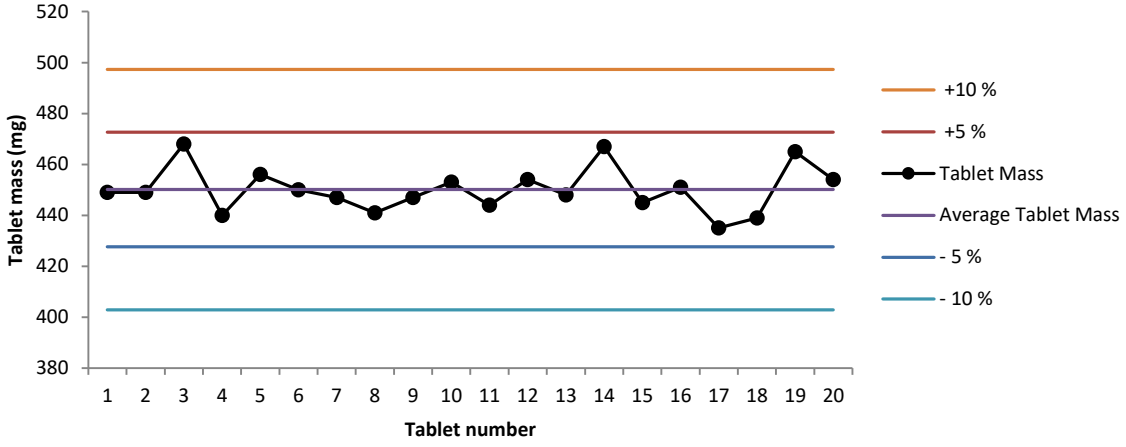
b)


520
500
480
460
440
420
400
380
Tablet mass (mg)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Tablet number
+10 %
+5 %
Tablet Mass
Average Tablet Mass
- 5 %
- 10 %

c)


520
500
480
460
440
420
400
380
Tablet mass (mg)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Tablet number
+10 %
+5 %
Tablet Mass
Average Tablet Mass
- 5 %
- 10 %

d)


520
500
480
460
440
420
400
380
Tablet mass (mg)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Tablet number
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+5 %
Tablet Mass
Average Tablet Mass
- 5 %
- 10 %

e)

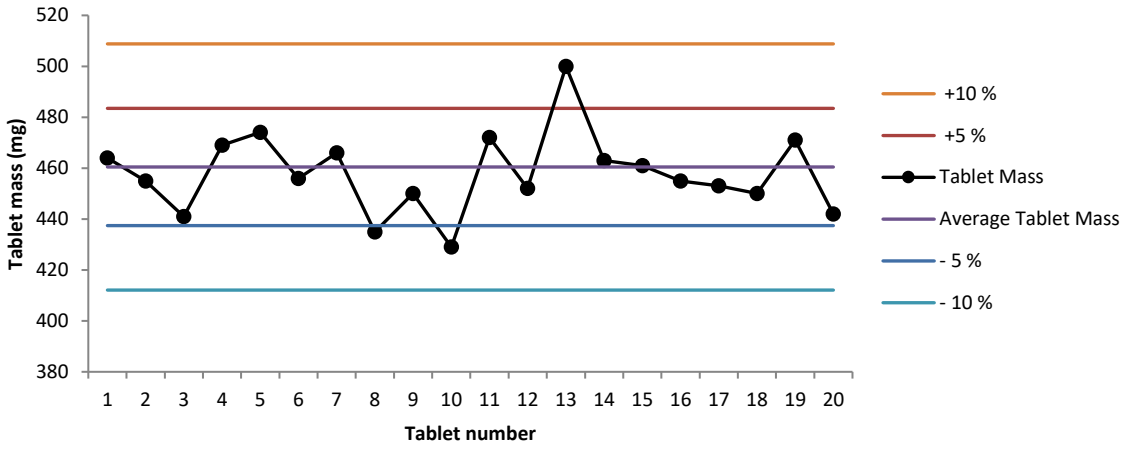

Figure C.4: Uniformity of mass of the paracetamol MUPS tablets containing a) 0.5 mm; b) 1,0 mm; c) 1,5 mm; d) 2,0 mm and e) 2,5 mm pellets

The various paracetamol MUPS tablet formulations all complied with the uniformity of mass specifications as specified in the BP (2015) except for the 2.5 mm paracetamol MUPS tablet formulation which had three tablets with individual masses that deviated more than 5% from the average tablet mass.

C.3.2 Hardness

The individual tablet hardness and average tablet hardness of the various MUPS tablet formulation are presented in Tables C.5–C.8.

Table C.5: Tablet hardness of the MicroceLac ® 200 MUPS tablet formulations

	MicroceLac® 200 MUPS tablets Tablet hardness (N)				
Tablet number	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
1	67	95	101	109	75
2	71	88	99	121	59
3	73	91	121	129	78
4	70	60	87	134	74
5	72	81	102	134	94
6	75	84	109	132	71
7	74	91	87	150	77
8	70	95	92	119	74
9	68	79	94	126	66
10	75	92	92	100	60
Average	***71.5***	***85.6***	***89.4***	***125.4***	***72.8***
Std Dev	*2.8*	*10.56*	*10.56*	*14.08*	*13.03*

The various MicroceLac ® 200 MUPS tablet formulations yielded acceptable tablet hardness results.

Table C.6: Tablet hardness of the doxylamine MUPS tablet formulations

	Doxylamine MUPS tablets Tablet hardness (N)				
Tablet number	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
1	117	80	106	77	95
2	118	68	112	101	96
3	124	77	113	93	90
4	120	92	84	91	98
5	148	97	78	109	99
6	135	95	113	107	90
7	137	90	106	68	97
8	114	95	126	93	86
9	123	74	121	94	62
10	121	109	132	93	107
Average	***125.7***	***87.7***	***109.1***	***92.6***	***92.0***
Std Dev	*10.78*	*12.56*	*17.02*	*12.47*	*12.04*

The various doxylamine MUPS tablet formulations yielded acceptable tablet hardness results.

Table C.7: Tablet hardness of the ibuprofen MUPS tablet formulations

	Ibuprofen MUPS tablets Tablet hardness (N)				
Tablet number	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
1	91	93	148	97	136
2	95	85	152	105	120
3	106	98	126	112	119
4	82	111	102	98	103
5	78	91	114	117	125
6	97	94	124	91	144
7	84	99	98	99	119
8	81	104	96	127	129
9	81	107	94	114	86
10	84	122	115	135	103
Average	***87.9***	***100.4***	***116.9***	***109.5***	***118.4***
Std Dev	*9.00*	*10.88*	*20.78*	*14.14*	*17.15*

The various ibuprofen MUPS tablet formulations yielded acceptable tablet hardness results.

Table C.8: Tablet hardness of the paracetamol MUPS tablet formulations

	Paracetamol MUPS tablets Tablet hardness (N)				
Tablet number	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
1	66	100	112	104	125
2	79	112	122	106	89
3	66	104	106	146	53
4	69	106	115	116	87
5	67	116	109	109	118
6	62	106	122	101	82
7	65	108	104	118	44
8	64	95	105	98	87
9	66	120	110	116	97
10	70	101	113	108	72
Average	***67.4***	***106.8***	***111.8***	***112.2***	***85.4***
Std Dev	*4.67*	*7.57*	*6.43*	*13.60*	*25.25*

The various paracetamol MUPS tablet formulations yielded acceptable tablet hardness results.

C.3.3 Friability

The friability of the various MUPS tablet formulations are presented in Table C.9–C.12.

Table C.9: Tablet friability of the MicroceLac ® 200 MUPS tablet formulations

	MicroceLac® 200 MUPS tablets Tablet friability (%)				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
Mass before	6.72	6.49	6.68	6.30	6.50
Mass after	6.70	6.47	6.65	6.29	6.49
Friability	***0.30***	***0.31***	***0.45***	***0.16***	***0.15***

The friability results of the various MicroceLac ® 200 MUPS tablet formulations were less than 1.0% indicating results that complied with the USP (2015) specifications for uncoated tablets.

Table C.10: Tablet friability of the doxylamine MUPS tablet formulations

	Doxylamine MUPS tablets Tablet friability (%)				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
Mass before	6.26	6.51	6.25	6.24	6.53
Mass after	6.24	6.49	6.24	6.22	6.52
Friability	***0.32***	***0.31***	***0.16***	***0.32***	***0.15***

The friability results of the various doxylamine MUPS tablet formulations were less than 1.0% indicating results that complied with the USP (2015) specifications for uncoated tablets.

Table C.11: Tablet friability of the ibuprofen MUPS tablet formulations

	Ibuprofen MUPS tablets Tablet friability (%)				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
Mass before	6.26	6.45	6.46	6.20	6.53
Mass after	6.25	6.44	6.45	6.19	6.52
Friability	***0.11***	***0.12***	***0.19***	***0.13***	***0.20***

The friability results of the various ibuprofen MUPS tablet formulations were less than 1.0% indicating results that complied with the USP (2015) specifications for uncoated tablets.

Table C.12: Tablet friability of the paracetamol MUPS tablet formulations

	Paracetamol MUPS tablets Tablet friability (%)				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
Mass before	6.27	6.52	6.67	6.73	6.40
Mass after	5.61	6.50	6.66	6.72	6.37
Friability	***10.53***	***0.31***	***0.28***	***0.13***	***0.50***

The friability results of the various paracetamol MUPS tablet formulations were less than 1.0% with the exception of the 0.5 mm formulation which did not comply with the USP (2015) specifications for uncoated tablets.

C.3.4 Disintegration

The disintegration of the various MUPS tablet formulations are presented in Table C.13–C16.

Table C.13: Tablet disintegration of the MicroceLac ® 200 MUPS tablet formulations

	MicroceLac® 200 MUPS tablets Disintegration (min)				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
Disintegration	***21.00***	***25.53***	***24.28***	***16.63***	***> 45.00***

Table C.14: Tablet disintegration of the doxylamine MUPS tablet formulations

	Doxylamine MUPS tablets Disintegration (min)				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
Disintegration	***> 45.00***	***> 45.00***	***> 45.00***	***> 45.00***	***> 45.00***

Table C.15: Tablet disintegration of the ibuprofen MUPS tablet formulations

	Ibuprofen MUPS tablets Disintegration (min)				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
Disintegration	***14.82***	***14.68***	***15.15***	***19.70***	***> 45.00***

Table C.16: Tablet disintegration of the paracetamol 200 MUPS tablet formulations

	Paracetamol MUPS tablets Disintegration (min)				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
Disintegration	***14.17***	***12.87***	***20.57***	***16.48***	***> 45.00***

The disintegration time of all the MUPS formulations were generally more than 15 min and the disintegration time of the doxylamine MUPS tablet formulations were more than 45 min.

C.3.5 Content uniformity

C.3.5.1 Doxylamine

The content uniformity of the various MUPS tablet formulations are presented in Table C.17–C.19

Table C.17: Tablet content uniformity of the doxylamine MUPS tablet formulations

	Doxylamine MUPS tablets Content uniformity (%) (Acceptance Value L1 < 15)				
Tablet number	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
1	103.63	105.76	112.41	111.10	110.94
2	104.07	104.26	113.97	111.39	112.44
3	104.22	106.84	113.61	106.75	107.57
4	105.48	104.83	110.74	110.32	114.15
5	103.71	107.65	110.61	110.12	108.20
6	104.10	102.52	108.97	110.55	108.83
7	103.87	103.38	109.30	109.37	109.01
8	105.54	101.73	110.54	111.67	106.06
9	103.28	99.36	110.45	111.31	108.12
10	103.15	105.57	109.67	106.13	112.04
Average	***104.11***	***104.19***	***111.03***	***109.87***	***109.74***
Std Dev	*0.82*	*2.51*	*1.74*	*1.94*	*2.54*
L1	*4.56*	*8.71*	*13.69*	*13.03*	*14.33*

The content uniformity results of the various doxylamine MUPS tablet formulations complied with the specification of the USP (2015) with an acceptance value of less than or equal to L1% (L1% = 15.0).

C.3.5.2 Ibuprofen

Table C.18: Tablet content uniformity of the ibuprofen MUPS tablet formulations

Tablet number	**Ibuprofen MUPS tablets Content uniformity (%)** (Acceptance Value L1 < 15)				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
1	96.88	100.63	116.39	111.38	120.63
2	98.39	106.28	108.79	110.08	108.04
3	102.60	101.02	105.03	115.08	115.97
4	103.09	102.05	115.79	102.89	110.82
5	94.63	105.45	107.81	113.44	116.81
6	97.10	109.06	107.59	111.24	122.81
7	93.71	102.70	107.57	115.34	110.80
8	95.21	101.68	105.55	114.06	116.73
9	100.36	100.36	104.68	111.26	119.85
10	98.08	99.72	116.10	104.17	108.44
Average	***98.01***	***102.89***	***109.53***	***110.89***	***115.09***
Std Dev	*3.21*	*3.04*	*4.72*	*4.27*	*5.27*
L1	*8.19*	*8.70*	*19.35*	*19.65*	*26.24*

The content uniformity results of the 0.5 mm and 1.0 mm ibuprofen MUPS tablet formulations complied with the specification of the UPS 39 (2015) with an acceptance value of less than or equal to L1% (L1% = 15.0). The content uniformity results of the 1.5 mm; 2.0 mm and 2.5 mm ibuprofen MUPS tablet formulations did not comply with the specification of the USP (2015) with an acceptance value of more than L1% (L1% = 15.0).

C.3.5.3 Paracetamol

Table C.19: Tablet content uniformity of the paracetamol MUPS tablet formulations

Tablet number	**Paracetamol MUPS tablets Content uniformity (%)** (Acceptance Value L1 < 15)				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
1	94.73	110.01	103.72	105.65	89.10
2	95.42	107.55	97.11	85.99	83.71
3	96.80	106.24	97.93	89.86	97.89
4	96.60	110.17	102.60	94.68	103.02
5	93.27	107.47	105.76	87.52	105.20
6	94.32	108.77	102.23	89.64	98.18
7	92.50	111.10	100.54	90.31	110.29
8	93.77	111.29	98.00	86.60	108.09
9	88.02	110.15	101.79	90.44	113.96
10	94.46	111.90	97.28	79.82	107.44
Average	***93.99***	***109.47***	***100.70***	***90.05***	***101.69***
Std Dev	*2.50*	*1.88*	*3.01*	*6.71*	*9.55*
L1	*10.50*	*12.47*	*6.42*	*4.65*	*23.11*

The content uniformity results of the various paracetamol MUPS tablet formulations complied with the specification of the USP (2015) with an acceptance value of less than or equal to L1% (L1% = 15.0) except for the 2.5 mm paracetamol MUPS tablet formulations which did not comply with the specification.

C.3.6 Dissolution

The dissolution results of the various MUPS tablet formulations are presented in Table C.20–C.37 and Figure C.5–C.7.

C.3.6.1 Doxylamine

Table C.20: Tablet dissolution results of the 0.5 mm doxylamine MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.40	0.41	0.40
15	33.16	36.91	40.24
30	60.66	66.52	65.40
45	83.12	86.50	83.81
60	96.98	96.94	94.60
90	102.45	101.78	102.02
120	101.34	100.77	101.17
150	100.53	100.01	99.74

Table C.21: Tablet dissolution results of the 1.0 mm doxylamine MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.40	0.41	0.40
15	29.71	29.17	30.11
30	54.46	54.11	50.91
45	74.50	73.99	67.18
60	87.33	88.92	80.11
90	101.31	101.44	101.27
120	100.84	100.76	100.85
150	100.28	100.01	100.56

Table C.22: Tablet dissolution results of the 1.5 mm doxylamine MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.47	0.50	0.48
15	14.56	14.63	16.94
30	28.02	30.26	31.60
45	42.73	50.63	46.07
60	62.28	67.89	64.99
90	93.10	99.07	99.86
120	101.59	100.46	102.10
150	101.20	100.00	101.54

Table C.23: Tablet dissolution results of the 2.0 mm doxylamine MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.48	0.47	0.45
15	18.31	16.54	19.01
30	38.27	32.44	35.00
45	58.03	47.94	51.40
60	74.14	66.38	67.16
90	100.62	93.05	96.42
120	101.24	101.74	100.48
150	100.55	101.34	100.17

Table C.24: Tablet dissolution results of the 2.5 mm doxylamine MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.45	0.47	0.51
15	12.16	13.74	11.25
30	24.92	26.81	23.55
45	34.86	41.21	35.36
60	46.36	58.14	47.10
90	72.08	87.02	76.84
120	97.40	99.20	98.09
150	100.32	99.02	98.85

Table C.25: Summary of the dissolution results of the various doxylamine MUPS tablet formulations

Time (min)	% Dissolved				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
5	0.40	0.40	0.48	0.46	0.48
15	36.77	29.66	15.38	17.95	12.39
30	64.19	53.16	29.96	35.24	25.09
45	84.47	71.89	46.48	52.46	37.14
60	96.18	85.45	65.05	69.23	50.53
90	102.08	101.34	97.34	96.70	78.65
120	101.10	100.82	101.38	101.15	98.23
150	100.09	100.28	100.91	100.69	99.40

At least 50% or more of the drug was released at 60 min for all of the various doxylamine MUPS tablet formulations. The formulations with a smaller pellet size exhibited a faster drug release rate than the formulations with a larger pellet size.

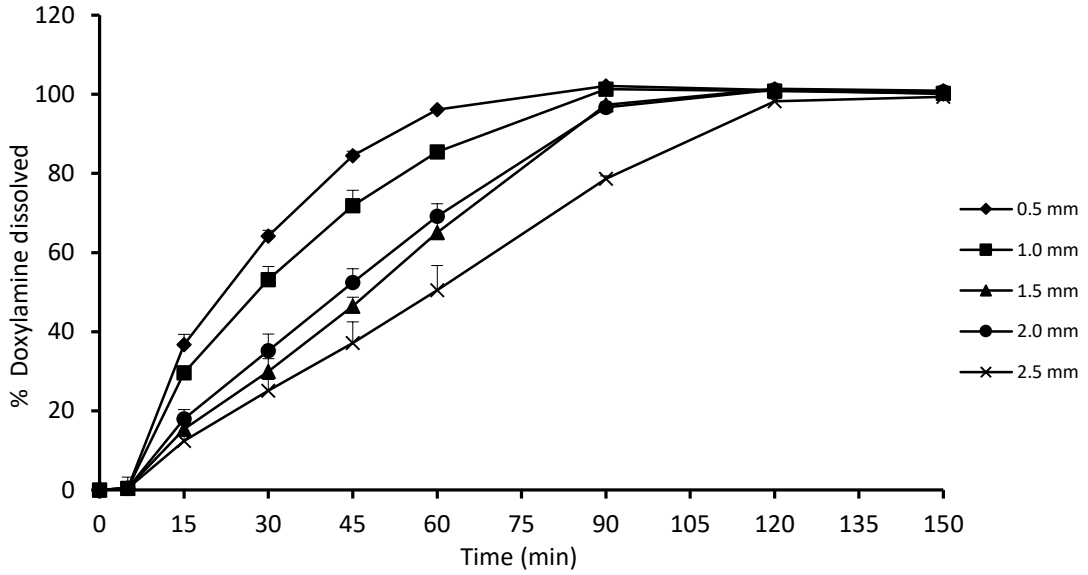

Figure C5: Dissolution results of the various doxylamine MUPS tablet formulations

C.3.6.2 Ibuprofen

Table C.26: Tablet dissolution results of the 0.5 mm ibuprofen MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.49	0.48	0.48
15	37.14	46.92	44.01
30	68.70	77.13	73.70
45	85.96	89.30	85.66
60	94.43	98.32	94.53
90	96.40	96.13	96.30
120	96.84	99.84	97.76
150	101.12	100.51	100.01

Table C.27: Tablet dissolution results of the 1.0 mm ibuprofen MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.44	0.45	0.44
15	17.36	13.76	17.92
30	47.74	40.69	48.61
45	69.58	61.95	70.85
60	83.62	77.88	86.76
90	91.16	87.93	92.55
120	94.79	93.24	94.97
150	99.29	99.61	99.38

Table C.28: Tablet dissolution results of the 1.5 mm ibuprofen MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.47	0.45	0.47
15	13.11	14.30	13.78
30	36.91	38.17	37.93
45	57.97	57.72	58.19
60	71.82	71.08	73.63
90	86.92	85.62	87.96
120	96.33	94.25	97.79
150	99.43	98.52	99.40

Table C.29: Tablet dissolution results of the 2.0 mm ibuprofen MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.45	0.46	0.45
15	25.65	18.12	13.16
30	52.05	45.75	39.66
45	66.63	63.55	58.60
60	75.01	73.79	70.80
90	88.95	87.09	80.94
120	96.54	95.65	88.07
150	100.13	100.12	98.37

Table C.30: Tablet dissolution results of the 2.5 mm ibuprofen MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.45	0.47	0.43
15	25.71	17.16	21.26
30	48.81	42.42	46.94
45	63.28	58.07	60.03
60	71.49	67.70	69.73
90	82.78	80.32	79.60
120	91.78	91.03	87.88
150	95.49	96.54	96.42

Table C.31: Summary of the dissolution results of the various ibuprofen MUPS tablet formulations

Time (min)	% Dissolved				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
5	0.48	0.44	0.46	0.46	0.45
15	42.69	16.35	13.73	18.98	21.38
30	73.18	45.68	37.67	45.82	46.06
45	86.97	67.46	57.96	62.93	60.46
60	95.76	82.75	72.18	73.20	69.64
90	96.28	90.55	86.83	85.66	80.90
120	98.15	94.34	96.13	93.42	90.23
150	100.54	99.43	99.12	99.54	96.15

At least 50% or more of the drug was released at 45 min for all of the various ibuprofen MUPS tablet formulations. The formulations with a smaller pellet size exhibited a faster drug release rate than the formulations with a larger pellet size.

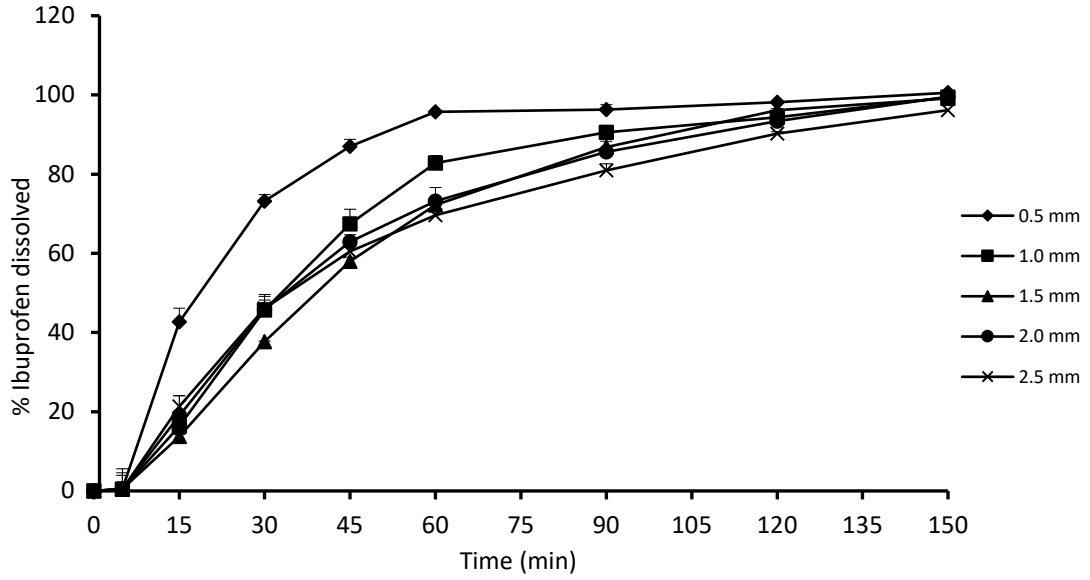

Figure C.6: Dissolution results of the various ibuprofen MUPS tablet formulations

C.3.6.3 Paracetamol

Table C.32: Tablet dissolution results of the 0.5 mm paracetamol MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.47	0.45	0.42
15	67.59	70.75	81.68
30	91.70	92.01	95.71
45	97.27	94.95	99.97
60	97.31	101.01	101.32
90	100.25	101.77	101.11
120	100.32	101.52	100.79
150	100.60	100.70	100.20

Table C.33: Tablet dissolution results of the 1.0 mm paracetamol MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.42	0.42	0.41
15	47.74	42.40	53.06
30	82.48	74.94	89.06
45	96.61	91.09	100.41
60	100.56	97.35	100.17
90	100.59	97.95	99.38
120	100.51	97.51	99.57
150	100.74	97.35	99.65

Table C.34: Tablet dissolution results of the 1.5 mm paracetamol MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.45	0.46	0.46
15	39.78	32.10	34.47
30	71.76	67.64	70.20
45	89.21	89.65	90.39
60	96.68	97.19	98.33
90	98.35	98.76	99.26
120	99.24	98.90	102.75
150	99.57	99.06	102.49

Table C.35: Tablet dissolution results of the 2.0 mm paracetamol MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.45	0.45	0.45
15	34.12	34.93	33.95
30	73.98	75.64	68.53
45	93.21	92.61	88.38
60	99.44	98.78	96.97
90	100.44	99.76	98.33
120	99.97	100.73	100.21
150	100.20	99.19	100.71

Table C.36: Tablet dissolution results of the 2.5 mm paracetamol MUPS tablet formulations

Time (min)	% Dissolved		
	Tablet 1	Tablet 2	Tablet 3
5	0.41	0.42	0.42
15	35.64	29.40	33.23
30	64.68	61.20	60.03
45	84.11	82.56	82.74
60	92.14	93.35	94.14
90	99.42	97.90	96.99
120	99.66	100.10	98.88
150	103.15	103.05	99.17

Table C.37: Summary of the dissolution results of the various paracetamol MUPS tablet formulations

Time (min)	% Dissolved				
	0.5 mm	1.0 mm	1.5 mm	2.0 mm	2.5 mm
5	0.45	0.42	0.45	0.45	0.42
15	73.34	47.74	35.45	34.33	32.75
30	93.14	82.16	69.87	72.72	61.97
45	97.40	96.04	89.75	91.40	83.13
60	99.88	99.36	97.40	98.40	93.21
90	101.04	99.31	98.79	99.51	98.10
120	100.88	99.20	100.30	100.30	99.54
150	100.50	99.25	100.38	100.03	101.79

At least 50% or more of the drug was released at 30 min for all of the various paracetamol MUPS tablet formulations. The formulations with a smaller pellet size exhibited a faster drug release rate than the formulations with a larger pellet size up to 45 min. After 45 min the drug release rate of all the formulations (irrespective of the pellet sizes) were similar.

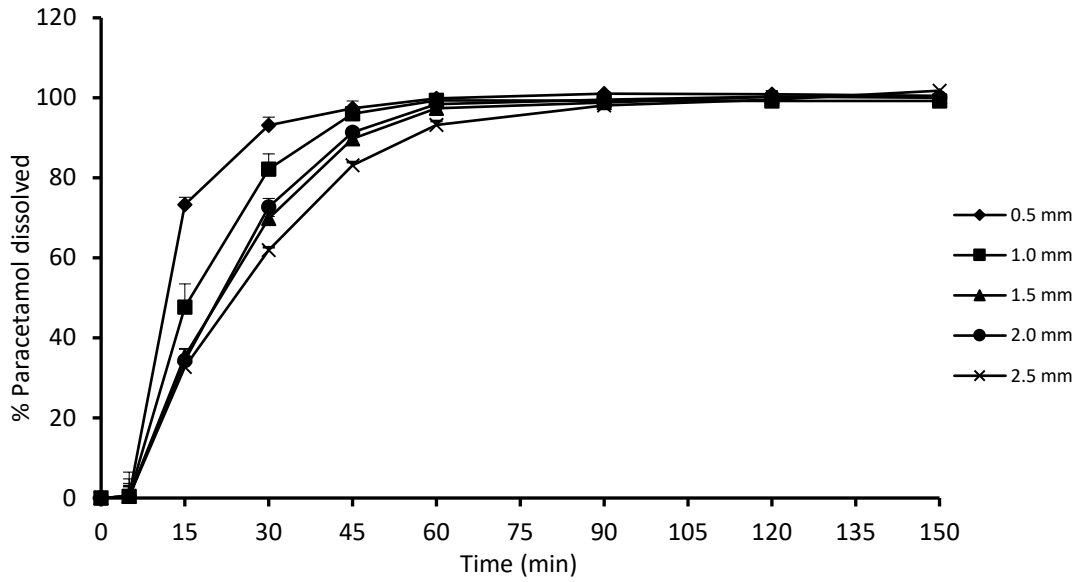

Figure C.7: Dissolution results of the various paracetamol MUPS tablet formulations

C.4. References

BP ***see*** BRITISH PHARMACOPOEIA

BRITISH PHARMACOPOEIA. 2015. Online version. https://www.pharmacopoeia.com/bp-2015/monographs. Date of access 23 April 2015.

USP ***see*** UNITED STATES PHARMACOPEIA

UNITED STATES PHARMACOPEIA AND NATIONAL FORMULARY (USP 39-NF 34). 2015 Rockville, MD: United States Pharmacopeial Convention.

Appendix D: Current Pharmaceutical Design: Guide for Authors

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The Journal publishes peer-reviewed mini- and full-length review articles and research papers written in English. Single topic/thematic issues may also be considered for publication.

D.3.1 Single topic issues

These special issues are peer-reviewed and may contain invited or uninvited review/mini-review articles. A Single Topic Issue Editor will offer a short perspective and co-ordinate the solicitation of manuscripts between 3-5 (for a mini-hot topic) to 6-10 (for full-length hot topic) from leading scientists. Authors interested in editing a single topic issue in an emerging topic of drug design may submit their proposal to the Editor-in-Chief at cpd@benthamscience.org for consideration.

D.3.2 Conference proceedings

For proposals to publish conference proceedings in this journal, please contact us at email: proceedings@benthamscience.org

D.4 Manuscript length

D.4.1 Mini-reviews

Mini-reviews should be 3000-6000 words excluding figures, structures, photographs, schemes, tables etc.

D.4.2 Full-length reviews

Full-length reviews should be 8000-40000 words excluding figures, structures, photographs, schemes, tables etc.

D.4.3 Research articles

Research articles should be 4000-8000 words excluding figures, structures, photographs, schemes, tables etc. There is a quota of 20% of published Research articles per issue in this journal.

There is no restriction on the number of figures, tables or additional files e.g. video clips, animation and datasets, that can be included with each article online. Authors should include all relevant supporting data with each article (Refer to Supplementary Material section).

D.5 Manuscript preparation

The manuscript should be written in English in a clear, direct and active style. All pages must be numbered sequentially, facilitating in the reviewing and editing of the manuscript. Download the Template

For further convenience, our contracted service provider Eureka Science can provide assistance to authors for the preparation of manuscripts.

D.5.1 Manuscript sections for papers

Manuscripts may be divided into the following sections:

- Copyright Letter
- Title
- Title page
- Structured Abstract
- Graphical Abstract
- Keywords
- Text Organization
- Conclusion
- List of Abbreviations (if any)
- Conflict of Interest
- Acknowledgements
- References
- Appendices
- Figures/Illustrations (if any)
- Chemical Structures (if any)
- Tables (if any)
- Supportive/Supplementary Material (if any)

D.5.2 Copyright letter

It is mandatory that a signed copyright letter should also be submitted along with the manuscript by the author to whom correspondence is to be addressed, delineating the scope of the submitted article declaring the potential competing interests, acknowledging contributions from authors and funding agencies, and certifying that the paper is prepared according to the *'Instructions for Authors'.* All inconsistencies in the text and in the reference section and any typographical errors must be carefully checked and corrected before the submission of the manuscript. The article should not contain any such material or information that may be unlawful, defamatory, fabricated, plagiarized, or which would, if published, in any way whatsoever, violate the terms and conditions as laid down in the copyright agreement. The authors acknowledge that the publishers have the legal right to take appropriate action against the authors for any such violation of the terms and conditions as laid down in the copyright agreement. Download the Copyright letter

D.5.3 Title

The title of the article should be precise and brief and must not be more than 120 characters. Authors should avoid the use of non-standard abbreviations. The title must be written in title case except for articles, conjunctions and prepositions.

Authors should also provide a short ‘running title’. Title, running title, byline, correspondent footnote and keywords should be written as presented in original manuscript.

D.5.4 Title page

Title page should include paper title, author(s) full name and affiliation, corresponding author(s) names complete affiliation/address, phone, fax, email and keyword should be written as presented in original manuscript.

D.5.5 Structured abstract

The abstract of an article should be its clear, concise and accurate summary, having no more than 250 words, and including the explicit sub-headings (as in-line or run-in headings in bold). Use of abbreviations should be avoided and the references should not be cited in the abstract. Ideally, each abstract should include the following sub-headings, but these may vary according to requirements of the article.

- Background
- Objective

- Method
- Results
- Conclusion

D.5.6 Graphical Abstract

A graphic must be included with each manuscript for use in the Table of Contents (TOC). This must be submitted separately as an electronic file (preferred file types are EPS, PDF, TIFF, Microsoft Word, PowerPoint and CDX etc.). A graphical abstract, not exceeding 30 words along with the illustration, helps to summarize the contents of the manuscript in a concise pictorial form. It is meant as an aid for the rapid viewing of the journals' contents and to help capture the readers' attention. The graphical abstract may feature a key structure, reaction, equation, etc. that the manuscript elucidates upon. It will be listed along with the manuscript title, authors' names and affiliations in the contents page, typeset within an area of 5 cm by 17 cm, but it will not appear in the article PDF file or in print.

Graphical Abstracts should be submitted as a separate file (must clearly mention graphical abstract within the file) online *via* Bentham's Content Management System by selecting the option "supplementary material".

D.5.7 Keywords

6 to 8 keywords must be provided.

D.5.8 Text organization

The main text should begin on a separate page and should be divided into title page, abstract and the main text. The text may be subdivided further according to the areas to be discussed, which should be followed by the Acknowledgements and Reference sections. For Research Articles the manuscript should begin with the title page and abstract followed by the main text, which must be structured into separate sections as Introduction, Materials and Methods, Results, Discussion, and Conclusion, List of Abbreviations, Conflict of Interest, Acknowledgements, and References. The Review article should mention any previous important old and recent reviews in the field and contain a comprehensive discussion starting with the general background of the field. It should then go on to discuss the salient features of recent developments. The authors should avoid presenting material which has already been published in a previous review. The authors are advised to present and discuss their observations in brief. The manuscript style must be uniform throughout the text and 10 pt Times New Roman fonts should be used. The full term for an abbreviation should precede its first appearance in the text unless it is a standard unit of measurement. The reference numbers should be given in square brackets in

the text. Italics should be used for Binomial names of organisms (Genus and Species), for emphasis and for unfamiliar words or phrases. Non-assimilated words from Latin or other languages should also be italicized e.g. *per se, et al. etc.*

Standard protocol on approvals, registrations, patient consents & animal protection

All clinical investigations must be conducted according to the Declaration of Helsinki principles. For all manuscripts reporting data from studies involving human participants, formal review and approval by an appropriate institutional review board or ethics committee is required. For research involving animals, the authors should indicate whether the procedures followed were in accordance with the standards set forth in the eighth edition of Guide for the Care and Use of Laboratory Animals (grants.nih.gov/grants/olaw/Guide-for-the-care-and-use-of-Laboratory-animals/; published by the National Academy of Sciences, The National Academies Press, Washington, D.C.).

A specific declaration of such approval must be made in the copyright letter and in a stand-alone paragraph at the end of the Methods section especially in the case of human studies where inclusion of a statement regarding obtaining the written informed consent from each subject or subject's guardian is a must. The original should be retained by the guarantor or corresponding author. Editors may request to provide the original forms by fax or email.

Authentication of cell lines

The NIH acknowledges the misidentification and/or cross-contamination of cell cultures e.g. HeLa cells being used in a research study as a serious problem. In order to ensure the validation of the work and proper utilization of resources, it is a prerequisite that correct reagents be used in studies dealing with established human (tumor) cell lines that have been cultured for more than 4 years up to the date of submission of the manuscript. Cell lines such as short-term cultures of human tumors, murine cell lines (as a catalog of DNA profiles is not yet available) and tumor cell lines established in the course of the study that is being submitted, are presently exempt from this rule. To minimize the risk of working with misidentified and/or contaminated cell lines, tests such as isoenzyme analysis, karyotyping/cytogenetic analysis and, more recently, molecular techniques of DNA profiling may be carried out to authenticate cell cultures. These tests may help confirm or establish the identify profile for a cell line. Bentham Science recommends that all cell lines be authenticated prior to submitting a paper for review. Authors are therefore required to provide authentication of the origin and identity of the cells by performing cell profiling either in their own laboratory or by outsourcing an approved laboratory or cell bank. Authentication is required when a new line is established or acquired, before

freezing a cell line, if the performance of the line is not consistent or results are unexpected, if using more than one cell line, and before publication of the study.

The cell lines profile should be cross-checked with the profile of the donor tissue of other continuous cell lines such as provided by the authentic data bank such as www.dsmz.de/fp/cgi-bin/str.html, ATCC® etc.

Greek symbols and special characters

Greek symbols and special characters often undergo formatting changes and get corrupted or lost during preparation of manuscript for publication. To ensure that all special characters used are embedded in the text, these special characters should be inserted as a symbol but should not be a result of any format styling (Symbol font face) otherwise they will be lost during conversion to PDF/XML comprising a list of items relevant to their specific research design. Chemical equations, chemical names, mathematical usage, unit of measurements, chemical and physical quantity & units must conform to SI and Chemical Abstracts or IUPAC.

All kinds of measurements should be reported only in International System of Units (SI).

D.5.9 Conclusion

A small paragraph summarizing the contents of the article, presenting the final outcome of the research or proposing further study on the subject, may be given at the end of the article under the Conclusion section.

D.5.10 List of abbreviations

If abbreviations are used in the text either they should be defined in the text where first used, or a list of abbreviations can be provided.

D.5.11 Conflict of interest

Financial contributions and any potential conflict of interest must be clearly acknowledged under the heading 'Conflict of Interest'. Authors must list the source(s) of funding for the study. This should be done for each author.

D.5.12 Acknowledgements

All individuals listed as authors must have contributed substantially to the design, performance, analysis, or reporting of the work and are required to indicate their specific contribution. Anyone

(individual/company/institution) who has substantially contributed to the study for important intellectual content, or who was involved in the article's drafting the manuscript or revising must also be acknowledged.

Guest or honorary authorship based solely on position (e.g. research supervisor, departmental head) is discouraged.

The specific requirements for authorship have been defined by the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). Examples of authors' contributions are: 'designed research/study', 'performed research/study', 'contributed important reagents', 'collected data', 'analyzed data', 'wrote paper' etc. This information must be included in the submitted manuscript as a separate paragraph under the heading 'Acknowledgements'. The corresponding author is responsible for obtaining permission from all co-authors for the submission of any version of the manuscript and for any changes in the authorship.

D.5.13 References

References must be listed in the numerical system (Vancouver). All references should be numbered sequentially [in square brackets] in the text and listed in the same numerical order in the reference section. The reference numbers must be finalized and the bibliography must be fully formatted before submission.

See below few examples of references listed in the correct Vancouver style:

Typical Paper Reference:

[1] Boehm M, Nabel EG. Angiotensin-converting enzyme 2-a new cardiac regulator. N Engl J Med 2002; 347: 1795-7.

[2] SoRelle R. Long reach of the N-terminal of B-type natriuretic peptide. Circulation 2002; 106: 9059-63.

[3] Leone A. Biochemical markers of cardiovascular damage from tobacco smoke. Curr Pharm Des 2005; 11: 2199-208.

[4] Meuillet EJ, Mahadevan D, Vankayalapati H, *et al.* Specific inhibition of the Akt1 pleckstrin homology domain by D-3-deoxyphosphatidyl- myo-inositol analogues. Mol Cancer Ther 2003; 2: 389-99.

Typical Chapter Reference:

[5] Ban Y, Tomer Y. Endocrine diseases. Graves's and Hashimoto's diseases. In: Oksenberg J, Brassat D, Eds. Immunogenetics of autoimmune disease. Medical Intelligence Unit. New York: Landes Bioscience and Springer Science-Business Media 2006; pp. 41-58.

[6] Astrup P. The arterial wall in atherogenesis. In Cavallero Ed. Atherogenesis. Padua: Piccin *Medical Books 1965: pp. 77-92.*

Book Reference:

[7] Carlson BM. Human embryology and developmental biology. 3rd ed. St. Louis: Mosby 2004.

[8] Rosai J. Histological typing of tumours of the thymus. 2nd ed. Berlin and Heidelberg: Springer-Verlag 1999.

Edited Book:

[9] Brown AM, Stubbs DW, Eds. Medical physiology. New York: Wiley 1983.

Conference Paper and Proceedings:

[10] Kimura J, Shibasaki H, Eds. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15-19; Kyoto, Japan. Amsterdam: Elsevier 1996.

[11] Cooper R, Cutler J, Desvigne-Nickens P, et al. Disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States: findings of the National Conference on Cardiovascular Disease Prevention. Circulation 2000; 102: 3137-47.

[12] Chao JT, Theriault A, Gapor A. Delta-tocotrienol is a potent inhibitor of monocyte-endothelial cell adhesion. In: Cutting edge technologies For sustained competitiveness. Proceedings of the 2001 PI POC International palm Oil Congress, Food Technology and Nutrition Conference, Kuala Lumpur, Malaysia, Aug. 20-22, 2001; pp. 225-34.

Journal Article on the Internet:

[13] Aylin P, Bottle A, Jarman B, Elliott P. Paediatric cardiac surgical mortality in England after Bristol: descriptive analysis of hospital episode statistics 1991-2002. BMJ [serial on the Internet]. 2004 Oct 9; [cited 2004 October 15]; 329: [about 10 screens]. Available from: (bmj.bmjjournals.com/cgi/content/full/329/7470/825)

[14] NCT01013350. Prospective observational long-term safety registry of multiple sclerosis patients who have participated in cladribine clinical trials (PREMIERE). Available at (clinicaltrials.gov/ct2/show/NCT01013350)

Book/Monograph on the Internet:

[15] Donaldson MS, Ed. Measuring the quality of health care [monograph on the internet]. Washington: National Academy Press 1999 [cited 2004 Oct 8]. Available from: (legacy.netlibrary.com)

[16] Silva ATA. Ed. Development of compounds potentially active against Helicobacter pylori. [monograph on the internet]. Araraquara: School of Pharmaceutical Science, Universidade Estadual Paulista 2008 [cited 2010 July 10]. Available from: (www.fcfar.unesp.br/posgraduacao/cienciasfarmaceuticas/Disertacoes/2008/antonio_tavora-completo.pdf) [monograph in Portuguese].

Web site/Homepage:

[17] HeartCentreOnline [homepage on the Internet]. Boca Raton, FL: HeartCentreOnline, Inc.; c2000-2004 [updated 2004 May 23; cited 2004 Oct 15]. Available from: (www.heartcentralonline.com)

[18] Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF), Global discovery program for novel anti-tuberculosis drugs [homepage on the Internet]. The National Institute of Allergy and Infectious Diseases (NIAID) [cited 2011 Jan10]. Available from: (www.taacf.org)

Journal with Part/Supplement:

If a journal carries continuous pagination throughout the volume, then the issue number can be omitted.

Issue with Supplement:

[19] Glauser TA. Integrating clinical trial data into clinical practice. Neurology 2002; 58(12 Suppl 7): S6-12.

[20] Durandy A, Kaveri SV, Kuijpers TW, *et al* . Intravenous immunoglobulins-- understanding properties and mechanisms. Clin Exp Immunol 2009; 158(Suppl 1): 2-13.

Volume with Part:

[21] Abend SM, Kulish N. The psychoanalytic method from an epistemological viewpoint. Int J Psychoanal 2002; 83(Pt 2): 491-5

[22] O'Riordan JI, Thompson AJ, Kingsley DP, *et al* . The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain 1998; 121(Pt 3): 495-503.

Issue with Part:

[23] Ahrar K, Madoff DC, Gupta S, Wallace MJ, Price RE, Wright KC. Development of a large animal model for lung tumors. J Vasc Interv Radiol 2002; 13(9 Pt 1): 923-8.

[24] Bluestone JA. Costimulation and its role in organ transplantation. Clin transplant 1996; 10 (1 Pt 2): 104-9.

Patent:

Pagedas AC, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug.

E-citations:

Citations for articles/material published exclusively online or in open access (free-to-view), must contain the accurate Web addresses (URLs) at the end of the reference(s), except those posted on an author's Web site (unless editorially essential), e.g. 'Reference: Available from: URL'.

Some important points to remember:

- All references must be complete and accurate.
- If the number of authors exceeds six then *et al* . will be used after three names (the term " *et al* ." should be in italics).
- Date of access should be provided for online citations.
- Journal names should be abbreviated according to the Index Medicus/MEDLINE.
- Punctuation should be properly applied as mentioned in the examples given above.
- Superscript in the in-text citations and reference section should be avoided.
- Abstracts, unpublished data and personal communications (which can only be included if prior permission has been obtained) should not be given in the references section. The details may however appear in the footnotes.

- The authors are encouraged to use a recent version of End Note (version 5 and above) or Reference Manager (version 10) when formatting their reference list, as this allows references to be automatically extracted.

D.5.14 Appendices

In case there is a need to present lengthy, but essential methodological details, use appendices, which can be a part of the article. An appendix must not exceed three pages (Times New Roman, 12 point fonts, 900 max. words per page).The information should be provided in a condensed form, ruling out the need of full sentences. A single appendix should be titled APPENDIX, while more than one can be titled APPENDIX A, APPENDIX B, and so on.

D.5.15 Figures/Illustrations

All authors must strictly follow the guidelines below for preparing illustrations for publication in ***Current Pharmaceutical Design***. If the figures are found to be sub-standard, then the manuscripts will be rejected and the authors offered the option of figure improvement professionally by. The costs for such improvement will be charged to the authors.

Illustrations should be provided as separate files, embedded in the text file, and must be numbered consecutively in the order of their appearance. Each figure should include only a single illustration which should be cropped to minimize the amount of space occupied by the illustration.

If a figure is in separate parts, all parts of the figure must be provided in a single composite illustration file.

Photographs should be provided with a scale bar if appropriate, as well as high-resolution component files.

Scaling/Resolution

Line Art image type is normally an image based on lines and text. It does not contain tonal or shaded areas. The preferred file format should be TIFF or EPS, with the color mode being Monochrome 1-bit or RGB, in a resolution of 900-1200 dpi.

Halftone image type is a continuous tone photograph containing no text. It should have the preferred file format TIFF, with color mode being RGB or Grayscale, in a resolution of 300 dpi.

Combination image type is an image containing halftone, text or line art elements. It should have the preferred file format TIFF, with color mode being RGB or Grayscale, in a resolution of 500-900 dpi.

Formats

Illustrations may be submitted in the following file formats:

Illustrator

- **EPS** (preferred format for diagrams)
- **PDF** (also especially suitable for diagrams)
- **PNG** (preferred format for photos or images)
- **Microsoft Word** (version 5 and above; figures must be a single page)
- **PowerPoint** (figures must be a single page)
- **TIFF**
- **JPEG** (conversion should be done using the original file)
- **BMP**
- **CDX** (ChemDraw)
- **TGF** (ISISDraw)

Bentham Science does not process figures submitted in GIF format.

For TIFF or EPS figures with considerably large file size restricting the file size in online submissions is advisable. Authors may therefore convert to JPEG format before submission as this results in significantly reduced file size and upload time, while retaining acceptable quality. JPEG is a 'lossy' format, however. In order to maintain acceptable image quality, it is recommended that JPEG files are saved at High or Maximum quality.

Zipit or Stuffit tools should not be used to compress files prior to submission as the resulting compression through these tools is always negligible.

Please refrain from supplying:

- Graphics embedded in word processor (spreadsheet, presentation) document.
- Optimized files optimized for screen use (like GIF, BMP, PICT, WPG) because of the low resolution.
- Files with too low a resolution.
- Graphics that are disproportionately large for the content.

Image conversion tools

There are many software packages, many of them freeware or shareware, capable of converting to and from different graphics formats, including PNG.

General tools for image conversion include Graphic Converter on the Macintosh, Paint Shop Pro, for Windows, and ImageMagick, available on Macintosh, Windows and UNIX platforms.

Bitmap images (e.g. screenshots) should not be converted to EPS as they result in a much larger file size than the equivalent JPEG, TIFF, PNG or BMP, and poor quality. EPS should only be used for images produced by vector-drawing applications such as Adobe Illustrator or CorelDraw. Most vector-drawing applications can be saved in, or exported as, EPS format. If the images were originally prepared in an Office application, such as Word or PowerPoint, original Office files should be directly uploaded to the site, instead of being converted to JPEG or another format of low quality.

D.5.16 Color figures/Illustrations

- The cost for each individual page of color figures/plates/illustrations is US$ 950.
- Color figures should be supplied in CMYK and not RGB colors.

Chemical structures

Chemical structures must be prepared in ChemDraw/CDX and provided as separate file.

Structure drawing preferences

[As according to the ACS style sheet]

Drawing Settings:	
Chain angle	120°
Bond spacing	18% of width
Fixed length	14.4 pt (0.500cm, 0.2in)
Bold width	2.0 pt (0.071cm, 0.0278in)
Line width	0.6 pt (0.021cm, 0.0084in)
Margin width	1.6 pt (0.096cm)
Hash spacing	2.5 pt (0.088cm, 0.0347in)
Text settings:	
Font	Times New Roman
Size	8 pt

Under the Preference Choose:	
Units	points
Tolerances	3 pixels
Under Page Setup Use:	
Paper	US letter
Scale	100%

D.5.17 Tables

- Data Tables should be submitted in Microsoft Word table format.
- Each table should include a title/caption being explanatory in itself with respect to the details discussed in the table. Detailed legends may then follow.
- Table number in bold font *i.e*. Table **1**, should follow a title. The title should be in small case with the first letter in caps. A full stop should be placed at the end of the title.
- Tables should be embedded in the text exactly according to their appropriate placement in the submitted manuscript.
- Columns and rows of data should be made visibly distinct by ensuring that the borders of each cell are displayed as black lines.
- Tables should be numbered in Arabic numerals sequentially in order of their citation in the body of the text.
- If a reference is cited in both the table and text, please insert a lettered footnote in the table to refer to the numbered reference in the text.
- Tabular data provided as additional files can be submitted as an Excel spreadsheet.

D.5.18 Supportive/Supplementary material

We do encourage to append supportive material, for example a PowerPoint file containing a talk about the study, a PowerPoint file containing additional screenshots, a Word, RTF, or PDF document showing the original instrument(s) used, a video, or the original data (SAS/SPSS files, Excel files, Access Db files etc.) provided it is inevitable or endorsed by the journal's Editor.

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Supportive/Supplementary material intended for publication must be numbered and referred to in the manuscript but should not be a part of the submitted paper. In-text citations as well as a section with the heading "Supportive/Supplementary Material" before the "References" section should be provided. Here, list all Supportive/Supplementary Material and include a brief caption line for each file describing its contents.

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D.10 Language and editing

Manuscripts submitted containing language inconsistencies will not be published. Authors must seek professional assistance for correction of grammatical, scientific and typographical errors. Professional team available at Eureka Science may assist you in the English language editing of your article. Please contact Eureka Science for a language editing quote at e-mail: info@eureka-science.com stating the total number of words of the article to be edited.

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All editors, board members and those authors who have contributed more than two articles in Bentham Science publications are entitled to a 40% discount on “Open Access Plus” fees.

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D.14 Featured article

Authors may opt to publicize their article(s) published with Bentham Science by highlighting their title(s) both at the journal's Homepage and the issue Contents page at a cost of US$ 600.

D.15 Reviewing and promptness of publication

All manuscripts submitted for publication will be immediately subjected to peer-reviewing, usually in consultation with the members of the Editorial Advisory Board and a number of external referees. Authors may, however, provide in their Copyright Letter the contact details (including e-mail addresses) of four potential peer reviewers for their paper. Any peer reviewers suggested should not have recently published with any of the authors of the submitted manuscript and should not be members of the same research institution.

All peer-reviewing will be conducted *via* the Internet to facilitate rapid reviewing of the submitted manuscripts. Every possible effort will be made to assess the manuscripts quickly with the decision being conveyed to the authors in due course.

D.16 Quick track publication

For this journal an optional fast publication fee-based service called QUICK TRACK is available to authors for their submitted manuscripts. Authors who opt for this fee-based service do not have to pay any additional page charges.

QUICK TRACK allows online publication within 2 weeks of receipt of the final approved galley proofs from the authors. Similarly the manuscript can be published in the next forthcoming PRINT issue of the journal. The total publication time, from date of first receipt of manuscript to its online publication is 10 weeks, subject to its acceptance by the referees and modification (if any) by the authors within one week.

Authors who have availed QUICK TRACK service in a BSP journal will be entitled for an exclusive 30% discount if they again wish to avail the same services in any Bentham journal.

For more information please contact the Editorial Office by e-mail at cpd@benthamscience.org.

D.17 Copyright

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D.18 Self-archiving

By signing the Copyright Letter the authors retain the rights of self-archiving. Following are the important features of self-archiving policy of Bentham Science journals:

Authors can deposit the first draft of a submitted article on their personal websites, their institution’s repositories or any non-commercial repository for personal use, internal institutional use or for permitted scholarly posting.

Authors may deposit the ACCEPTED VERSION of the peer-reviewed article on their personal websites, their institution's repository or any non-commercial repository such as PMC, arXiv after 12 MONTHS of publication on the journal website. In addition, an acknowledgement must be given to the original source of publication and a link should be inserted to the published article on the journal's/publisher's website.

If the research is funded by NIH, Wellcome Trust or any other Open Access Mandate, authors are allowed the archiving of published version of manuscripts in an institutional repository after the mandatory embargo period. Authors should first contact the Editorial Office of the journal for information about depositing a copy of the manuscript to a repository. Consistent with the copyright agreement, Bentham Science does not allow archiving of FINAL PUBLISHED VERSION of manuscripts.

The link to the original source of publication should be provided by inserting the DOI number of the article in the following sentence: "The published manuscript is available at EurekaSelect via http://www.eurekaselect.com/openurl/content.php?genre=article&doi= [insert DOI]

There is no embargo on the archiving of articles published under the OPEN ACCESS PLUS category. Authors are allowed deposition of such articles on institutional, non-commercial repositories and personal websites immediately after publication on the journal website.

D.19 Plagiarism prevention

Bentham Science Publishers uses the iThenticate software to detect instances of overlapping and similar text in submitted manuscripts. iThenticate software checks content against a database of periodicals, the Internet, and a comprehensive article database. It generates a similarity report, highlighting the percentage overlap between the uploaded article and the published material. Any instance of content overlap is further scrutinized for suspected plagiarism according to the publisher's Editorial Policies. Bentham Science allows an overall similarity of 20% for a manuscript to be considered for publication. The similarity percentage is further checked keeping the following important points in view:

Low text similarity

The text of every submitted manuscript is checked using the Content Tracking mode in iThenticate. The Content Tracking mode ensures that manuscripts with an overall low percentage similarity (but which may have a higher similarity from a single source) are not overlooked. The acceptable limit for similarity of text from a single source is 5%. If the similarity level is above 5%, the manuscript is returned to the author for paraphrasing the text and citing the original source of the copied material.

It is important to mention that the text taken from different sources with an overall low similarity percentage will be considered as a plagiarized content if the majority of the article is a combination of copied material.

High text similarity

There may be some manuscripts with an overall low similarity percentage, but a higher percentage from a single source. A manuscript may have less than 20% overall similarity but there may be 15% similar text taken from a single article. The similarity index in such cases is higher than the approved limit for a single source. Authors are advised to thoroughly rephrase the similar text and properly cite the original source to avoid plagiarism and copyright violation.

Types of plagiarism

We all know that scholarly manuscripts are written after thorough review of previously published articles. It is therefore not easy to draw a clear boundary between legitimate representation and plagiarism. However, the following important features can assist in identifying different kinds of plagiarized content. These are:

- Reproduction of others words, sentences, ideas or findings as one's own without proper acknowledgement.
- Text recycling, also known as self-plagiarism. It is an author's use of a previous publication in another paper without proper citation and acknowledgement of the original source.
- Paraphrasing poorly: Copying complete paragraphs and modifying a few words without changing the structure of original sentences or changing the sentence structure but not the words.
- Verbatim copying of text without putting quotation marks and not acknowledging the work of the original author.
- Properly citing a work but poorly paraphrasing the original text is considered as unintentional plagiarism. Similarly, manuscripts with language somewhere between paraphrasing and quoting are not acceptable. Authors should either paraphrase properly or quote and in both cases, cite the original source.
- Higher similarity in the abstract, introduction, materials and methods, and discussion and conclusion sections indicates that the manuscript may contain plagiarized text. Authors can easily explain these parts of the manuscript in many ways. However, technical terms and sometimes standard procedures cannot be rephrased; therefore Editors must review these sections carefully before making a decision.

Plagiarism in Published Manuscripts

Published manuscripts which are found to contain plagiarized text are retracted from the journal website after careful investigation and approval by the Editor-in-Chief of the journal. A 'Retraction Note' as well as a link to the original article is published on the electronic version of the plagiarized manuscript and an addendum with retraction notification in the journal concerned.

D.20 E-Pub ahead of schedule

Bentham Science Publishers are pleased to offer electronic publication of accepted papers prior to scheduled publication. These peer-reviewed papers can be cited using the date of access and the unique DOI number. Any final changes in manuscripts will be made at the time of print publication and will be reflected in the final electronic version of the issue. Articles ahead of schedule may be ordered by pay-per-view at the relevant links by each article stated *via* the E-Pub Ahead of Schedule.

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Member of Cope

Appendix E: Drug Delivery Letters: Guide for Authors

E.1 Online manuscript submission

An online submission and tracking service via Internet facilitates a speedy and cost-effective submission of manuscripts. The full manuscript has to be submitted online via Bentham's Content Management System (CMS) at bsp-cms.eurekaselect.com / View Submission Instructions

Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The principal/corresponding author will be required to submit a Copyright Letter along with the manuscript, on behalf of all the co-authors (if any). The author(s) will confirm that the manuscript (or any part of it) has not been published previously or is not under consideration for publication elsewhere. Furthermore, any illustration, structure or table that has been published elsewhere must be reported, and copyright permission for reproduction must be obtained.

For all online submissions, please provide soft copies of all the materials (main text in MS Word or Tex/LaTeX), figures/illustrations in TIFF, PDF or JPEG, and chemical structures drawn in ChemDraw (CDX)/ISISDraw (TGF) as separate files, while a PDF version of the entire manuscript must also be included, embedded with all the figures/illustrations/tables/ chemical structures etc. It is advisable that the document files related to a manuscript submission should always have the name of the corresponding author as part of the file name, i.e., Cilli MS text.doc", Cilli MS Figure 1 *etc*.

It is imperative that before submission, authors should carefully proofread the files for special characters, mathematical symbols, Greek letters, equations, tables, references and images, to ensure that they appear in proper format.

References, figures, tables, chemical structures etc. should be referred to in the text at the appropriate place where they have been first discussed. Figure legends/captions should also be provided.

A successful electronic submission of a manuscript will be followed by a system-generated acknowledgement to the principal/corresponding author. Any queries therein should be addressed to info@benthamscience.org

E.2 Editorial policies

The editorial policies of Bentham Science Publishers on publication ethics, peer-review, plagiarism, copyrights/licenses, errata/corrections and article retraction/ withdrawal can be viewed at Editorial Policy

E.3 Manuscripts published

The journal accepts peer-reviewed short papers for publication. Single topic/thematic issues may also be considered for publication.

E.3.1 Single topic issues

These special issues are peer-reviewed and may contain invited or uninvited mini-review articles. A Single Topic Issue Editor will offer a short perspective and co-ordinate the solicitation of manuscripts (at least 10) for full-length thematic issues from leading scientists. Authors interested in editing a single topic issue in an emerging topic of drug delivery, gene delivery, and drug targeting may submit their proposal to the Editor-in-Chief at ddl@benthamscience.org for consideration.

E.3.2 Conference proceedings

For proposals to publish conference proceedings in this journal, please contact us at email: proceedings@benthamscience.org

E.4 Manuscript length

E.4.1 Letter articles

The total number of words for a published letter/short communication article is from 3000 to 6000 words excluding figures, structures, photographs, schemes, tables, *etc*.

E.4.2 Mini-reviews

Mini-reviews should be 3000-6000 words excluding figures, structures, photographs, schemes, tables, etc.

There is no restriction on the number of figures, tables or additional files e.g. video clips, animation and datasets, that can be included with each article online. Authors should include all relevant supporting data with each article (Refer to Supplementary Material section).

E.5 Manuscript preparation

The manuscript should be written in English in a clear, direct and active style. All pages must be numbered sequentially, facilitating in the reviewing and editing of the manuscript.

E.5.1 Microsoft Word template

It is advisable that authors prepare their manuscript using the template available on the Web, which will assist in preparation of the manuscript according to Journal's Format.

Our contracted service provider Eureka Science can, if needed, provide professional assistance to authors for the improvement of English language and figures in manuscripts.

E.5.2 Manuscript sections for papers

Manuscripts may be divided into the following sections:

- Copyright Letter
- Title
- Title Page
- Structured Abstract
- Graphical Abstract
- Keywords
- Text Organization
- Conclusion
- List of Abbreviations (if any)
- Conflict of Interest
- Acknowledgements
- References
- Appendices
- Figures/Illustrations (if any)
- Chemical Structures (if any)
- Tables (if any)
- Supportive/Supplementary Material (if any)

E.5.3 Copyright letter

It is mandatory that a signed copyright letter also be submitted along with the manuscript by the author to whom correspondence is to be addressed, delineating the scope of the submitted article, declaring the potential competing interests, acknowledging contributions from authors and funding agencies, and certifying that the paper is prepared according to the 'Instructions for Authors'. All inconsistencies in the text and in the reference section, and any typographical errors must be carefully checked and corrected before the submission of the manuscript. The article contains no such material or information that may be unlawful, defamatory, fabricated, plagiarized, or which would, if published, in any way whatsoever, violate the terms and conditions as laid down in the copyright agreement. The authors acknowledge that the publishers have the legal right to take appropriate action against the authors for any such violation of the terms and conditions as laid down in the copyright agreement.

E.5.4 Title

The title of the article should be precise and brief and must not be more than 120 characters. Authors should avoid the use of non-standard abbreviations. The title must be written in title case except for articles, conjunctions and prepositions.

Authors should also provide a short ‘running title’. Title, running title, byline, correspondent footnote and keywords should be written as presented in the original manuscript.

E.5.5 Title page

Title page should include paper title, author(s) full name and affiliation, corresponding author(s) names and complete affiliation/address, along with phone, fax and email.

E.5.6 Structured abstract

The abstract of an article should be its clear, concise and accurate summary, having no more than 250 words, and including the explicit sub-headings (as in-line or run-in headings in bold). Use of abbreviations should be avoided and the references should not be cited in the abstract. Ideally, each abstract should include the following sub-headings, but these may vary according to requirements of the article.

- Background
- Objective
- Method
- Results
- Conclusion

E.5.7 Graphical abstract

A graphic must be included with each manuscript for use in the Table of Contents (TOC). This must be submitted separately as an electronic file (preferred file types are EPS, PDF, TIFF, Microsoft Word, PowerPoint, CDX, etc.). A graphical abstract, not exceeding 30 words along with the illustration, helps to summarize the contents of the manuscript in a concise pictorial form. It is meant as an aid for the rapid viewing of the journals' contents and to help capture the readers' attention. The graphical abstract may feature a key structure, reaction, equation, etc. that the manuscript elucidates upon. It will be listed along with the manuscript title, authors' names and affiliations in the contents page, typeset within an area of 5 cm by 17 cm, but it will not appear in the articles' PDF file or in print.

Graphical abstracts should be submitted as a separate file (must clearly mention graphical abstract within the file) online *via* Bentham's Content Management System by selecting the option "Supplementary material".

E.5.8 Keywords

6 to 8 keywords must be provided in alphabetical order.

E.5.9 Text organization

The main text should begin on a separate page and should be divided into title page, abstract and the main text. The text may be subdivided further according to the areas to be discussed, which should be followed by the Acknowledgements and Reference sections.

For Letters, the manuscript should begin with the title page and abstract followed by the main text, which must be structured into separate sections as Introduction, Materials and Methods, Results, Discussion, Conclusion, Acknowledgements and References.

The Review Article should mention any previous important recent and old reviews in the field and contain a comprehensive discussion starting with the general background of the field. It should then go on to discuss the salient features of recent developments. The authors should avoid presenting material which has already been published in a previous review.

Standard Protocol on Approvals, Registrations, Patient Consents & Animal Protection

All clinical investigations must be conducted according to the Declaration of Helsinki principles. For all manuscripts reporting data from studies involving human participants, formal review and approval by an appropriate institutional review board or ethics committee is required. For research involving animals, the authors should indicate whether the procedures followed were in accordance with the standards set forth in the eighth edition of Guide for the Care and Use of Laboratory Animals (grants.nih.gov/grants/olaw/guide-for-the-care-and-use-of-laboratory-animals_prepub.pdf); published by the National Academy of Sciences, The National Academies Press, Washington, D.C.).

A specific declaration of such approval must be made in the copyright letter and in a stand-alone paragraph at the end of the Methods section especially in the case of human studies where inclusion of a statement regarding obtaining the written informed consent from each subject or subject's guardian is a must. The original should be retained by the guarantor or corresponding author. Editors may request to provide the original forms by fax or email.

Greek Symbols and Special Characters

Greek symbols and special characters often undergo formatting changes and get corrupted or lost during preparation of manuscript for publication. To ensure that all special characters used are embedded in the text, these special characters should be inserted as a symbol but should not be a result of any format styling (Symbol font face) otherwise they will be lost during conversion to PDF/XML.

Authors are encouraged to consult reporting guidelines. These guidelines provide a set of recommendations comprising a list of items relevant to their specific research design. Chemical equations, chemical names, mathematical usage, unit of measurements, chemical and physical quantity & units must conform to SI and Chemical Abstracts or IUPAC.

All kinds of measurements should be reported only in International System of Units (SI).

E.5.10 Conclusion

A small paragraph summarizing the contents of the article, presenting the final outcome of the research or proposing further study on the subject, may be given at the end of the article under the Conclusion section.

E.5.11 List of abbreviations

If abbreviations are used in the text either they should be defined in the text where first used, or a list of abbreviations should be provided.

E.5.12 Conflict of interest

Financial contributions and any potential conflict of interest must be clearly acknowledged under the heading 'Conflict of Interest'. Authors must list the source(s) of funding for the study. This should be done for each author.

E.5.13 Acknowledgements

All individuals listed as authors must have contributed substantially to the design, performance, analysis, or reporting of the work and are required to indicate their specific contribution. Anyone (individual/company/institution) who has substantially contributed to the study for important intellectual content, or was involved in drafting or revising the manuscript must also be acknowledged.

Guest or honorary authorship based solely on position (e.g. research supervisor, departmental head) is discouraged.

E.5.14 References

References must be listed in the ACS Style only. All references should be numbered sequentially [in square brackets] in the text and listed in the same numerical order in the reference section. The reference numbers must be finalized and the bibliography must be fully formatted before submission.

See below few examples of references listed in the ACS Style:

Journal Reference:

- [1] Bard, M.; Woods, R.A.; Bartón, D.H.; Corrie, J.E.; Widdowson, D.A. Sterol mutants of *Saccharomyces cerevisiae*: chromatographic analyses. *Lipids*, **1977**, 12(8), 645-654.
- [2] Zhang, W.; Brombosz, S.M.; Mendoza, J.L.; Moore, J.S. A high-yield, one-step synthesis of o-phenylene ethynylene cyclic trimer via precipitation-driven alkyne metathesis. *J. Org. Chem*., **2005**, 70, 10198-10201.

Book Reference:

- [3] Crabtree, R.H. *The Organometallic Chemistry of the Transition Metals*, 3rded.; Wiley & Sons: New York, 2001.

Book Chapter Reference:

- [4] Wheeler, D.M.S.; Wheeler, M.M. Stereoselective Syntheses of Doxorubicin and Related Compounds In: *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science B. V: Amsterdam, **1994**; Vol. *14*, pp. 3-46.

Conference Proceedings:

- [5] Jakeman, D.L.; Withers, S.G.E. In: *Carbohydrate Bioengineering: Interdisciplinary Approaches*. In: Proceedings of the 4th Carbohydrate Bioengineering Meeting, Stockholm, Sweden, June 10-13, 2001; Teeri, T.T.; Svensson, B.; Gilbert, H.J.; Feizi, T., Eds.; Royal Society of Chemistry: Cambridge, UK, **2002**; pp. 3-8.

URL (WebPage):

- [6] National Library of Medicine. Specialized Information Services: Toxicology and Environmental Health. sis.nlm.nih.gov/Tox/ToxMain.html [Accessed May 23, 2004].(Accessed May 23, 2004).

Patent:

- [7] Hoch, J.A.; Huang, S. Screening methods for the identification of novel antibiotics. U.S. Patent 6,043,045, March 28, **2000**.

Thesis:

- [8] Mackel, H. *Capturing the Spectra of Silicon Solar Cells*. PhD Thesis, The Australian National University: Canberra, December **2004**.

E-citations:

- [9] Citations for articles/material published exclusively online or in open access (free-to-view) , must contain the exact Web addresses (URLs) at the end of the reference(s), except those posted on an author's Web site unless editorially essential, e.g. 'Reference: Available from: URL'.

Some important points to remember:

- All references must be complete and accurate.
- All authors must be cited and there should be no use of the phrase *et al*.
- Date of access should be provided for online citations.
- Journal names should be abbreviated according to the Index Medicus/MEDLINE.
- Punctuation should be properly applied as mentioned in the examples given above.
- Superscript in the in-text citations and reference section should be avoided.
- Abstracts, unpublished data and personal communications (which can only be included if prior permission has been obtained) should not be given in the references section. The details may however appear in the footnotes
- The authors are encouraged to use a recent version of EndNote (version 5 and above) or Reference Manager (version 10) when formatting their reference list, as this allows references to be automatically extracted.

E.5.15 Appendices

In case there is a need to present lengthy, but essential methodological details, use appendices, which can be a part of the article. An appendix must not exceed three pages (Times New Roman, 12 pt fonts, 900 max. words per page).The information should be provided in a condensed form, ruling out the need of full sentences. A single appendix should be titled APPENDIX, while more than one can be titled APPENDIX A, APPENDIX B, and so on.

E.5.16 Figures/Illustrations

All authors must strictly follow the guidelines below for preparing illustrations for publication in ***Drug Delivery Letters***. If the figures are found to be sub-standard, then the manuscripts will be rejected and the authors offered the option of figure improvement professionally by Eureka Science. The costs for such improvement will be charged to the authors.

Illustrations should be provided as separate files, embedded in the text file, and must be numbered consecutively in the order of their appearance. Each figure should include only a single illustration which should be cropped to minimize the amount of space occupied by the illustration.

If a figure is in separate parts, all parts of the figure must be provided in a single composite illustration file.

Photographs should be provided with a scale bar if appropriate, as well as high-resolution component files.

Scaling/Resolution

Line Art image type is normally an image based on lines and text. It does not contain tonal or shaded areas. The preferred file format should be TIFF or EPS, with the color mode being Monochrome 1-bit or RGB, in a resolution of 900-1200 dpi.

Halftone image type is a continuous tone photograph containing no text. It should have the preferred file format TIFF, with color mode being RGB or Grayscale, in a resolution of 300 dpi.

Combination image type is an image containing halftone, text or line art elements. It should have the preferred file format TIFF, with color mode being RGB or Grayscale, in a resolution of 500-900 dpi.

Formats

Illustrations may be submitted in the following file formats:

- **Illustrator**
- **EPS** (preferred format for diagrams)
- **PDF** (also especially suitable for diagrams)
- **PNG** (preferred format for photos or images)
- **Microsoft Word** (version 5 and above; figures must be a single page)
- **PowerPoint** (figures must be a single page)
- **TIFF**
- **JPEG** (conversion should be done using the original file)
- **BMP**
- **CDX** (ChemDraw)
- **TGF** (ISISDraw)

Bentham Science does not process figures submitted in GIF format.

For TIFF or EPS figures with considerably large file size restricting the file size in online submissions is advisable. Authors may therefore convert to JPEG format before submission as this results in significantly reduced file size and upload time, while retaining acceptable quality. JPEG is a 'lossy' format. However, in order to maintain acceptable image quality, it is recommended that JPEG files are saved at High or Maximum quality.

Zipit or Stuffit tools should not be used to compress files prior to submission as the resulting compression through these tools is always negligible.

Please refrain from supplying:

1. Graphics embedded in word processor (spreadsheet, presentation) document.
2. Optimized files optimized for screen use (like GIF, BMP, PICT, WPG) because of the low resolution.
3. Files with too low a resolution.
4. Graphics that are disproportionately large for the content.

Image Conversion Tools

There are many software packages, many of them freeware or shareware, capable of converting to and from different graphics formats, including PNG.

General tools for image conversion include Graphic Converter on the Macintosh, Paint Shop Pro, for Windows, and ImageMagick, available on Macintosh, Windows and UNIX platforms.

Bitmap images (e.g. screenshots) should not be converted to EPS as they result in a much larger file size than the equivalent JPEG, TIFF, PNG or BMP, and poor quality. EPS should only be used for images produced by vector-drawing applications such as Adobe Illustrator or CorelDraw. Most vector-drawing applications can be saved in, or exported as, EPS format. If the images were originally prepared in an Office application, such as Word or PowerPoint, original Office files should be directly uploaded to the site, instead of being converted to JPEG or another format of low quality.

Color Figures/Illustrations

- The cost for color figures/plates/illustrations is US$ 490 per article for up to 3 colour pages and subsequently US$ 195.00 per page for any additional colour pages.
- Color figures should be supplied in CMYK and not RGB colors.

Note for authors: To maintain publication quality, figures submitted in colour will be published in colour only.

E.5.17 Chemical structures

Chemical structures MUST be prepared in ChemDraw/CDX and provided as separate file.

Structure Drawing Preferences

[As according to the ACS style sheet]

Drawing Settings:	
Chain angle	120°
Bond spacing	18% of width
Fixed length	14.4 pt (0.500cm, 0.2in)
Bold width	2.0 pt (0.071cm, 0.0278in)
Line width	0.6 pt (0.021cm, 0.0084in)
Margin width	1.6 pt (0.096cm)
Hash spacing	2.5 pt (0.088cm, 0.0347in)
Text settings:	
Font	Times New Roman
Size	8 pt
Under the Preference Choose:	
Units	points
Tolerances	3 pixels
Under Page Setup Use:	
Paper	US letter
Scale	100%

E.5.18 Tables

- Data Tables should be submitted in Microsoft Word table format.
- Each table should include a title/caption being explanatory in itself with respect to the details discussed in the table. Detailed legends may then follow.
- Table number in bold font *i.e*. Table **1**, should follow a title. The title should be in small case with the first letter in caps. A full stop should be placed at the end of the title.
- Tables should be embedded in the text exactly according to their appropriate placement in the submitted manuscript.
- Columns and rows of data should be made visibly distinct by ensuring that the borders of each cell are displayed as black lines.
- Tables should be numbered in Arabic numerals sequentially in order of their citation in the body of the text.
- If a reference is cited in both the table and text, please insert a lettered footnote in the table to refer to the numbered reference in the text.
- Tabular data provided as additional files can be submitted as an Excel spreadsheet.

E.5.19 Supportive/Supplementary material

We do encourage to append supportive material, for example a PowerPoint file containing information about the study, a PowerPoint file containing additional screenshots, a Word, RTF, or PDF document showing the original instrument(s) used, a video, or the original data (SAS/SPSS files, Excel files, Access Db files etc.) provided it is inevitable or endorsed by the journal's Editor.

Supportive/Supplementary material intended for publication must be numbered and referred to in the manuscript but should not be a part of the submitted paper. In-text citations as well as a section with the heading "Supportive/Supplementary Material" before the "References" section should be provided. All Supportive/Supplementary Material must be listed and a brief caption line for each file describing its contents should be included.

Any additional files will be linked to the final published article in the form supplied by the author, but will not be displayed within the paper. They will be made available in exactly the same form as originally provided only on our Web site. Please also make sure that each additional file is a single table, figure or movie (please do not upload linked worksheets or PDF files larger than one sheet). Supportive/ Supplementary material must be provided in a single zipped file not larger than 4 MB.

Authors must clearly indicate if these files are not for publication but meant for the reviewers'/editors' perusal only.

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E.7 Authors and institutional affiliations

The names of the authors should be provided according to the previous citations or as the authors would want them to be published along with the institutional affiliations, current address, telephone, cell & fax numbers and the email address. Email address must be provided with an asterisk in front of the name of the principal author. The corresponding author(s) should be designated and their complete address, business telephone and fax numbers and e-mail address must be stated to receive correspondence and galley proofs.

E.8 Page charges

No page charges will be levied to authors for the publication of their article.

E.9 Language and editing

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