Prediction of compressibility of pharmaceutical excipients in solid oral dosage forms

Jacques C. Scholtz
20056087

Thesis submitted for the degree *Doctor Philosophiae* in Pharmaceutics at the Potchefstroom Campus of the North-West University

Promoter: Prof Jan H. Steenekamp
Co-Promoter: Prof Josias H. Hamman

November 2016

Acknowledgements

What an interesting and strange journey this has been. Many challenges, many hurdles, a few pitfalls as well as great triumphs. Being able to complete this journey would not have been possible without the help of a great many people, and therefore I want to take the time to say a special thank you to these individuals.

I cannot begin without thanking my **Heavenly Father** for all the abilities, opportunities and blessings that I have received. The Lord is my shepherd, I want for nothing. Thank you Father, for allowing me to reach this point in my life.

Michelle Scholtz (a.k.a. **Mau5**) you are my soul mate and my reason, my love and my life. Thank you for standing by me through thick and thin. Thank you for your love, your patience and for always supporting me. With you by my side I can take on the entire world. Thank you for being my partner and my love.

I would like to thank my parents **Jacques** and **Sarita Scholtz,** as well as my new parents, **Mike** and **Lizelle du Toit**. Having a safe haven to retreat to, as well as people to share my joy and disappointments with, made this challenge possible. My sisters, **Nadia Viljoen** and **Lizl Kruger**, as well as their husbands, **Jaco Viljoen** and **Rohann Kruger**, the support from you guys got me through the tough times. Thank you.

I would like to express my sincere gratitude to my advisor, mentor and friend, **Prof. Jan Steenekamp**, for his continuous support of my research, for his patience, insights and motivational speaking. Without your guidance and advice, this project would not have been possible. I could not imagine having a better advisor or mentor for my doctorate study.

Thank you **Prof. Sias Hamman**, my co-promoter. Your insights, advice, comments and encouragement, as well as the hard questions, have helped to make me the best researcher I can be. Thank you for always making time to see me and discussing all the aspects of my work, no matter the time of day.

Thank you to the **National Research Fund** for their monetary support.

To my family (especially the **Bothmas**), your support in difficult times made all the difference.

To all my **colleagues** at the Department of Pharmaceutics, thank you for the fun times, the chatting and joking in the office. I wish you all the best and success for your future.

I would like to say a special thank you to **Dr. Joe Viljoen** for always having an open door and giving me a place to vent my frustrations, as well as providing me with opportunities to broaden my experience.

I want to extend my thanks to all my friends, new and old. You are the people that keep me grounded, sane and in good spirits. Thank you **Jaco**, **Angelique**, **Righard**, **HeLska**, **Jandre**, **Theunis**, **Anke**, **Carlemi**, **Daleen**, **Jeanine**, **Caaaaarl**, **Jean-Pierre**, **Leorika**, **Cerenus**, **Michael**, **Christo**, **Stephnie** and **Johanni**. And I can't forget to mention the **GG group** and **PAWS**. Thank you all very much.

And I have to extend a special thanks to my homies, **Karin Minnaar**, **Etienne Marais** and **Cathrin van der Watt**. Coming home to you guys lifted my spirits every day. (I am sure the sundowners played no role in this.) You guys and girls mean the world to me.

Thank you to each and every one that contributed to this study or my own wellness. I shall repay in kind. I am eternally grateful to you all.

Jacques C. Scholtz

Potchefstroom

November 2016

"The true delight is in the finding out,

rather than the knowing."

-Isaac Asimov

"Sometimes science is a lot more *art* than *science*.

A lot of people don't get that."

- Rick Sanchez (Rick and Morty)

Table of Contents

List of Figures

Chapter 3 ~ Research article

Appendix H ~ SeDeM determination results (Including 12 sided paragons)

List of Tables

Appendix H ~ SeDeM determination results (Including 12 sided paragons)

Appendix I ~ Tabletting results: Paracetamol.

List of Abbreviations

%<50	Particle size
%H	Hygroscopicity
%HR	Loss on drying
API	Active pharmaceutical ingredient
APS	Ammonium peroxy disulfate
ATRP	Atom transfer radical polymerisation
BSA	Bovine serum albumine
Carr	Carr's index
Cmax	Peak plasma concentration
CMC	Carboxymethyl cellulose
Coh-Index	Cohesion index
CP	Carbopol-934P
Da	Bulk density
Dc	Tapped density
ESEM	Environmental scanning electron microscope
f	Reliability factor
GCI	Good compressibility index
GMA	Glycidyl methacrylate
Hausner	Hausner ratio
HM	High methoxylated
HPMC	Hydroxypropyl methylcellulose
Ie	Inter-particle porosity
Iθ	Homogeneity index
LCST	Lower critical solution temperature
LM	Low methoxylated
MBAA	N,N'methylbensacrylamide
MCC	Microcrystalline cellulose
σ_x	Tensile strength
PI	Parameter index
PNIPAAm	Poly(N-isopropylacrylamide)
PPI	Parameter profile index
PVP	Polyvinylpolypyrrolidone

SEM	Scanning electron microscopy
SPION's	Super-paramagnetic iron oxide nanoparticles
t	Powder flow
UCST	Upper critical solution temperature
USP	United States Pharmacopoeia
θ	Angle of Repose

Abstract

Title: Prediction of compressibility of pharmaceutical excipients in solid oral dosage forms

Tablets are one of the most preferred dosage forms for patients, but pre-formulation studies for tablets are often time consuming and expensive. The SeDeM Expert Diagram System attempts to address this problem by decreasing the amount of experiments required to develop an acceptable direct compression tablet formulation. This is done by processing and interpreting data obtained from known techniques already widely in use in the pharmaceutical industry to characterise active pharmaceutical ingredients (API's) and excipients. In this study, the prediction ability of the SeDeM Expert Diagram System with a special focus on testing the limits of the system was investigated.

Three different API's with different direct compression properties (i.e. paracetamol, furosemide and pyridoxine) as well as seven excipients representing different classes and types of widely used direct compression excipients (i.e. Tablettose® 80, FlowLac® 100, Avicel® PH200, Emcompress®, Cellactose® 80, MicroceLac® 100 and StarLac®) were selected and characterised by applying the SeDeM Expert Diagram System. Predicted formulations were tableted and evaluated according to the set criteria. If a tablet formulation failed to meet the criteria, the ratio of excipient to API was increased in 5 % w/w increments until a successful formulation was obtained, whereas the reverse was applied if a formulation was successful to determine failure point.

The SeDeM Expert Diagram System proved to be proficient at predicting acceptable tablet formulations, with a few exceptions. This was specifically the case where paracetamol and furosemide were concerned as well as some excipients. While SeDeM predicted that paracetamol would only be able to deliver acceptable tablets with three excipients (i.e. FlowLac® 100, Avicel® PH200 and StarLac®), all the selected excipients were in fact able to create acceptable direct compression tablets. When all the paracetamol formulations were considered, tablet failure most often occurred due to capping. However, the reason for failure of the novel direct-compression excipients (i.e. Cellactose® 80, MicroceLac® 100 and StarLac®) was due to problems other than capping.

In the case of furosemide, the limits of five parameters were not met, including particle size limits, powder flow as well as the cohesion index. The SeDeM System was unable to successfully predict any furosemide direct-compression tablet formulations because the powder mixtures exhibited poor powder flow properties. This can be explained by the fact that furosemide has

very small particles, which coated the excipient particle surfaces and thereby formed interactive powder mixtures, which was confirmed with the use of SEM microscopy.

SeDeM was able to correctly predict five of the seven selected excipients for successful direct-compression tablet formulations for pyridoxine within an acceptable margin of error. Only two excipients (Emcompress® and Cellactose® 80) performed better than expected by the SeDeM System.

From the results of this study it is evident that certain physicochemical properties of API's such as elasticity and cohesive behaviour are not compensated for or compensated for sufficiently by the SeDeM System. Furthermore, some novel direct-compression excipients (e.g. co-processed excipients) proved to exceed the SeDeM Expert Diagram Systems' expectations and predictions to correct for API failure to produce direct compressible tablets.

Keywords: Tablets, Excipients, SeDeM Expert Diagram System, Direct compression, Pre-formulation, Formulation prediction, Paracetamol, Furosemide, Pyridoxine.

Uittreksel

Titel: Voorspelling van die saampersbaarheid van farmaseutiese vulstowwe in soliede orale doseervorms.

Tablette is een van die gewildste doseervorms vir menslike gebruik, maar preformuleringstudies is tydrowend en duur om te voltooi. Die SeDeM-Deskundige-Diagram-Sisteem poog om hierdie probleem op te los deur die hoeveelheid eksperimente wat benodig word om 'n werkbare direk-samepersbare formule te identifiseer, te verminder. Die sisteem gebruik standaardtegnieke wat tans in algemene gebruik in die wyer farmaseutiese industrie is, om hulpstowwe en aktiewe bestanddele te karakteriseer. In hierdie studie is die voorspellingsvermoë van die SeDeM-Deskundige-Diagram-Sisteem ondersoek met 'n fokus op die limiete van die sisteem.

In dié studie is drie verskillende aktiewe bestanddele (naamlik parasetamol, furosemied en piridoksien), wat almal oor verskillende direkte samepersingseienskappe beskik, en sewe verskillende algemeen gebruikte direksaampersbare vulstowwe (Tablettose® 80, FlowLac® 100, Avicel® PH200, Emcompress®, Cellactose® 80, MicroceLac® 100 en StarLac®) gebruik. Die karakteriseringsdata is vervolgens verwerk en SeDeM-diagramme is opgestel vir elk van die farmaseutiese poeiers. Die SeDeM Deskundige Diagram Sisteem is daarna ingespan om moontlike konsentrasieverhoudings van geneesmiddel teenoor vulstof te voorspel, met die doel om aanvaarbare direk-saampersbare tablette te vervaardig. Indien die tablette wat deur die formule gelewer is, nie aan die vereistes voldoen het nie, is die persentasie geneesmiddel in die formule verminder in inkremente van 5 % m/m, totdat aanvaarbare tablette gelewer is. Indien die tablette wel voldoen het aan die vereistes, is die geneesmiddelpersentasie in die formule met 5 % m/m inkremente vermeerder totdat die tablette nie aan die vereiste tableteienskappe voldoen het nie.

Die SeDeM Deskundige Diagram Sisteem was daartoe instaat om verskeie formules suksesvol te voorspel, met 'n paar uitsonderings. Dit was spesifiek die geval waar parasetamol en furosemied gebruik was. SeDeM het voorspel dat slegs drie van die vulstowwe (naamlik FlowLac® 100, Avicel® PH200 and StarLac®) aanvaarbare tablette sou lewer in kombinasie met parasetamol. In teenstelling hiermee het al die vulstowwe aanvaarbare tablette gelewer. Wanneer al die verskillende parasetamol en vulstof kombinasies in ag geneem is, is daar gevind dat die meeste formules probleme ondervind het met dekselvorming. Slegs in die geval van nuwe innoverende direk-saampersbare vulstowwe naamlik Cellactose® 80, MicroceLac® 100 sowel as StarLac®, was die rede vir mislukking as gevolg van swak vloeieienskappe en of massavariasie. Hierdie waarneming dui daarop dat hierdié vulstowwe oor die vermoë beskik om vir parasetamol se elastiese vervormingseienskappe te kan kompenseer en daardeur dekselvorming te voorkom.

Furosemied het vyf van die parameters van die SeDeM Sisteem se limiete oorskry wat daartoe gelei het dat SeDeM geen van die geneesmiddel/vulstof-kombinasies se formules korrek voorspel nie. Soos deur die deeltjiegroottebepalings, sowel as die elektronmikroskoopmikrograwe is daar gevind dat furosemied se deeltjiegroottes baie klein is, wat maak dat die furosemieddeeltjies die vulstofdeeltjies se oppervlaktes bedek, daaraan vaskleef en dan sogenaamde aktiewe mengsels veroorsaak. Die aktiewe mengsels maak dat die poeierkombinasie die eienskappe van furosemied aanneem wat verswakte poeiervloei toon. Daarom moes die furosemiedkonsentrasie in so mate verlaag word dat aktiewe mengsels nie gevorm kan word nie.

SeDeM het die piridoksien bevattende formules die beste voorspel, met vyf van die sewe vulstowwe se voorspellings was binne die aanvaarbare foutgrens van 5 % geval het. Die twee oorblywende vulstowwe naamlik, Emcompress® en Cellactose® 80 het beter resultate gelewer as deur SeDeM voorspel.

In die studie is daar dus gevind dat die SeDeM sekere fisies-chemiese eienskappe van poeiers nie in ag neem nie (soos byvoorbeeld elastiese vervorming) of onderskat word (soos byvoorbeeld die impak van kohesie) en dat die effektiwiteit van innoverende direk-saampersbare vulstowwe onderskat word.

Sleutelwoorde: Tablette, Vulstowwe, SeDeM Deskundige Diagram Sisteem, Direkte samepersing, Tablet preformuleringstudies, Tabletmengsel voorspelling, Parasetamol, Furosemied, Piridoksien.

Foreword

This study aimed to evaluate the ability of the SeDeM Expert Diagram System to predict formulations, which would produce acceptable tablets when directly compressed. Different active pharmaceutical ingredients (APIs, namely paracetamol, furosemide and pyridoxine) were selected as well as a range of direct compressible excipients. Excipients were selected to include conventional as well as novel excipients (e.g. co-processed excipients). The API's and excipients were selected to test the versatility of the SeDeM Diagram Expert System and in effect tested the limits of the system. Acceptability of the resulting direct compressible tablets were defined in terms of selected criteria stated in the major Pharmacopoeia (British Pharmacopoeia, European Pharmacopoeia and United States Pharmacopoeia) namely mass variation and friability.

This thesis is presented in article format as described in the North-West University's guidelines. It therefore consists of an introductory chapter, a review article (as published in the peer-reviewed journal "Current Drug Targets"), a full length research manuscript (as submitted for publication in the Elsevier science journal, "Powder Technology") as well as a conclusion chapter. The articles are presented in the format required by each journal, these instructions can be viewed in Appendix L and M, respectively. Additionally, further experimental data and results can be viewed in the appendices of this thesis.

Chapter 1

Introduction

This chapter contains an introduction to this thesis, along with a statement of the research problem and the aims and objectives thereof.

1.1. Introduction

The importance of dosage form design is often underestimated. The first principle of dosage form design is to administer a drug in such a fashion as to illicit a predictable, repeatable therapeutic response in patients (York, 2013:7). This is only possible when constant, repeatable mechanisms of drug delivery are used. Tablets is one dosage form that fulfils this requirement. Modern formulation scientists are making use of multi-functional excipients to improve the performance of drug delivery systems (Hamman & Steenekamp, 2012:220) and this is especially true when tablets are concerned. This broadening scope of excipients that are available is of vital importance to the modern formulation scientist, but these excipients can only be optimally used in tablets if the interactions in the dosage form between active pharmaceutical ingredient (API) and excipient are understood.

In the larger pharmaceutical industry, it is often true that the cost of the development of new tablet formulations are relatively high as there are many possible combinations of excipients that could be used with each API as well as methods that could be employed to formulate tablets. Of the many methods available to prepare tablets, direct compression is one of the simplest methods with the fewest steps. Fewer steps decrease handling time, production time and the number of mistakes that could be made during production, while increasing productivity (McCormick, 2005:52). Other advantages of direct compression include fewer stability problems, especially where temperature or moisture sensitive API's are concerned (Alderborn, 2013:512).

Unfortunately direct compression tableting is not without disadvantages, as it is classically known for not being able to accommodate large API loads as well as requiring tailor made excipients (Jivraj *et al.*, 2000:58). Problems for example, segregation and issues with flowability often arise with direct compression as the excipients have to be able to compensate for the insufficient flow and compression properties of the API in the formulation (Hentzschel *et al.*, 2012:650). As stated before, these interactions between API and excipients need to be explored and tested, especially as the number of API's as well as the number and types of excipients are constantly increasing. Experiments to test these interactions are time consuming as well as raw materials due to the large amount of experiments required to test these physical interactions between API and excipient (Aguilar-Díaz *et al.*, 2014:222).

A galenic tablet pre-formulation method called the SeDeM Expert Diagram System was developed to decrease the amount of experiments required to formulate tablets, especially for the direct compression method (Suñé Negre *et al.*, 2008:1038). This is firstly done by creating a profile of the tablet components (i.e. the API and the excipients) according to pre-

determined parameters. These profiles are created by using existing and often basic powder analysis or characterisation techniques, which are widely used and often described in the Pharmacopoeia, along with a few techniques especially developed for the SeDeM System (Suñé Negre *et al.*, 2014:16). The suitability of the different ingredients for direct compression can be assessed as well as to identify the deficiencies posed by each component. This would theoretically allow formulation scientists the ability to create a library of excipient and API profiles which can visually show the advantages as well as disadvantages of each ingredient (Suñé Negre *et al.*, 2011:26; Aguilar-Díaz *et al.*, 2014:225).

1.2. Research problem

Tablets are considered to be one of the most popular dosage forms in use today for drug administration, as it is has high patient compliance because of the convenience and ease of use. Unfortunately, the formulation of tablets has its own challenges and difficulties (Mazel *et al.*, 2015:63). Creating acceptable tablets that can repeatedly be produced is a priority, but simultaneously keeping the cost of dosage form development and production down is of great importance. This includes the time taken to develop new formulations as well as production times (McCormick, 2005:52). All these factors affect the pricing of medication as well as the time taken before new medication can reach markets and reaction times to existing and new health threats. Direct compression specifically addresses many of these aspects, as the actual production process is relatively simple, with very few steps, requiring very little equipment, few stability problems are encountered as no solvents are used and energy costs are low (Alderborn, 2013:512; McCormick, 2005:52). Unfortunately, direct compression does not easily contend with flowability and compaction problems like wet granulation is able to, because wet granulation modifies the properties of the API by combining the API into granules with other excipient particles to create a better flowing powder mass. Direct compression is completely reliant on excipients to compensate for poor flow properties or compression problems associated with the API. This contributes to increased dosage form development time, as the API has to be tested with many different excipients and excipient concentration combinations before an acceptable formulation is obtained, which still needs to be refined for the intended purpose (Alderborn, 2013:512; McCormick, 2005:52).

The broader pharmaceutical industry is in need of a system, which is able to streamline direct compression tablet development. This need is addressed by the SeDeM Expert Diagram System (Aguilar-Díaz *et al.*, 2014:235; Suñé Negre *et al.*, 2008:1029; Suñé Negre

et al., 2011:17; Suñé Negre *et al.*, 2014:15), but the limits and applications of this system has not yet been fully explored, especially with co-processed multifunctional excipients.

1.3. Aims and objectives

This study aimed to evaluate the SeDeM Expert Diagram System in terms of its ability to predict direct compression tablet formulations for selected API's and excipients based on criteria stated in the Pharmacopoeias (British Pharmacopoeia, European Pharmacopoeia and United States Pharmacopoeia).

The objectives of this study were to:

- Select a range of API's with divergent flow and compressibility properties as well as excipients developed for direct compression tablet formulations.
- Create a SeDeM profile of the selected API's and excipients by testing the SeDeM parameters of each powder individually, namely: 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.
- Construct SeDeM diagrams (or polygons) from indices calculated from the powder flow results to identify whether the different API's and excipients surpassed minimum or maximum values as stated in the SeDeM System.
- Use the SeDeM System to predict API to excipient ratios for acceptable direct compression tablet formulations for each of the selected APIs.
- Prepare tablets from the predicted tablet formulations and evaluate them, to identify which formulations complied with the criteria.
- Increase the API concentration for each tablet formulation to a point where it is possible to identify the actual limit at which each excipient would produce an acceptable direct compression tablet.
- Compare the results of the tablets prepared by the predicted formulations from the SeDeM System for each of the selected excipients with that of the formulations that produced acceptable tablets after modifications.
- Conduct scanning electron microscopic investigations on the powder particles (API and excipient) to explain why some of the SeDeM predicted formulations did not result in acceptable tablets.

During this study, the SeDeM Expert Diagram System was applied to three selected API's namely paracetamol (acetaminophen), furosemide and pyridoxine, as well as seven selected

excipients, e.g. Tablettose® 80, FlowLac® 100, Avicel® PH200, Emcompress®, Cellactose® 80, MicroceLac® 100 and StarLac®. Each API was selected for a specific reason, e.g. paracetamol is known to form tablets that are prone to capping; furosemide has a relatively small particle size and causes problems with powder flow; and pyridoxine is an API which is compatible with direct compression. Each excipient also represents a different approach to overcome the challenges of the selected API's. For example, Tablettose® 80 represents standard, conventional lactose type excipients; FlowLac® 100 represents newer, improved flowing lactose based excipients. Avicel® PH200 is an excipient manufactured from microcrystalline cellulose, which represents the popular alternative to lactose excipients. Emcompress® represents the inorganic excipients with a completely brittle fracture binding method. The new generation novel direct-compression specific excipients is represented by Cellactose® 80, MicroceLac® 100 and StarLac®.

1.4. References

Aguilar-Díaz, J.E., García-Montoya, E., Pérez-Lozano, P., Suñé Negre, J.M., Miñarro-Carmona, M. & Ticó-Grau, J.R. 2014. SeDeM expert system a new innovator tool to develop pharmaceutical forms. *Drug Development and Industrial Pharmacy*, 40(2):222-236.

Alderborn, G. 2013. Tablets and compaction. (*In* Aulton, M.E. & Taylor, K., *ed*. Aulton's Pharmaceutics: The design and manufacture of medicines, 4th ed. London: Churchill Livingstone. p. 504-549).

Hamman, J.H. & Steenekamp, J.H. 2012. Excipients with specialized functions for effective drug delivery. *Expert Opinion Drug Delivery*, 9(2):219-230.

Hentzschel, C.M., Sakmann, A. & Leopold, C.S. 2012. Comparison of traditional and novel tabletting excipients: Physical and compaction properties. *Pharmaceutical development and technology*, 17(6):649-653.

Jivraj, M., Martini, L.G. & Thompson, C.M. 2000. An overview of the different excipients useful for the direct compression of tablets. *Pharmaceutical Science & Technology Today*, 3(2):58-63.

Mazel, V., Diarra, H., Busignies, V. & Tchoreloff, P. 2015. Evolution of the die-wall pressure during the compression of biconvex tablets: Experimental results and comparison with FEM simulation. *Journal of Pharmaceutical Sciences*, 104:4339-4344.

McCormick, D. 2005. Evolution in direct compression. *Pharmaceutical Technology*, 4:52-62.

Suñé-Negre, J.M., García-Montoya, E., Pérez-Lozano, P., Aguilar-Díaz, J.E., Roig-Carreras, M., Fuster-Garcia, R., Miñarro-Carmona, M. & Ticó-Grau, J.R. 2011. SeDeM Diagram: A New Expert System for the Formulation of Drugs in Solid Form. (*In* Vizureanu, P., *ed*. Expert Systems for Human, Materials and Automation, Rijeka: InTech. 17-34 p).

Suñé Negre, J.M., Pérez-Lozano, P., Miñarro, M., Roig, M., Fuster, R., Hernández, C, Ruhí, R., García-Montoya, E. & Ticó-Grau, J.R. 2008. Application of the SeDeM Diagram and a new mathematical equation in the design of direct compression tablet formulation. *European Journal of Pharmaceutics and Biopharmaceutics*, 69:1029-1039.

Suñé-Negre, J.M., Roig, M., Fuster, R., Hernández, C, Ruhí, R., García-Montoya, E., Pérez-Lozano, P., Miñarro, M. & Ticó, J.R. 2014. New classification of directly compressible (DC) excipients in function of the SeDeM Diagram Expert System. *International Journal of Pharmaceutics*, 470:15-27.

York, P. 2013. The design of dosage forms. (*In* Aulton, M.E. & Taylor, K., *ed*. Pharmaceutics: The science of dosage form design, 4th ed. London: Churchill Livingston. p. 7-19).

Chapter 2

Review article

This chapter is presented in the form of a review article that was published in the journal titled “Current Drug Targets” in May of 2014 (Volume 15, issue number 5 p. 486-501). The complete guidelines for authors is presented in Appendix L. These guidelines state that submitted manuscripts be written in the format of the supplied Microsoft Word template file (i.e. 11 pt Times New Roman font). This article highlights the increased development of new pharmaceutical excipients with a wide variety of uses, with a special emphasis on excipients derived from natural sources.

Send Orders for Reprints to reprints@benthamscience.net

Current Drug Targets, **2013**, *14*, 000-000

More Good News About Polymeric Plant- and Algae-Derived Biomaterials in Drug Delivery Systems

Jacques Scholtz, Jaco Van der Colff, Jan Steenekamp, Nicole Stieger and Josias Hamman*

North-West University, Unit for Drug Research and Development, Private Bag X6001, Potchefstroom, 2520, South Africa

Abstract: Natural polymers are continuously investigated for use in pharmaceutical and tissue engineering applications due to the renewability of their supply. Besides the conventional use of natural materials in dosage form design such as fillers, they are progressively investigated as functional excipients in specialised dosage forms. The hydrophilic nature of natural polymers together with their non-toxic and biodegradable properties makes them useful in the design of modified release dosage forms. Matrix type tablets and beads made from natural gums and mucilages often exhibit sustained drug release through erosion in combination with swelling. Natural polymers are used to reach different pharmaceutical objectives, for instance, inulin and pectin are plant derived polymers that have suitable properties to produce colon-specific drug delivery. Alginate is an example of a natural polymer that has been used in the formulation of gastro-retentive dosage forms. Different cellulose derived polymers have been investigated as coating materials for dosage forms. Natural polymers can be chemically modified to produce molecules with specific properties and formation of co-polymers or polymer mixtures provide new opportunities to develop innovative drug delivery systems.

Keywords: Algae, alginate, cellulose, drug delivery system, pectin, plant polymers, starch.

1. INTRODUCTION

Development of novel products from renewable and sustainable plant-derived resources is not only driven by strategic motives, but also by economic pressures due to limited fossil fuel resources [1]. Although both synthetic and natural polymers are used as excipients in drug delivery systems, natural polymers are of particular interest due to their non-toxic, biocompatible and biodegradable nature [2]. Furthermore, the diverse properties and wide variety of applications of compounds from natural origin have resulted in them becoming an integral part of the human health care system. The applications of natural polymers in health sciences include drug delivery, gene delivery, wound healing and tissue engineering such as scaffolds for implants to simulate specific cell functions [3, 4]. The use of natural polymers in different pharmaceutical applications is far from exhausted with many opportunities available through chemical modifications such as preparation of composites that exhibit unique properties for specific needs and combining different materials in mixtures [5].

Plant polymers perform diverse functions in their native setting, for example, they provide structure in membranes, are involved in intracellular communication, are used for storage of water and energy and may act as catalysts [6]. Carbohydrates from plants may be divided into storage polysaccharides such as starch (amylase, amilopectin) and cell wall polysaccharides or non-starch polysaccharides (cellulose, hemicelluloses, pectin) [7]. Other polymers that originate from plants include those obtained from seeds and exudates such as gums and mucilages and those obtained from seaweeds and algae. Although cellulose, one of the most abundant polysaccharides in nature, has been used in its unmodified form, several chemically modifications such as formation of ethers and esters have been utilised to produce polymers with specific characteristics and functions [5].

Medicinal plants provide a continuous source for new lead compounds against different pharmacological targets [8], but plants also serve as a renewable source for a sustainable supply of cost-effective pharmaceutical excipients for use in dosage form design [9]. Plant derived polymers have been employed for a variety of pharmaceutical applications such as diluents, binders, disintegrants, gelling agents and thickeners. Furthermore, natural polymers of plant origin have been investigated for the design of dosage forms such as matrix type controlled release drug delivery systems, buccal films, microspheres, nanoparticles, implants, viscous solutions, suspensions and film coatings [10]. Innovative biotechnology derived drugs demand development of sophisticated drug delivery systems, which in turn need functional excipients that can produce delivery systems with specific drug release patterns and/or assist in the manufacturing process [11]. Novel dosage forms that have emerged over the past two decades that need functional excipients include different types of modified release dosage forms, stimuli-responsive drug delivery systems, rapid-dissolving formulations, self-emulsifying systems for oral delivery of poorly soluble drugs and the delivery of macromolecules [12, 13].

Many plant derived polymers are used to produce commercially available medicinal products and they are available

*Address correspondence to this author at the North-West University, Unit for Drug Research and Development, Private Bag X6001, Potchefstroom, 2520, South Africa; Tel: +27 18 299 4035; Fax: +27 87 231 5432;
Email: sias.hamman@nwu.ac.za

1389-4501/13 $58.00+.00

on the market as pharmaceutical excipients for use in dosage form design. On the other hand, some plant polymers are currently under investigation as potential excipients in pharmaceutical formulations. A representative example of a commercially available plant derived excipient is cellulose (e.g. Arbocel®), which is widely used as a tablet diluent and hard gelatin capsule filler. Many physically or chemically derived analogues exist for cellulose:

- microcrystalline cellulose (e.g. Avicel®) is used as a diluent in direct compressed tablets,
- cellulose acetate (e.g. CA-398-10NF®) and cellulose acetate phthalate (e.g. Aquacoat cPD®) are used as film coating agents,
- hydroxyethyl cellulose (e.g. Cellosize HEC®), hydroxyethylmethyl cellulose (e.g. Culminal MHEC®) and hydroxypropyl cellulose (e.g. Klucel®) are used as coating agents, tablet binders or thickening agents,
- hypromellose or hydroxypropylmethyl cellulose (e.g. Methocel®) is used as coating agent, sustained release component, stabilising agent, tablet binder and viscosity-increasing agent,
- hypromellose acetate succinate (e.g. Aqoat®) is used as component for controlled release dosage forms, enteric coating agent and film forming agent,
- hypromellose phthalate (e.g. HP-55®) is used as coating agent,
- carboxymethyl cellulose sodium (e.g. Akucell®) is used as coating agent, stabilising agent, suspending agent, tablet and capsule disintegrant, tablet binder and viscosity-increasing agent [14].

Examples of plant derived materials that are not commercially available as pharmaceutical excipients, but that are under investigation for use in formulation design includes extracts from *Hibiscus rosasinensis* and *Ficus awkeotsang*.

Examples of plant derived polymers that have pharmaceutical applications in novel dosage form design that are discussed in this article are given in Table **1**.

This review article focuses on the use of plant-derived polymers in specialised dosage forms and will therefore not cover the use of plant materials as excipients in conventional dosage forms. The use of both commercially available plant derived polymers as well as those under investigation will be discussed. Use of plant derived polymers in the design of following drug delivery systems is discussed: matrix type modified release dosage forms, site-specific delivery systems, tissue-targeted drug delivery systems, gastro-retentive drug delivery systems, bioadhesive drug delivery systems and coatings for dosage forms.

2. MATRIX TYPE DRUG DELIVERY SYSTEMS

A matrix system refers to a dosage form in which solid drug particles are dispersed in a porous solid medium formed by a polymer to prolong drug release over an extended period. Most commercially available matrix type drug delivery systems are prepared by compression of the drug together with a release-limiting polymer, which is then referred to as matrix type tablets [15]. However, multiple-unit matrix systems may also be manufactured by extrusion spheronisation, spray congealing and casting. Matrix drug delivery systems can be diffusion-controlled in which case the core remains intact and the dissolved drug molecules diffuse through pores in the system. They can also be erosion controlled where the polymer and drug is continuously liberated from the surface of the matrix system [16].

In the design of modified release dosage forms, the self-assembling properties of some natural polysaccharides proved most useful in the spontaneous formation of gel networks without the use of harsh reaction conditions and solvents. On the other hand, some natural polysaccharides are highly soluble in water and this can greatly reduce their potential for use as release modifying excipients in matrix type drug delivery systems. To overcome this limitation, the functional groups on natural polysaccharides can be chemically modified, which creates many opportunities for development of modified release dosage forms with specific drug delivery properties [17, 18].

2.1. Matrix Type Tablets

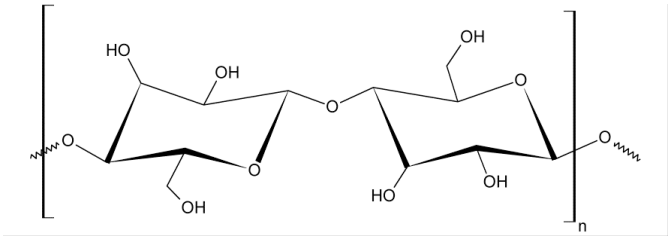
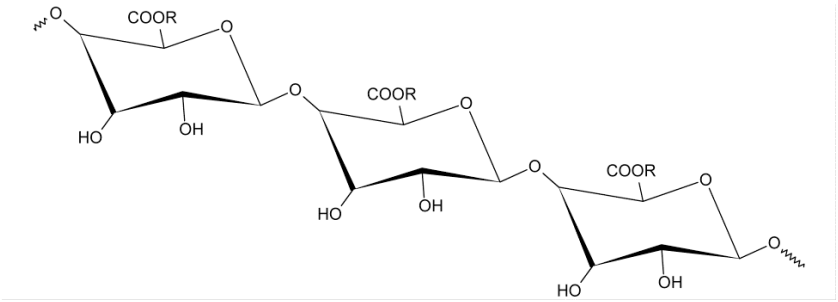
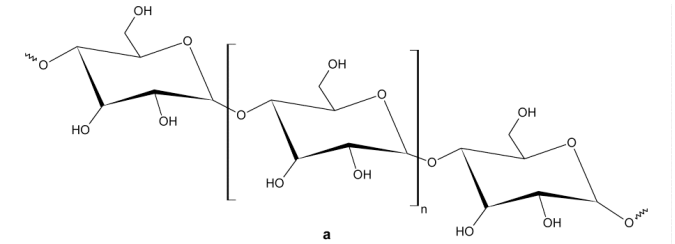
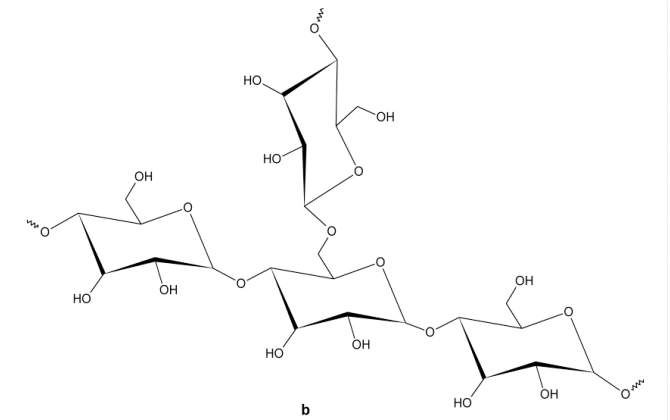
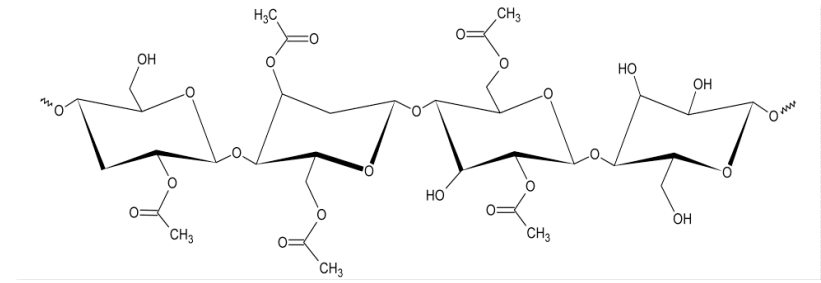
Mucilage obtained from the leaves of *Hibiscus rosasinensis* consists basically of L-rhamnose, D-galactose and D-galacturonic acid units. Matrix type tablets were prepared from the dried mucilage of *Hibiscus rosasinensis* by direct compression, incorporating diclofenac sodium as model compound. Dissolution studies conducted on these matrix type tablets confirmed the potential of this mucilage material as a release modifying excipient because sustained release over a 12 h period approaching zero-order release kinetics was obtained [19].

Jelly fig extract is isolated from the seeds of *Ficus awkeotsang* and contains a polysaccharide consisting of Ã(1–4)-D-glucuronic acid units that gels spontaneously in aqueous solutions. Matrix type tablets were prepared by direct compression from jelly fig extract containing theophylline as model drug. These matrices exhibited sustained release of theophylline over an 8 h period, following diffusion controlled non-Fickian release kinetics. The rate of theophylline release was shown to be independent of pH and the matrix tablets remained intact even after all the theophylline was released [20].

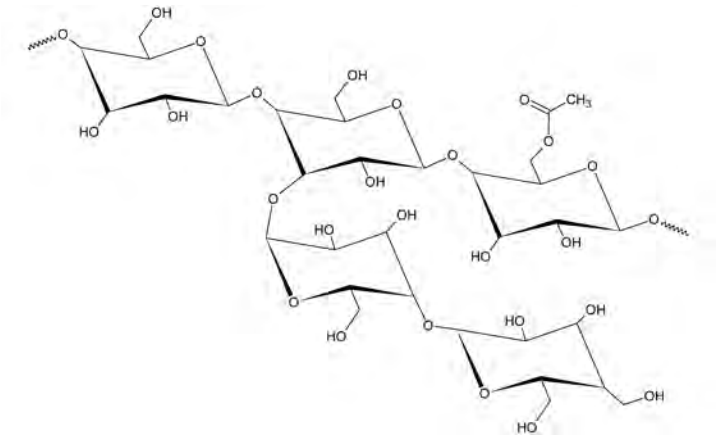
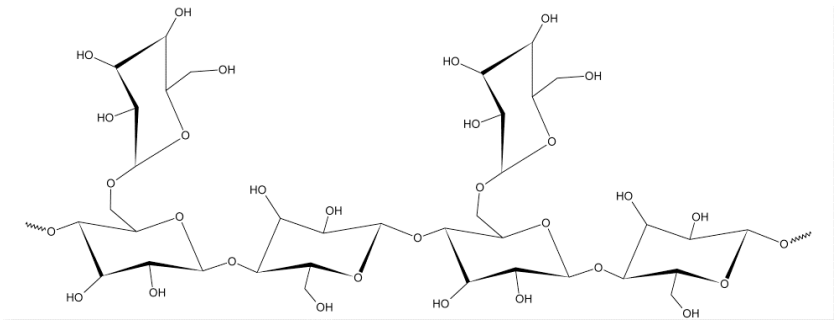
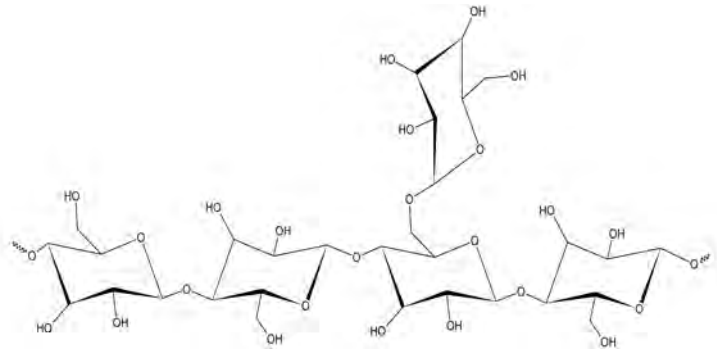
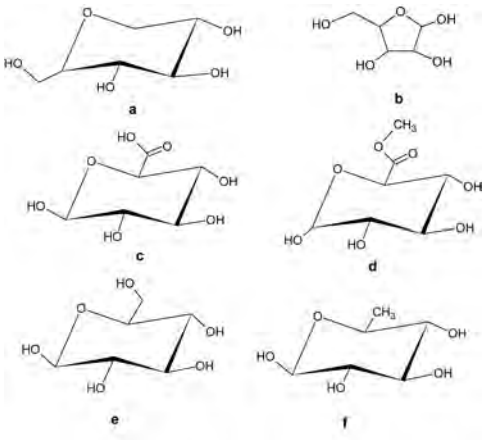
In another study involving direct compression where diltiazem was used as model drug, matrix type tablets were prepared from acrylamide grafted guar gum. *In vitro* studies confirmed controlled release of diltiazem HCl over a 12 h period [21]. Karaya gum is a natural polysaccharide obtained from the *Sterculia* tree. Matrix type tablets were prepared from Karaya gum by direct compression for the purpose of controlled drug release. The release of both diclofenac and caffeine were found to approach zero-order kinetics over a period of 8 h released by a combination of erosion and diffusion mechanisms [22].

In a study involving wet granulation as part of the manufacturing process, matrix type tablets containing diclofenac sodium were prepared from the mucilage extracted from the seeds of the plant *Mimosa pudica*. The mucilage mainly contained D-xylose and D-glucuronic acid. Diclofenac sodium release from the matrix tablets followed Higuchi's square root kinetics over a 24 h period. Drug release was found to

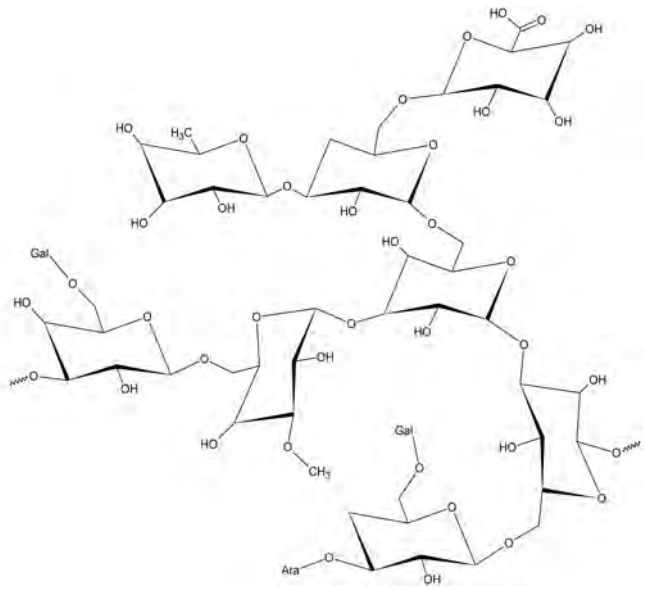
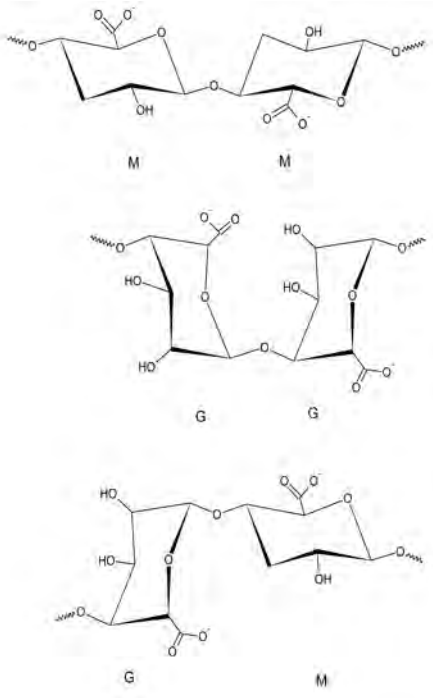
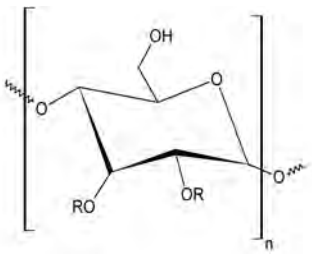
Table 1. Examples of Different Classes of Polymers from Plants and Algae that have Pharmaceutical Applications

Polysaccharide	Chemical structure
CLASS 1: CELL WALL POLYSACCHARIDES	
i) Cellulose Structural component of green plants, commonly derived from wood pulp and cotton. Commonly used in the form of microcrystalline cellulose. Insoluble in water. Commercially available.	
ii) Pectin R = H or CH_3 Structural component of terrestrial plant cells, commercially extracted from citrus plants. Soluble in water. Gellation occurs in the presence of calcium ions or an acidic medium. Used as emulsifying agent, gelling agent, controlled release and stabilising agent. Commercially available.	
CLASS 2: STORAGE POLYSACCHARIDES	
i) Starch Energy store in green plants. Main component of staple foods such as wheat, potatoes, tapioca and maize. Two basic components determine properties of each individual starch: a) amylose and b) amylopectin Mostly insoluble in cold ethanol and water. Starch swells between 5 and 10% in water at 37 °C. Gelling properties start at 59 °C, dependant on origin of the starch. Used as filler in tablets and capsules, disintegrant in both capsules and tablets, binder, thickening agent. Commercially available.	 a  b
ii) Aloverose (acetylated polymannan) Component of *Aloe vera* leaf gel. Swells in contact with water. Exhibits mucoadhesive properties. Used as matrix forming agent in tablets Not commercially available	

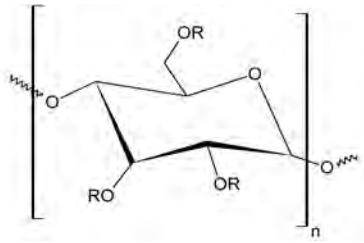
(Table 1) contd….

Polysaccharide	Chemical structure
ii) Glucomannan Also known as konjac glucomannan. Hydrophilic compound. Solubility dependant on amount of acetylation (higher acetylation = higher solubility). Forms a gel when heated with a base medium. Used in controlled release beads and particles. Gelling ability. Not commercially available.	
CLASS 3: SEEDS AND EXUDATES (MUCILAGES AND GUMS)	
i) Guar gum Also known as guar galactomannan. Obtained from ground endosperm of guar beans. Swells in water to form a highly viscous gel. Used as disintegrant, tablet binder, suspending agent, as well as viscosity increasing agent. Often works synergistically with other polysaccharides Commercially available.	
ii) Locust bean gum Also known as Ceratonia or carob bean gum or galactomannan. Primarily extracted from carob tree seeds. Often works synergistically with other polysaccharides. Forms a gel in hot water or if sodium borate is added. Used as viscocity increasing agent, tablet binder, controlled release agent. Commercially available	
iii) Tragacanth gum Obtained from *Astralgus*. Many different variations exist from 6 basic carbohydrate monomers: a) Ä-D-xylose, b) l-arabinose, c) Ā-D-galacturonic acid, d) Ā-D-galacturonic acid methylester, e) Ä-D-galactose and f) Ā-l-fructose Used as suspending and emulsifying agent. Practically insoluble in water. Swells up to 10 times its original size in water, forming either semigels or colloidal sols. Commercially available	

(Table 1) contd….

Polysaccharide	Chemical structure
iv) Acacia gum Also known as gum Arabic or Chaar gund. It is obtained from *Acacia senegal* and *Acacia seyal*. Used as bioadhesive agent, modified release agent, suspending agent, tablet binder, emulsifying agent. Commercially available.	
CLASS 4: ALGAE	
i) Alginates Derived from brown algae, also known as aligin or alginic acid. Mostly available as ammonium alginate, calcium alginate, potassium alginate or sodium alginate. Chemically modified forms are available such as propylene glycol alginate. Used as sustained release agent, tablet binder, suspending agent, stabilising agent, disintegrant, viscosity increasing agent. Cross-links in the presence of many ions. Alginates swell in water, absorbing between 200 and 300 times its own weight in water. Commercially available.	
CLASS 5: CHEMICALLY MODIFIED PLANT DERIVED POLYSACCHARIDES	
i) Hydroxypropyl methylcellulose (HPMC) R = H or CH_3 or $CH_2CH(OH)CH_3$ Forms a gel when added to water and heated. Acts as a controlled release agent and binder in tablets. Commercially available.	

(Table 1) contd….

Polysaccharide	Chemical structure
ii) Carboxymethyl cellulose (CMC) R = H or CH_2CO_2H Available as carboxymethyl-cellulose calcium and sodium. Used as stabilising agent, disintegrant, water-absorbing agent, emulsifying agent and viscosity increasing agent. Highly hygroscopic. Insoluble in water. Swells in water to create a suspension. Commercially available.	

be controlled by a combination of diffusion and erosion of the matrices [23].

Fenugreek mucilage also showed promising results with regard to controlled release from matrix type tablets. This mucilage is extracted from the seeds of *Trigonella foenum-graceum* and consists of mannose, galactose and xylose. Matrix type tablets produced from fenugreek mucilage were capable of controlling the release of propranolol HCl over an 8 h period exhibiting Fickian release kinetics [24].

Mucilage extracted from *Aloe vera* (*Aloe barbadensis* Miller) leaves has been investigated as a matrix forming excipient for modified release of diclofenac sodium. Matrix type tablets containing different ratios of the dried *A. vera* mucilage powder in relation to sodium carboxymethyl cellulose were prepared by direct compression. Dissolution studies revealed that increasing the relative amount of *A. vera* mucilage in the formulation increased swelling of the tablets and prolonged the release of the model compound. Sustained release of diclofenac sodium for up to 8 h was achieved [25]. Mini-matrix type tablets were prepared from gel and whole leaf materials extracted from different aloe species (i.e. *Aloe vera* and *Aloe ferox*) by direct compression. It was shown that the aloe materials enhance the swelling properties of mini-tablets containing Carbopol®. *Aloe vera* whole leaf powder enhanced the muco-adhesiveness of formulations containing hydroxypropyl methyl cellulose and when used alone, it formed mini-tablets that demonstrated stronger muco-adhesiveness than those mini-tablets prepared from Carbopol®. Furthermore, the mini-tablet formulations containing *A. vera* and *A. ferox* gels showed controlled drug release properties approaching zero-order kinetics over a 12 h period [26].

2.2. Multiple-Unit Matrix Type Systems

Multiple-unit drug delivery systems consist of small discrete subunits, each containing a portion of the dose. The small units are typically loaded into sachets or hard gelatin capsules or compressed into tablets in order to administer the recommended dose. Multiple-unit dosage forms have advantages over single-unit dosage forms such as being less dependent on gastric emptying rate and therefore often exhibit less inter- and intra-subject variability. They also provide a better distribution throughout the gastrointestinal tract and are less likely to cause local irritation [27].

Soluble fiber isolated from fenugreek seeds was used to prepare microgranules for sustained release of curcumin. Dissolution studies showed sustained release over 24 h, improving release of curcumin from 0.08 % to 28.6 % compared to unformulated curcumin. *In vivo* studies in 8 healthy human volunteers indicated improved oral bioavailability with the microgranule formulation equivalent to 600 mg curcumin achieving an area under the plasma concentration-time curve 15.8 times higher than 1000 mg of unformulated curcumin [28].

Tamarind mucilage is isolated from the seeds of *Tamarindus indica*. Kulkarni *et al.* [29] used this mucilage to prepare modified release beads prepared by extrusion-spheronisation. Zero-order release of diclofenac sodium was achieved over a period of 8 h. Bioavailability studies were conducted in six healthy human volunteers, which showed that the beads provided an AUC for diclofenac almost four times higher than that of a commercially available sustained release diclofenac formulation [29]. Similarly, calcium alginate nanoparticles were prepared by cross-linking bovine serum albumin (BSA) and alginate in a microemulsion. Nanoparticles with a mean diameter of approximately 350 nm were prepared with 40% BSA encapsulation efficiency. The nanoparticles demonstrated sustained release of BSA for up to 16 h [30].

Akhgari *et al.* [31] prepared beads, using small amounts of microcrystalline cellulose (10% of total weight) and starch as filler with varied amounts of acacia gum and tragacanth gum as binder. The model drugs used in this study were theophylline and ibuprofen. The resulting beads proved to be mechanically strong, but beads with no tragacanth disintegrated during dissolution, releasing the entrapped drug in a short time, giving a mean dissolution times as low as 28.130 min (±2.68 min) for ibuprofen and 15.574 min (±0.89 min) for theophylline. With the addition of tragacanth gum in the beads, the beads stayed intact during dissolution studies. When the ratio of tragacanth increased, the rate of drug release was reduced for both drugs, often more than doubling the mean dissolution time when the ratio of acacia gum to tragacanth gum reached 8:2. Mean dissolution times of up to 55.585 min (±1.66 min) for ibuprofen and 43.795 min (±2.71 min) for theophylline were obtained. Unfortunately the addition of the tragacanth to the formulations led to a decrease in the spherical nature of the beads.

Another study combined three anti-tuberculosis drugs isoniazid, pyrazinamide and rifampicin in alginate nanoparticles with between 70% and 90% loading efficiency and nearly 80.5% of the nanoparticles were in the respirable size range. Guinea pigs, inoculated with *Mycobacterium tuberculosis*, received either the free anti-tuberculosis drugs or nanoparticles by nebulisation. When the drugs were nebulised in their free form, they were completely cleared from the body within 24 h. However, after a single four minute nebulisation of the nanoparticles all three drugs were detected at concentrations above their minimum inhibitory concentrations in the lungs, liver and spleen for up to 15 days. In a follow up study, the nanoparticles were administered every 15 days, while the free drugs were administered daily. The different treatments were found to be equally effective against tuberculosis [32].

2.3. Matrix Type Hydrogel/Gelling Systems

Hydrogels are defined as three-dimensional, cross-linked networks formed by water-soluble polymers that can be formulated into different physical forms such as slabs, films and particles. The density of the cross-links in the gel network as well as its affinity for the surrounding aqueous environment are factors that can be manipulated to control drug release from these systems [33].

Itoh *et al.* [34] devised a system administered as a liquid that gels *in situ* to form a matrix capable of controlled release. The system consisted of two natural polysaccharides namely methylcellulose that undergoes thermo-responsive gelation and pectin that undergoes ionotropic gelation in the presence of calcium ions. The concentration of calcium ions have been shown to have a marked effect on the rate of drug release from pectinate gels [35]. Therefore, a calcium complex that releases a predetermined amount of Ca^{2+} when exposed to the acidic environment of the stomach was incorporated in the liquid system. *In vivo* studies in rats confirmed sustained release and maintenance of plasma levels of the model compound, paracetamol, over a 6 h period [34].

Juby *et al.* [36] used hydrogel matrices composed of different ratios of acacia gum to polyvinyl alcohol to create silver containing nanoparticles. The hydrogels with entrapped silver nanoparticles were created with the use of radiation. This method has the advantage of being able to control the size of the resulting nanoparticles, sterilizing the hydrogel, as well as increasing the biocompatibility of the mixture, because no toxic chemicals are required for the formation of the metal containing nanoparticles. The antimicrobial activity of the silver containing nanoparticles in combination with a hydrophilic hydrogel is especially applicable in the field of wound dressing design as the hydrogels slowly releases the nanoparticles as well as creating a moist environment, which is preferred for more effective wound healing. An increase in the amount of acacia gum increased the swelling properties of the matrices as well as increasing the biocompatibility and the initial amount of silver nanoparticles that are released. The amount of swelling was linked to the pH, but the hydrogel was found to be unstable Ā pH 12.

3. SITE-SPECIFIC DRUG DELIVERY SYSTEMS

Targeting the release of a drug to a specific site in the gastrointestinal tract that provides increased dissolution or absorption can greatly improve the therapeutic efficacy and reduce the side-effects of certain drugs [37, 38]. A dosage form encounters many environmental changes during transit through the gastro-intestinal tract. Factors such as the pH, enzyme activity and intestinal flora vary considerably between the different regions of the gastro-intestinal tract. These factors are further subjected to considerable inter- and intra-individual variation due to differences in diet composition, disease and medication use [39]. The harsh and varying conditions in the gastrointestinal tract can cause premature degradation of drugs that can be seen as an obstacle that reduces bioavailability. On the other hand, these region specific differences can be utilised as opportunities to optimise drug delivery. Novel drug delivery systems have been developed that use the unique characteristics of a specific region of the gastro-intestinal tract to induce drug release and optimise bioavailability [40]. Plant-derived materials have been most widely investigated in the formulation of drug delivery systems that target drug release in the colon.

3.1. Colon Specific Drug Delivery

The colon has been identified as a specific site for improved local or systemic effects of certain drugs. The colon has for example lower levels of digestive and proteolytic enzymes than the rest of the gastro-intestinal tract, which can be exploited to improve the bioavailability of protein and peptide drugs. Although the colon has a relatively small surface area, it has a longer residence time than the rest of the gastro-intestinal tract, which may be beneficial to increase bioavailability as well as to improve local effects in the colon due to increased exposure time to the drug [35].

Several polysaccharides of natural origin have been utilised in colon specific drug delivery systems. These dosage forms are capable of protecting the drug from degradation during transit through the distal part of the gastro-intestinal tract and then degrade in the colon to release the drug. Many of these colon specific drug delivery systems exploit the most distinctive property of the colon namely its abundant microflora, to accomplish the release of the drug in the colon [41]. The microflora of the colon produces digestive enzymes such as -glucuronidase, -xylosidase, -galactosidase, Ā-arabinosidase, azo-reductase and pectinase that are not present in the rest of the gastro-intestinal tract [42].

Inulin is a natural polysaccharide that consists of 2-1 linked D-fructose units and is found in plants such as onion and garlic that form part of a normal human diet. Inulin is not digested by the enzymes produced by the human body, but is digested by the *Bifidobacteria* in the colon. Its possible application as a carrier for protein delivery to the colon was investigated in the form of a methacrylated inulin hydrogel that only released 12.6% of its BSA content after 4 h in conditions mimicking the environment of the small intestine. This hydrogel released 100% of the BSA after 24 h in the presence of the inulinase enzyme [43].

Jain *et al.* [44] prepared beads containing 5-fluorouracil by ionotropic gelation of a pectin solution. The beads where approximately 1.35 mm in diameter after coating with Eudragit S-100 and were evaluated for drug release behavior in a 4% w/v solution of rat caecal contents to simulate the con-

ditions of the colon. Only 6.7% of the drug content was released in simulated gastric and intestinal conditions, while 98.7 % of the drug was released under the simulated colonic conditions.

Beads containing 5-fluorouracil were prepared by extrusion-spheronisation, which were subsequently coated with pectin/ethylcellulose. The drug delivery properties of the beads were evaluated *in vivo* in rats. Compared to immediate release beads, the coated beads resulted in a reduction in 5-fluorouracil blood levels from 23.54 Āg/ml to 3.65 Āg/ml and an increase in 5-fluorouracil concentration in colon tissue from 0.10 Āg/g to 0.31 Āg/g. This system could therefore substantially reduce the systemic side-effects and simultaneously increase the efficacy of 5-fluorouracil treatment in colon cancer [37].

Pectin microcapsules were prepared for colon-specific drug delivery of the experimental peptide drug LK-423. The microcapsules combined pH, time and enzyme controlled drug release mechanisms to ensure colon-specific drug delivery. Calcium pectin microcapsules were prepared by ionotropic gelation with 89.4 % encapsulation efficiency. The micorcapsules were subsequently coated with an inner coating of Eudragit® RS and RL, and an outer enteric coating of Eudragit® L 30D-55 to delay dissolution in the upper gastro-intestinal tract. Colon-specific drug release was ensured by the degradation of pectin specifically by colonic microflora. *In vivo* studies were conducted in rats with TNBS-induced colitis. The result showed that orally administered LK-423 microparticles produced a higher percentage of healing than rectally administered LK-423 [38].

Guar gum is a galactomannan obtained from the seeds of *Cyamopsis tetragonalobus* and is also known as Guar galactomannan. Fast-disintegrating tablets containing tinidazole were compression-coated with guar gum. Only 0.5% of the tinidazole was released in conditions mimicking the environment of the stomach and small intestine and 99% of the tinidazole was released in simulated colonic fluid (containing rat caecal contents) at the end of the 24 h dissolution study [45]. An *in vivo* study was then conducted using six healthy human volunteers. It was found that it took 14 h longer for the blood levels to reach the peak plasma concentration (C_{max}) in the volunteers that received the coated tablets and that the C_{max} was only two thirds that observed in the volunteers who received the uncoated immediate release tablets. The authors maintain that the lower C_{max} in conjunction with the time delay proves that the tinidazole was released selectively in the colon [46].

Because of the variety of conditions that a dosage form are exposed to during transit through the gastro-intestinal tract, it is unlikely that a single material will possess all of the properties necessary to provide complete site-specific targeted delivery. A combination of natural materials in a dosage form, each fulfilling a specific function, may provide a more successful strategy.

Matrix type tablets were prepared from guar gum containing diltiazem hydrochloride as model drug. The tablets were then coated with an inner coating of inulin and an outer coating of shellac (a secretion of the insect *Laccifer lacca*). The shellac acted as an enteric coating to protect the core tablets from the simulated gastric environment, while inulin prevented the guar gum core from dissolving in the simulated intestinal environment. The guar gum core specifically release drug in the colon because it is selectively degraded by colonic bacteria. *In vivo* studies revealed that no drug was released in the stomach and approximately 20% was released in small intestinal environment. The remainder of the drug was released in the colonic environment [42].

Glucomannan is a polysaccharide that is found in many plant bulbs and tubers, most notably the tubers of *Amorphophallus konjac*. This is why glucomannan is often referred to as konjac glucomannan. Alonso-Sande *et al.* [47] reported that glucomannan can dissolve in water or become insoluble in water, depending on the degree of acetylation of the molecule. Higher acetylation degrees led to improved water solubility. In its pure form, this polymer does not exhibit very strong gel forming properties, but small chemical changes or combining glucomannan with other polymers revealed a very different profile.

Glucomannan is not degraded by any enzymes in the human body, but the intestinal flora in the colon produces an enzyme known as Ä-mannanases. Alonso-Sande *et al.* [47] tested the effect of Ä-mannanases on glucomannan and complexes made from glucomannan and xanthan gum (obtained from bacteria, specifically *Xanthomanos campestris*). Both of the formulations showed sufficient degradation in the presence of Ä-mannanases to be used as a colon targeted drug delivery system. Alonso-Sande *et al.* [47] then compared glucomannan from different origins (which have different degrees of acetylation) with one another, as well as different ratios of glucomannan and glucomannan/xanthan gum formulated into tablets through wet granulation. The authors used a highly soluble drug, namely diltiazem for drug release studies. Tablets of most combinations/ratios exhibited sufficient tablet strength and near zero-order release rates of the drug from the tablets as soon as Ä-mannanases were present. The tablets consisting of glucomannan with lower degrees of acetylation took longer to swell than those consisting of glucomannan with higher degrees of acetylation as well as to release the entrapped drug content. This study proved that a sustained release formulation specifically designed for colonic drug release could be prepared using simple and inexpensive equipment and techniques with glucomannan and xantham gum.

4. TISSUE TARGETED DRUG DELIVERY SYSTEMS

The concept of tissue-specific drug delivery refers to a carrier in the formulation that could take the drug dose to the specific anatomical site affected by the disease without harming healthy tissues [48]. Different mechanisms of action are utilised by carriers to target specific tissues such as using physiological aspects of tissues (e.g. antibodies against tumor derived vascular endothelial cells) or using formulation aspects such as poly(ethylene glycol) conjugated microparticles or fusogenic liposomes [49].

Nanoparticles were prepared from guar gum cross-linked with glutaraldehyde to specifically target the delivery of tamoxifen to breast tissue. *In vitro* studies revealed that the nanoparticles released 87.36% of the model drug over 12 h following zero-order kinetics. During *in vivo* studies in fe-

male albino mice, the amount of tamoxifen found in excised breast tissue from the nanoparticle treated mice was double the ammount observed in mice that received tamoxifen in the form of conventional tablets [50].

Nanoparticles with an average size of 80 nm containing plasmid DNA was prepared from a micro-emulsion by cross-linking alginate with calcium ions. The ability of the nanoparticles to transfer genes into non-phagocytic cells was evaluated *in vitro* on NIH 3T3 cells. A transfection efficiency of 48% was achieved after a 48 h incubation period [51].

5. GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

Gastro-retentive drug delivery systems are formulated to remain within the stomach of the patient until the total drug dose is released. The therapeutic interest in gastro-retentive dosage forms lies in their ability to maintain the drug above the absorption window for a prolonged period of time and they have many advantages over conventional drug delivery systems. These advantages include more effective delivery of drugs that are locally active in the stomach and prevention of the degradation of drugs that are unstable in the small intestine or colon. They are also very useful for delivery of drugs that are poorly soluble at high pH values [52].

Gastro-retentive drug delivery systems are classified as follows by Bardonnet *et al.* [53]: High-density systems, low-density systems (or floating systems), expandable systems, superporous hydrogel systems, mucoadhesive systems and magnetic systems. The following sections describe the use of plant derived polymers in each of these classes of gastro-retentive drug delivery systems.

5.1. High Density Drug Delivery Systems

High density drug delivery systems offer gastric retention by small, dense particles (i.e. more than 2.5 g/cm^3) that get trapped in-between the folds of the stomach lining in the pyloric region and thereby resist movement through peristalsis in the stomach [54].

High density spherical beads for gastro retentive purposes were designed by combining natural polymers and high density particles. Gellan gum (a polysaccharide of bacterial origin, specifically *Pseudomonas elodea*) and Karaya gum (obtained from plants of the genus *Sterculia*) were combined to provide a sustained drug release effect, while titanium oxide was used to increase the density of the beads. Famotidine, which is used to treat gastric ulcers, was the model drug incorporated into the beads that were prepared by using a coacervation phase-separation method. This method produced beads with uniform sizes and drug entrapment efficiencies of up to 92% that exhibited extended drug release for up to 12 h [55].

5.2. Low-Density (or Floating) Drug Delivery Systems

Floating gastro-retentive drug delivery systems can be divided into effervescent and non-effervescent systems. Effervescent systems contain compounds that release CO_2 when it comes into contact with the gastric content. Non-effervescent systems are based on polymers that have swelling properties (that are often pH sensitive) with a resultant low density. The total bulk density of these systems has to be less than 1 g/cm^3 after swelling to ensure that the system remains floating [56, 57].

Malakar *et al.* [58] prepared a multi-unit non-effervescent floating bead system prepared from alginates. Liquid paraffin and cloxacillin were entrapped within sodium-alginate matrix-type beads. The beads were prepared by an emulsion gelation method and were optimised using a factorial design. An entrapment efficiency of between 57 and 66% was attained with a floating time of well over 12 h and lag times before floating of less than 10 min. Dissolution studies revealed that the model drug (i.e. cloxacillin) was steadily released over an 8 h period. An increase in alginate concentration and simultaneous decrease in paraffin concentration in the bead formulations led to an increase in the rate and amount of drug released. This increased dissolution was attributed to the fact that most of the model drug was being entrapped in the liquid paraffin.

Floating bead drug delivery systems formulated with alginate or pectin containing diclofenac sodium as model drug were prepared by inotropic gelation using sodium chloride or calcium chloride as cross-linking cations. When the plant polymers were cross-linked with sodium chloride, irregular shaped beads were obtained, while calcium chloride as cross-linker rendered stronger and more consistent beads. Furthermore, the sodium bicarbonate concentration in the beads greatly affected the beads' strength as well as floating times. The optimum formulations contained a sodium bicarbonate to pectin ratio of more than 0.25:1 but less than 1:1. Too little sodium bicarbonate gave beads that did not float and too much caused the beads to be weak and irregularly shaped. The optimum formulations exhibited encapsulation efficiencies of between 77 and 80.5% with buoyancy between 7 and 12 h. The floating beads were tested in rabbits and the results showed that only 3 to 4% of the encapsulated drug was released in an acidic medium over a 2 h period. After the pH began to increase to a more neutral pH, the model drug was released completely within 30 to 45 min. This drug release profile was attributed to the calcium and pectin complex becoming more insoluble in an acidic environment with rapid swelling and release of the drug in a more alkaline environment. These properties make pectin a good candidate carrier for drugs that are insoluble in acidic environments or drugs that irritate or harm the stomach mucosa [59].

A combination of alginate and cashew gum was formulated with calcium carbonate (as cross-linking agent) to create a floating bead drug delivery system for *Lippia sidoides* oil, which is used as an anti-fungal, anti-bacterial and anti-larval agent. Different drying methods were investigated including freeze-drying and conventional drying in an oven. The drying methods greatly influenced the external morphology of the beads as well as drug release, lag time before the beads floated and float time. Oven dried beads floated for an average of 1.25 days, whereas all the freeze-dried beads floated for up to 5 days. The beads gave encapsulation efficacies of between 15.2 and 23.8%. Decreasing the cashew gum concentration in the beads extended release of the *Lippia sidoides* oil. The study also compared the efficacy of

non-floating delivery systems with floating drug delivery on the mortality rate of the targeted larvae, which are known vectors of the dengue virus. Floating alginate and cashew gum beads gave a mortality rate of 85% after 48 h with sinking beads only reaching a mortality rate of 33% over the same time period [60].

Ji & Deng [61] used konjac glucomannan to create a non-effervescent floating tablet for gastro-retentive drug release. To create a floating form of konjac glucomannan, the raw polysaccharide powder was firstly deionized in water. The deionized glucomannan was fractionized using the ethanol (70%) precipitation method. The resulting precipitate was vacuum freeze dried resulting in a powder that is capable of floating. Floating tablets were prepared using the direct compression technique of a formulation consisting of the model drug (metronidazole), polyvinylpolypyrrolidone (PVP), magnesium stearate and the precipitated konjac glucomannan fraction. This yielded tablets that started floating almost immediately after being immersed in the simulated gastric fluid (0.1 N HCl) and continued to float between 12 and 24 h. The floating tablets released up to 30% of the incorporated drug over the first 12 h period.

A controlled release, floating, effervescent microbead system was designed by Okunlola *et al.* [62] from pregelatinized starch (from Chinese yams) and sodium alginate cross-linked by inotropic gelation as main functional ingredients sodium containing bicarbonate as effervescent compound and metformin as drug. An increase in the amount of starch in the formulation increased the time for the formulation to start floating in an acidic environment. It was also found that the amount of starch in the beads was directly proportionate to the buoyancy shown by the beads even more so than the concentration of sodium bicarbonate. Dissolution studies of the beads revealed that the drug was released in a controlled way but an increase in the amount of starch led to a faster release of the metformin over a 10 h period. The authors attributed this characteristic to starch creating a more porous gel matrix, which can then release the drug quicker.

Rajamma *et al.* [63] combined three plant derived polymers to create floating, effervescent, controlled release tablets. These three polymers were hydroxypropyl methylcellulose, locust bean gum (also known as carob gum) and ocra gum (a water soluble polysaccharide obtained from the fruit of *Hibiscus esculentus L.*). The hydroxypropyl methylcellulose was used as a hydrophilic matrix, with the ocra gum and locust bean gum as gelling agents to control the release of the drug. The author found that all three components were indeed necessary to attain acceptable tablet properties, which include tablet hardness and mass variation. Increasing the amount of hydroxypropyl methylcellulose decreased the amount of time before the tablet started to float, but it increased the initial drug release rate. Higher ratios of ocra gum and locust bean gum slowed initial drug release rate down, but kept drug release constant over the next 24 h. The floatability was tested *in vivo* in rabbits using x-ray and opaque barium sulphate, which showed that tablets were still floating in the stomach of the rabbits after 24 h.

5.3. Bioadhesive Drug Delivery Systems

Bioadhesion occurs when a compound such as a polymer adheres to biological tissue, while mucoadhesion specifically refers to the situation where a drug delivery system adheres to mucosal membranes such as those of the gastrointestinal tract, buccal or vaginal mucosal surfaces [53, 64, 65].

Liu *et al.* [64] formulated mucoadhesive amoxicillin containing ethylcellulose microspheres for the treatment of *Helicobacter pylori* by an emulsification/evaporation method. The spheres were dried at room temperature under vacuum. This resulted in spheres with a diameter ranging between 400 and 1000 Ām. Entrapping the amoxicillin within the microspheres protected it for extended periods of time against degradation in an acidic environment. Dissolution studies on the mucoadhesive microspheres showed that 90% of the entrapped amoxicillin was released at a pH of 1 after 4 h, but in a phosphate buffered solution (pH of 7.8) less than 50% of the drug was released after 4 h. The *in vivo* mucoadhesive properties of the spheres were tested and compared with other non-adhesive spheres. The quantity of the ethylcellulose microspheres remaining on the mucosa after a period of 4 h was significantly higher than the other spheres. The clearance of *H. pylori* from rats was tested for the microspheres compared to similar doses of amoxicillin powder. The results showed more effective clearance of *H. pylori* by the microspheres.

Aceclofenac is known to have poor bioavailability because of its low aqueous solubility. On the other hand, high doses of aceclofenac within the gastro-intestinal tract cause mucosal irritation which leads to vomiting, nausea, constipation and abdominal pain. A controlled release dosage form is therefore required to keep the amount of free drug low, but keep a constant supply to maintain blood levels. Mucoadhesive microcapsules containing aceclofenac were prepared with a mixture of 80% hydroxypropyl cellulose and 20% alginate. The mucoadhesive microspheres were prepared by ionic gelation, using calcium chloride to complete the cross-linking of the polymers. The effect of the coating thickness was also evaluated. The microspheres showed very high entrapment efficiency (between 96 and 100%) with the drug slowly being released over a period of 12 h. Mucoadhesive properties were tested by comparing the hydroxypropyl cellulose/alginate microspheres to that of non-adhesive spheres with a wash-off test method, in both a gastric environment pH (pH 1.2) as well as an intestinal environment (pH 6.2). The hydroxypropyl cellulose/alginate beads showed similar adhesion in both environments with at least 40% of the adhesive spheres still adhering to the mucosa after 4 h while only trace amounts of the non-adhesive spheres where left [66].

Ameye *et al.* [67] created buccal adhesive tablets for the delivery of testosterone using different starch based formulations. The different formulations consisted of starch combined with poly(acrylic acid) in different ways, including chemical graft polymerisation to form starch-g-poly(acrylic acid) by irradiating or freeze drying the components together to combine the complexes. The different formulae were then compressed into buccal tablets. An *ex vivo* study was conducted using fresh porcine gingival tissue to determine the mucoadhesive strength that each formulation had. The starch formulations that were irradiated and chemically polymerised gave equal or even better mucoadhesion than a reference formulation made from Carbopol® 974P as described by Voorspoels *et al.* [68]. This was followed by *in vivo* testing

of the testosterone formulations by measuring drug plasma levels in dogs. The buccal tablets created from the chemically modified starch showed a fast initial release of testosterone, reaching the 3 mg/ml target and sustaining it for 7 h. The freeze dried polymer complex could not equal this performance, but the irradiated polymer complex did give longer release times of up to 13.5 h.

Hydrogel film formulations were prepared from hydroxypropyl cellulose, carbopol-934P (CP) and polyvinylpyrrolidone-K30 (PVP) each separately and combined. Pre-formulation studies showed the drug to be compatible with all the excipients used in the formulation. *Ex vivo* studies on sheep buccal mucosa showed adequate mucoadhesion by each different formulation to stay in place for the duration of drug release, but by combining all three, the strongest adhesion was achieved. *In vitro* drug release from the different formulations was similar, following zero-order release patterns with similar results seen *in vivo* [69].

Sharma *et al.* [70] formulated mucoadhesive tablets containing clotrimazole for the treatment of *Candida albicans* vaginal infections using different ratios of carbopol 934P, sodium carboxymethyl cellulose and sodium alginate. Tablets were compressed by standard techniques with the three polymers in different combination ratios being used as filler materials. The bioadhesion was tested in fresh porcine vaginal mucosa. Carbopol 934P proved to be the best mucoadhesive agent, but the plant-derived polymers showed swelling to a larger extent. Most of the formulations showed zero-order drug release over extended periods of time, but the best formulation was found to be tablets with a 2:1 ratio of carbopol:sodium alginate as these tablets released 99% of the drug over a 24 h period.

Although bioadhesive drug delivery systems exhibited high potential during *in vitro* tests, they seem to be less effective when tested *in vivo* because of the high turnover and sloughing rates of the mucus layer within living organisms [71].

6. STIMULI-RESPONSIVE DRUG DELIVERY SYSTEMS

Stimuli such as temperature, ionic strength, pH and the application of a magnetic field can change the conformation or packing of responsive polymers in a dosage form and in so doing affect the drug release or change the affinity to water of the dosage form [72, 73]. Some of the advantages associated with responsive polymeric drug delivery systems include prolonging the exposure of specific targets to certain drugs, reducing the chance and or time of contact with non-targeted tissue, increased stability of the drug and targeted delivery. In many cases, natural polymers are used in conjunction with other polymers to achieve stimuli responsive properties [74].

6.1. pH Responsive Drug Delivery Systems

The use of pH-sensitive hydrogels is specifically applicable for drug delivery in the gastro-intestinal tract where the pH varies substantially between the different regions. This variation in pH provides the opportunity to formulate responsive delivery systems that are capable of protecting drugs in certain regions of the gastro-intestinal tract, reducing irritation caused by high amounts of free drug and/or optimising drug absorption [75]. Poly(N-isopropylacrylamide) (PNIPAAm) is used in combination with pectin to form a pH sensitive hydrogel for targeted drug delivery. Ceric ammonium nitrate was used to create free radicals on the pectin molecules so that cross-linking can occur in the presence of N,N-methylbensacrylamide (MBAA). This reaction is called radical-induced polymerisation. The amount of PNIPAAm grafted onto the pectin was varied together with the temperature at which the polymerisation was performed. The resulting pectin-g-PNIPAAm hydrogels were tested for use as drug delivery systems in pH 5.5 and pH 7.4 buffered environments with theophylline as model drug. The percentage theophylline released was considerably lower at pH 5.5 than at pH 7.4 for all the formulations tested. It was further established that the higher the amount of PNIPAAm in the grafted polymer, the slower the drug was released from the drug delivery systems [76].

Abd El-Ghaffar *et al.* [77] created a hydrogel and beads using alginate as the functional polymer. Alginate beads were created by ionotropic gelation using calcium as cross-linking ions. The hydrogels were formed by reacting glycidyl methacrylate (GMA) with ammonium peroxy disulfate (APS) and sodium alginate by a process known as emulsion polymerisation to create PGMA-g-SA hydrogels. The hydrogels were then set and cut into cubes with dimensions of 5 mm. In the hydrogels, the amount of sodium alginate could not be raised above 1% w/w as the mixtures became too viscous. The swelling of both pre-wetted and dry beads and hydrogels was tested in double distilled water, as well as simulated gastric fluid (at a pH of 1.2) and simulated intestinal fluid (at an pH of 7.5). Wet beads and gels showed swelling in distilled water and a little less swelling in the pH 7.5 medium. At a low pH environment the gels and beads shrank. The dried beads showed more dramatic changes in swelling with weight changes of up 3500% for the calcium alginate beads within the pH 7.5 medium. In the low pH medium, the beads and the gel showed a very small degree of swelling. The biggest swelling of the dried gels and beads was observed at pH 7.5, with the degree of swelling for the beads and gels in distilled water fitting in the middle between the degrees of swelling exhibited in the acidic and alkaline media. This proves the sensitivity to pH changes. The release of riboflavin from the gel matrix as well as the calcium alginate was determined in a pH of 1.2 and pH 7.5. Drug release followed the same trend as the swelling, much faster drug release was achieved in the pH 7.5 solutions and the slowest drug release came from the pH 1.2 solutions. This shows alginates to be a viable candidate as a pH-sensitive controlled release drug delivery system.

6.2. Thermo-Responsive Drug Delivery Systems

Thermo-responsive hydrogels can turn into gels from solutions or vice versa according to the temperature of the environment, which is known as a sol-gel transition. Most polymers and macromolecules become more soluble when heated. The temperature above which a gel turns into a solution is known as the upper critical solution temperature (UCST). Some polymers become less soluble as the temperature rises and this phenomenon is known as inverse temperature-dependent solubility. The temperature above which a

solution forms a gel is known as the lower critical solution temperature (LCST) [72, 78].

Thermo-responsive polymers can be exploited to slow down the release of a drug or to restrict its release at a specific temperature. The LCST of PNIPAAm is in the area of 31 to 34 °C [63, 64], which is close to body temperature and therefore makes it a good candidate to be used in combination with natural polymers as "smart" hydrogels [79].

By combining calcium alginate with poly-[(3-acrylamidoppropyl)-trimethylammonium chloride-b-N-isopropylacrylamide] in a process known as atom transfer radical polymerisation (ATRP), Oddo *et al.* [80] was able to create microspheres with thermo-sensitive properties. This co-polymer has an LCST between 36 and 38 °C, which means that it exists in solution at room temperature and as soon as it reaches body temperature, the polymer changes into an insoluble gel-like structure. Drug release studies were completed on the microspheres below the LCST (i.e. 25 °C) and at a temperature within the transition phase (i.e. 37 °C) to see how this affects the release of both water soluble (FITC-labelled dextran) and poorly water soluble (pyroxicam) drugs. Below the LCST the drug release occurred in a single burst, but an increase in the temperature to a value above the LCST, the drug release was slowed down with maximum drug release only occurring after 20 h. An increase in the alginate content caused a reduction in drug release rate at higher temperatures. Regular calcium alginate beads were compared to beads prepared from the modified polymer containing an enzyme (i.e. horseradish peroxidase) as model compound. As the concentration of the co-polymer increased in the formulation, the rate of release of the enzyme decreased.

Another thermo-responsive polymer was created by attaching PNIPAAm to sodium alginate in the presence of *N*-hydroxybenzotriazole. The rheological properties of the alginate-*g*-PNIPAAm co-polymer were tested at different temperatures. At lower temperatures (i.e. 25 °C) an increase in the amount of PNIPAAm as side-chains, reduced the viscosity of the mixture, which was attributed to the fact that PNIPAAm side-chains have a lower molecular weight than the original side-chains. Depending on the quantity of PNIPAAm in the side chains of the alginate, the LCST varied. Polymers with more PNIPAAm in the side-chains showed a decrease in the LCST temperature. The LCST for low PNIPAAm containing alginate polymers was above 40 °C, which could be reduced to 32 °C by increasing the amount of PNIPAAm grafted onto the alginate backbone. This effectively means that the sol/gel transition may take place well below body temperature. This lowered transition temperature combined with the bio-compatibility inherent to alginate means that these grafted polymers are excellent candidates for further study in the pharmaceutical industry, possibly as depot drug delivery systems or for other sustained release applications [81].

Uraki *et al.* [82] determined the LCST for hydropropyl cellulose to be 43 °C. This means it does not conform to the requirements needed to be a viable thermo-responsive drug delivery system in humans. Subsequently, hydroxypropylated unbleached pulp, which is hydroxypropyl cellulose with lignin and an ethylene glycol-based cross-linking agent, was investigated further for possible thermo-responsive behaviour. Lignin is seen as an undesired by-product from wood pulp when paper or feedstock is produced. It was found that by varying the cross-linking agents (urethane-type versus epoxy type) and the extent of cross-linking with lignin, the LCST of the gels could be changed considerably. The epoxy-type gel's volume changed at temperatures between 35 - 50 °C and the volume of the urethane-type gel changed at a temperature as low as 20 °C. This means that these newly formed polymers may have application in thermo-responsive sustained release formulations.

Karewicz *et al.* [83] combined two very different polymers to take advantage of each of the polymer's unique properties. Alginate was combined with hydroxypropyl cellulose using an emulsification gelation method to develop microbeads that are themosensitive. Analysis of the microbeads showed a LCST of between 34 and 37 °C, which falls within the physiological range and this makes these microbeads applicable for use in humans. Heparin as model drug was entrapped within these microbeads with encapsulation efficiencies varying between 55 and 64%. An increase in hydroxypropyl cellulose content gave a slight decrease in the extent of drug encapsulation. The release of heparin from the microbeads with different ratios of hydroxypropyl cellulose to alginate was tested at varying temperatures. All formulations gave an initial burst release within 4 h with a second phase of slow release that lasted for 16 h, thereafter, the drug was released at a very slow rate over a period of 16 days. Higher temperatures caused a reduction in the rate at which the drug was released from the mirobeads. The microbeads prepared with a ratio of alginate:hydroxypropyl cellulose of 4:1 was chosen as the optimum formula for heparin release because of the high entrapment efficiency, LCST and favourable drug release profile.

6.3. Magnetic-Field Responsive Drug Delivery Systems

Magnetic-field responsive drug delivery systems containing plant-derived polymers are being developed for many different applications in the pharmaceutical field. To obtain a magnetic responsive effect, a paramagnetic or superparamagnetic material is added into the structure of the polymer or the drug delivery system. By using alternating magnetic fields, the drug release can be timed and the rate of release can be controlled [74] or the site where the drug delivery should occur can be controlled to a certain extent [84, 85].

Beads were prepared from sodium-alginate by ionotropic gelation with calcium and insulin was entrapped as model drug, after which they were coated with chitosan. To obtain the magnetic-field responsive effect, iron was incorporated into the beads in the Fe(III) and Fe(II) ion forms. The alginate/chitosan beads showed an entrapment efficiency of 34% for insulin. Coating with chitosan caused a tendency in the beads to agglomerate, which means the suspension had to be kept stirring during the production of the beads to keep them separated. It was postulated that the iron-ions did also cross-link with the alginate, but only to a low extent because of the cross-linking priority with calcium. When the *in vitro* release of the insulin was tested, beads containing alginate only released the insulin faster than the alginate/chitosan beads. The alginate/chitosan beads released the insulin in three distinct

phases that can be described as follows: the beads released 18% of the total insulin within the first hour, which was attributed to the insulin trapped in the outer layers of the beads. For the following 48 h, the insulin release rate remained constant, and then it reached a plateau. The release profile for alginate/chitosan beads that included the magnetic ions was similar to that described for the beads without iron ions until a fluctuating magnetic field was applied to them. Application of an external magnetic field caused a sharp increase in the rate and extent of insulin release. This was attributed to the iron-ions oscillating and in doing so widening the pores and channels within the polymer matrix. *In vivo* tests were done on different groups of Swiss mice to determine if the insulin retained its efficacy after being entrapped in the bead matrix. The magnetic alginate/chitosan beads were re-formulated to enable implantation under the skin of the mice. This test proved that the insulin released from these devices retained its efficacy [86].

6.4. Multi-Stimuli Responsive Drug Delivery Systems

Ying *et al.* [87] created beads that were responsive to temperature, pH and ionic strength. This was achieved by using poly vinyl acetate grafted onto sodium alginate and using bovine serum albumin (BSA) as model compound in beads formed with the co-polymer. Since proteins are extremely sensitive to different environmental factors, they need to be protected against degradation. Two methods were used to incorporate the BSA in beads namely 'pre-polymerisation gelation' and 'gelation *in situ*-grafting'. Pre-polymerisation gelation involves grafting the poly vinyl acetate onto the sodium-alginate and then cross-linking it with calcium to form the beads. The 'gelation *in situ* grafting' method starts with the formation of calcium-alginate and then the BSA is added to form a BSA-calcium-alginate complex, which was used to prepare the beads. The different production methods gave similar beads that provided protection against BSA degradation and the beads were responsive to changes in pH, temperature as well as strong ions.

A magnetic responsive drug delivery system was developed by Dutta & Sahu [85], wherein pectin was used to provide pH sensitivity as well as being resistant to enzyme breakdown. These factors contribute to make pectin a valuable asset in the formulation of colon specific drug delivery. Super-paramagnetic iron oxide nanoparticles (SPION's) were prepared. Pectin was then mixed with 5-fluorouacil as model drug and cross-linked on the surface of the SPION using calcium to create magnetic beads. The production process involved sonication during the forming step of the beads in an effort to increase the entrapment efficacy of 5-fluorouacil. At optimum levels of sonication, the amount of drug entrapped was close to double that previously reported for pectin and 5-fluorouacil. The beads showed alignment to the manipulation of an external magnet at room temperature. This brings the possibility of manipulating the beads externally to a specific location. *In vitro* drug release studies showed a release of 11.8% of the drug within simulated gastric fluid (pH 1.2) after 2 h. Within the first 2 h in the simulated intestinal fluid, 23% of the drug was released with another 19% being released over the 3rd h. In simulated colonic fluid (pH 5.5), the beads released the drug relatively slow with only 43% of the entrapped drug released over a 43 h period.

7. COATING MATERIALS

Coatings for drug delivery systems are being researched more and more as they have the ability to change the external properties of dosage forms without interfering with the internal structure. The uses of coatings on drug delivery systems include protection against chemical and physical degradation of the drug or delivery system, alteration of the drug release profile, improvement of the appearance or organoleptic properties and addition of benefits such as bio-adhesion or responsiveness to external stimuli. Different plant-derived polymers have exhibited properties favourable to act as coating materials for dosage forms [88].

A coating was designed by using high amylose corn starch as well as pectin. This coating was specifically prepared to protect the internal core of a formulation from enzymatic and gastric breakdown and to release the drug in the colon. This was achieved by microbial breakdown of the coating only in the colon. High amylose corn starch and pectin was combined in different ratios, formed into a thin layer and then evaluated. The tests included dissolution studies in a number of dissolution media with different pH values and digestion tests with weighing of coated slides to determine if any dissolution of the films took place. Scanning electron microscopy (SEM) analysis of the films was conducted before and after each test. Increases in the high amylase corn starch concentration caused a decrease in the dissolution of the coating. The coatings showed high resistance to pancreatin breakdown with SEM images showing intact coating surfaces when exposed to this enzyme in 0.04% NaCl solution with a pH value of 7 [89].

Many drawbacks of liposomes such as instability, agglomeration and fast removal from the systemic circulation by the reticulo-endothelial system [90] can be bypassed by adding a coating to the liposomes. Nguyen *et al.* [91] prepared liposomes, but as an additional step to the production process, the liposomes were added to a pectin solution in the form of drops. Two different pectins were used in this coating process, namely a low-methoxylated (LM) and high-methoxylated (HM) pectin. Pectin added to liposomes with an original positive zeta potential caused a shift to a negative zeta potential, which may contribute to a slower removal of liposomes from the systemic circulation by the reticulo-endothelial system. The type of pectin influenced the liposome size and charge with LM-pectin giving the largest negative charge and an increase in size to a lower extent compared to HM-pectin that gave the largest increase in liposome size but the smallest negative charge. Analysis of the coated liposomes by a dynamic light scattering technique revealed that very little agglomeration occurred in the coated liposomes.

8. OTHER NOVEL USES OF PLANT-ORIGIN POLYMERS

A technique was developed to entrap mammalian cells (e.g. pancreatic islets or ĀTC3 cells) within alginate beads. This was done in order to implant the cells into a patient to help treat type 1 diabetes. Early indication is that this type of

treatment may be a viable treatment option for diabetes patients [92, 93]. From previous studies it was found that the cells need to be protected during and after implantation as well as that more cells need to be put into a single graft to obtain adequate levels of insulin release. By entrapping and protecting the islets in alginate, the cells expressed more insulin and more islets could be implanted. Furthermore, cross-linking (e.g. emulsion gelation) of alginate is already in use in other areas of pharmaceutical product development and has been investigated for cell entrapment. This process was found to be more effective as well as making larger scale production possible [94]. By increasing the amount of alginate used to entrap ĀTC3 cells, the need for immunosuppression was decreased further, as well as increasing the viability and longevity of the entrapped cells [95].

CONCLUSION

The emergence of biotechnology produced drugs highlights the need for more modern drug delivery systems as conventional delivery systems have limited applicability in the delivery of these type of active ingredients. The use of modern drug delivery systems requires the inclusion of functional excipients. Functional excipients are included to fulfil specialised functions and impart specialised properties or characteristics to a delivery system. Examples of specialised functions or properties include gastro-retentive properties, modified release behaviour, targeted release, mucoadhesive properties and stimuli-responsive behaviour. Plant derived polymers and their derivatives are actively researched for their use as functional excipients in pharmaceutical dosage forms due to their renewable supply, favourable toxicity profile, biocompatibility and biodegradable nature. Plant derived polymers and their derivatives have the potential to improve dosage form performance and decrease production cost and are therefore an attractive and promising area of research.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENT

Declared none.

REFERENCES

[1] Mohanty AK, Misra M, Drzal LT. Sustainable bio-composites from renewable resources: Opportunities and challenges in the green materials world. J Polym Environ 2002; 10: 19-26.

[2] Sonia TA, Sharma CP. An overview of natural polymers for oral insulin delivery. Drug Discov Today 2012; 17: 784-92.

[3] Shanmugam S, Manavalan R, Venkappayya D, *et al.* Natural polymers and their applications. Nat Prod Radiance 2005; 4: 478-81.

[4] Rana V, Rai P, Tiwary AK, Singh RS, Kennedy JF, Knill CJ. Modified gums: Approaches and applications in drug delivery. Carbohyd Polym 2011; 83: 1031-47.

[5] Gandini A. Polymers from renewable resources: A challenge for the future of macromolecular materials. Macromol 2008; 41: 9491-504.

[6] Malafaya PD, Silva GA, Reis RL. Natural-origin polymers as carriers and scaffolds of biomolecules and cell delivery in tissue engineering applications. Adv Drug Deliv Rev 2007; 59: 207-33.

[7] Cummings JH, Stephen AM. Carbohydrate terminology and classification. Eur J Clin Nutr 2007; 61: 5-18.

[8] Balunas MJ, Kinghorn AD. Drug discovery from medicinal plants. Life Sci. 2005; 78: 431-41.

[9] Kreer M, Swami G, Kumar R, *et al.* Applications of novel excipients in the allophatic and herbal formulations. J Chem Pharml Res. 2010; 2: 851-60.

[10] Prajapati VD, Jani KJ, Moradiya NG, Randeria NP. Pharmaceutical applications of various natural gums, mucilages and their modified forms. Carbohyd Polym 2013; 92: 1685-99.

[11] Yuan J. Excipient selection: Some factors to consider. Innovations in Pharmaceutical Technology 2006; 74-6

[12] Murty R.Changes in pharmaceutical formulations and drug delivery systems. Pharm Tech 2007; 31: 60.

[13] Bajpai AK, Shukla SK, Bhanu S, Kankane S. Responsive polymers in controlled drug delivery. Prog Poly Sci 2008; 33: 1088-118.

[14] Rowe RC, Shesky PJ, Quinn ME, editors. Handbook of Pharmaceutical Excipients. 6th ed. London: Pharmaceutical Press; 2009.

[15] Maderuelo C, Zarzuelo A, Lanao JM. Critical factors in the release of drugs from sustained release hydrophilic matrices. J Control Release 2011; 154: 2-19.

[16] Alderborn G. Tablets and compaction. In Aulton's Pharmaceutics; Aulton ME, Ed. 3rd ed. Philadelphia: Churchill Livingstone; 2007. pp 441-82.

[17] Xiao Y, Xu W, Zhu Q, *et al.* Preparation and characterization of a novel pachyman-based pharmaceutical aid. II: A pH-sensitive, biodegradable and biocompatible hydrogel for controlled release of protein drugs. Carbohyd Polym 2009; 77: 612-20.

[18] Hu Y, Yang T, Hu X. Novel polysaccharides-based nanoparticle carriers prepared by polyelectrolyte complexation for protein drug delivery. Polym Bull 2012; 68: 1183-99.

[19] Jani GK, Shah DP. Evaluation of mucilage of hibiscus rosasinensis linn as rate controlling matrix for sustained release of diclofenac. Drug Dev Ind Pharm 2008; 34: 807-16.

[20] Miyazaki Y, Yakou S, Takayama K. Study on jelly fig extract as a potential hydrophilic matrix for controlled drug delivery. Int J Pharm 2004; 287: 39-46.

[21] Toti US, Aminabhavi TM. Modified guar gum matrix tablet for controlled release of diltiazem hydrochloride. J Control Release 2004; 95: 567-77.

[22] Munday DL, Cox PJ. Compressed xanthan and karaya gum matrices: hydration, erosion and drug release mechanisms. Int J Pharm 2000; 203: 179-92.

[23] Singh K, Kumar A, Langyan N, Ahuja M. Evaluation of mimosa pudica seed mucilage as sustained-release excipient. AAPS PharmSciTech 2009; 10: p. 1121-7.

[24] Nokhodchi A, Nazemiyeh H, Khodaparast A, Sorkh-Shahan T, Valizadeh H, Ford JL. An *in vitro* evaluation of fenugreek mucilage as a potential excipient for oral controlled-release matrix tablet. Drug Dev Ind Pharm 2008; 34: 323-9.

[25] Jani GK, Shah DP, Jain VC, Patel MJ, Vithalani DA. Evaluating Mucilage from Aloe Barbadensis Miller as a Pharmaceutical Excipient for Sustained-Release Matrix Tablets. PharmTech 2007; 31: 90-8.

[26] Jambwa T, Viljoen A, Hamman J. Matrix forming excipients from natural origin for controlled release matrix type tablets. J Drug Deliv Sci Tech 2011; 21: 433-9.

[27] Dey NS, Majumdar S, Rao MEB. Multiparticulate drug delivery systems for controlled release. Tropical J Pharm Res 2008; 7: 1067-75.

[28] Krishnakumar IM, Ravi A, Kumar D, Kuttan R, Maliakel B. An enhanced bioavailable formulation of curcumin using fenugreek-derived soluble dietary fibre. J Funct Food 2012; 4: 348-57.

[29] Kulkarni GT, Gowthamarajan K, Dhobe RR, Yohanan F, Suresh B. Development of controlled release spheroids using natural polysaccharide as release modifier. Drug Deliv 2005; 12: 201-6.

[30] Nesamony J, Singh PR, Nada SE, Shah ZA, Kolling WM. Calcium alginate nanoparticles synthesized through a novel interfacial crosslinking method as a potential protein drug delivery system. J Pharm Sci 2012; 101: 2177-84.

[31] Akhgari A, Abbspour MR, Pirmoradi S. Preperation and evaluation of pellets using acacia and tragacanth by extrusion-spheronization. DARU J Pharm Sci 2011; 19: 417-23.

[32] Zahoor A, Sharma S, Khuller GK. Inhalable alginate nanoparticles as antitubercular drug carriers. Int J Antimicrob Ag 2005; 36: 298-303.

[33] Hoare TR, Kohane DS. Hydrogels in drug delivery: Progress and challenges. Polymer 2008; 49: 1993-2007.
[34] Itoh K, Hatakeyama T, Shimoyama T, Miyazaki S, D'Emanuele A, Attwood D. In situ gelling formulation based on methylcellulose/pectin system for oral-sustained drug delivery to dysphagic patients. Drug Dev Ind Pharm 2011; 37: 790-7.
[35] Wei X, Sun N, Wu B, Yin C, Wu W. Sigmoidal release of indomethacin from pectin matrix tablets: Effect of in situ crosslinking by calcium cations. Int J Pharm 2006; 318: 132-8.
[36] Juby KA, Dwivedi C, Kumar M, Kota S, Misra HS, Bajaj PJ. Silvernanoparticles-loaded PVA/gum acacia hydrogel: Synthesis, characterization and antibacterial study. Carbohyd Polym 2012; 89: 906-13.
[37] Wei H, Qing D, De-Ying C, Bai X, Li-Fang F. Study on colon-specific pectin/ethylcellulose film-coated 5-fluoroucil pellets in rats. Int J Pharm 2008; 348: 35-45.
[38] Smrdel P, Cerne M, Bogataj M, Urleb U, Mrhar A. Enhanced therapeutic effect of LK-423 in treating experimentally induced colitis in rats when administered in colon delivery microcapsules. J Microencapsul 2010; 27: 572-82.
[39] Basit AW. Advances in Colonic Drug Delivery. Drugs 2006; 65: 1991-2007.
[40] Pinto JF. Site-specific drug delivery systems within the gastrointestinal tract: From the mouth to the colon. Int J Pharm 2010; 395: 44-52.
[41] Sinha VR, Kumria R. Microbially triggered drug delivery to the colon. Eur J Pharm Sci 2003 January; 18: 3-18.
[42] Ravi V, Siddaramaiah SR, Pramod Kumar TM. Influence of natural polymer coating on novel colon targeting drug delivery system. J Mater Sci: Mater Med 2008; 19: 2131-6.
[43] Van den Mooter G, Vervoort L, Kinget R. Characterization of methacrylated inulin hydrogels designed for colon targeting: *In vitro* release of BSA. Pharm Res 2003; 20: 303-7.
[44] Jain A, Gupta Y, Jain SK. Potential of calcium pectinate beads for target specific drug release to colon. J Drug Target 2007; 15: 285-94.
[45] Krishnaiah YSR, Indira Muzib Y, Srinivasa Rao G, Bhaskar P, Satyanarayana V. Design and *in vitro* evaluation of oral colon targeted drug delivery systems for tinidazole. J Drug Target 2002; 10: 579-84.
[46] Krishnaiah YSR, Muzib YI, Bhaskar P, Satyanarayana V, Latha K. Pharmacokinetic Evaluation of Gaur Gum-Based Colon-Targeted Drug Delivery Systems of Tinidazole in Healthy Human Volunteers. Drug Deliv 2003; 10: 263-8.
[47] Alonso-Sande M, Teijeiro-Osorio D, Remuñán-López C, Alonso MJ. Glucomannan, a promising polysaccharide for biopharmaceutical purposes. Eur J Pharm Biopharma 2009; 72: 453-62.
[48] Petrak K. Essential properties of drug-targeting delivery systems. Drug Discov Today 2005; 10: 1667-73.
[49] Petit DK, Gombotz WR. The development of site specific drug delivery systems for protein and peptide biopharmaceuticals. Trends Biotechnol 1998; 16: 343-9.
[50] Sarmah JK, Mahanta R, Bhattacharjee SK, Mahanta R, Biswas A. Controlled release of tamoxifen citrate encapsulated in cross-linked guar gum. Inter J Biol Macromol 2011; 49: 390-6.
[51] You JO, Peng CA. Calcium-alginate nanoparticles formed by reverse microemultion as gene carriers. Macromol Symp 2005; 219: 147-53.
[52] Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. Expert Opi Drug Del 2006; 3: 217-33.
[53] Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. J Control Release 2006; 111: 1-18.
[54] Vijayakumar A, Senthilnathan B, Ravichandiran V. A review article on different types of floating drug delivery systems. Int J Pharm Pharm Sci 2012; 4: 45-50.
[55] Hindustan AA, Sreeramulu J, Narasimha RD, Guru PP, Ramyasree P. Fabrication and *in vitro* evaluation of high density gastro retentive microspheres of famotidine with synthetic and natural polymers. Indian J Pharm Educ 2012; 46: 45-51.
[56] Samyuktha Rani B, Vedha Hari BN, Brahma Reddy A, Punitha S, Devi P, Rajamanickam V. The recent developments on gastric floating drug delivery systems: An overview. Int J Pharm Technol Res 2010; 2: 524-534.
[57] Narang N. An updated review on: Floating drug delivery systems (FDDS). Int J Appl Pharm 2011; 3: 1-7.
[58] Malakar J, Nayak AK, Pal D. Development of cloxacillin loaded multiple-unit alginate -based floating system by emulsion-gelation method. Int J Biol Macromol 2012; 50: 138-47.
[59] Badve SS, Sher P, Korde A, Pawar AP. Development of hollow/porous calcium pectinate beads for floating-pulsatile drug delivery. Eur J Pharm Biopharma 2007; 65: 85-93.
[60] Paula HCB, de Oliveira EF, Abreu FOMS, de Paula RCM. Alginate /cashew gum floating bead as matrix for larvicide release. Mater Sci Eng C 2012; 32: 1421-7.
[61] Ji Y, Deng Y. *In vitro* evaluation of Konjac glucomannan as novel excipients for floating systems. J Control Release 2011; 152: Doi:10.1016/j.jconrel.2011.08.106. 34-36.
[62] Okunlola A, Odeku OA, Patel RP. Formulation optimization of floating microbeads containing modified chinese yam starch using factoral design. J Excipients and Food Chem 2012; 3: 17-25.
[63] Rajamma AJ, Yogesha HN, Sateesha SB. Natural gums as sustained release carriers: Development of gastroretentive drug delivery system of ziprasidone HCl. DARU J Pharm Sci 2012; 20: Doi:10.1186/2008-2231-20-58.
[64] Liu A, Lu W, Qian L, Zhang X, Zeng P, Pan J. *in vitro* and *in vivo* studies on mucoadhesive microspheres of amoxicillin. J Control Release 2005; 102: 135-44.
[65] Muthukumaran M, Dachinamoorthi D, Chandra Sekhar KB, Sririam N. A review on polymers used in mucoadhesive drug delivery system. Int J Pharm Ind Res 2011; 01: 122-7.
[66] Chowdary KPR, Madhavi BLR. Preparation and evaluation of HPMC-alginate mucoadhesive microcapsules of aceclofenac for controlled release. IJPRD 2012; 3: 72-8.
[67] Ameye D, Voorspoels J, Foreman P, *et al.* Ex vivo bioadhesion and *in vivo* testosterone: bioavailibility study of different bioadhesive formulations based on starch-g-poly(acrylic acid) copolymers and starch/poly(acrylic acid) mixtures. J Control Release 2002; 79: 173-82.
[68] Voorspoels J, Remon JP, Eechaute W, De Sy W. Buccal absorption of testosterone and its esters using a bioadhesive tablet in dogs. Pharma Res 1996; 13: 1228-32.
[69] Alagusundaram M, Madhusudhana Chetty C, Dhachinamoorthi D. Development and evaluation of novel-trans-buccoadhesive films of famotidine. J Adv Pharm Tech Res 2011; 2: 17-23.
[70] Sharma S, Jain S, Tiwary AK, Kaur G. Once daily bioadhesive vaginal clotrimazole tablets: Design and evaluation. Acta Pharmaceutica 2006; 56: 337-45.
[71] Hamman JH, Enslin GM, Kotze AF. Oral delivery of peptide drugs. Biodrugs 2005; 19: 165-77.
[72] Dimitrov I, Trzebicka B, Muller AHE, Dworak A, Tsvetanov CB. Thermosensitive water-soluble copolymers with doubly responsive reversible interacting entities. Prog Polym Sci 2007; 32: 1275-343.
[73] Recillas M, Silva LL, Peniche C, *et al.* Thermo and pH responsive polyelectrolyte complex membranes from chitosan-g-N-isopropylacrylamine and pectin. Carbohyd Polym 2011; 86: 1336-43.
[74] Fleige E, Quadir MA, Haag R. Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds and applications. Adv Drug Deliver Rev 2012; 64: 866-84.
[75] Piyakulawat P, Praphairaksit N, Chantarasiri N, Muangsin N. Preperation and evaluation of chitosan, carrageenan beads for controlled release of sodium diclofenac. AAPS PharmSciTech 2007; 8: 1-11.
[76] Assaf SM, Abul-Haija YM, Fares MM. Versatile pectin grafted poly (N-isopropylacrylamide); Modulated target release. J Macromol Sci A 2011; 48: 493-502.
[77] Abd El-Ghaffar MA, Hashem MS, El-awady MK, Rabie AM. pH-sensitive sodium alginate hydrogels for riboflavin controlled release. Carbohyd Polym 2012; 89: 667-75.
[78] Klouda L, Mikos AG. Thermoresponsive hydrogels in biomedical applications. Eur J Pharm Biopharm 2008; 68: 34-45.
[79] Yoshida R, Okuyama Y, Sakai T, Sakurai Y. Sigmoidal swelling profiles for temperature-responsive poly (N-isopropylacrylamide-co-butyl methacrylate) hydrogels. J Membrane Sci 1994; 89: 267-77.
[80] Oddo L, Masci G, Di Meo C, *et al.* Novel thermosensitive calcium alginate microspheres: Physico-chemical characterisation and delivery properties. Acta Biomater 2010; 6: 3657-64.
[81] Cheaburu CN, Ciocoiu O, Staikos G, Vasile C. Thermoresponsive sodium alginate-g-poly(N-isopropylacrylamide) copolymers III:

Solution properties. J Appl Poly Sci 2012; Doi: 10.1002/app.37789: 1-9.

[82] Uraki Y, Imura T, Kishimoto T, Ubukata M. Body temperature-responsive gels derived from hydroxypropylcellulose bearing lignin. Carbohyd Polym 2004; 58: 123-30.

[83] Karewicz A, Zasada K, SzczubiaÅka K, Zapotoczny S, Lach R, Nowakowska M. "Smart"-alginate-hydroxypropylcellulose microbeads for controlled release of heparin. Int J Pharm 2010; 385: 163-9.

[84] Dutta RK, Sahu S. Development of a novel probe sonication assisted enhanced loading of 5-FU in SPION encapsulated pectin nanocarriers for magnetic targeted drug delivery system. Eur J Pharm Biopharma 2012; 82: 58-65.

[85] Dutta RK, Sahu S. Development of oxalipatin encapsulated in magnetic nanocarriers of pectin as potential targeted drug delivery for cancer therapy. Results in Pharma Science 2012; 2: 38-45.

[86] Finotelli PV, Da Silva D, Sola-Penna M, *et al.* Microcapsules of alginate/chitosan containing magnetic nanoparticles for controlled release of insulin. Colloid Surface B 2010; 81: 206-11.

[87] Ying X, Qi L, Li X, Zhang W, Cheng G. Stimuli-responsive recognition of BSA-imprinted poly vinyl acetate grafted calcium alginate core-shell hydrogel microspheres. J Appl Poly Sci 2012; Doi: 10.1002/app.37730: 1-12.

[88] Jain AK, Jain CP. Naturally occuring biodegradeable polymers for controlled release of ciprofloxacin for treatment of inflammatory bowel disease. Asian J Pharm Clin Res 2011; 4: 16-22.

[89] Dimantov A, Kesselman E, Shimoni E. Surface characterisation and dissolution properties of high amylose corn-starch-pectin coatings. Food Hydrocolloid 2004; 18: 29-37.

[90] Gregoriadis G. Engineering liposomes for drug delivery: progress and problems. Trends Biotechnol 1995; 13: 527-37.

[91] Nguyen S, Alund SJ, Hiorth M, Kjøniksen A, Smistad G. Studies on pectin coatings of liposomes for drug delivery. Colloid Surface B 2011; 88: 664-73.

[92] Hirshberg B. Lessons learned from the international trial of the Edmontol protocol for islet transplantation. Curr Diabetes Rep 2007; 7: 301-3.

[93] Kaddis JS, Danobeitia JS, Niland JC, Stiller T, Fernandez LA. Multicenter analysis of novel and established variables associated with succesful human islet isolation outcomes. Am J Transplant 2010; 10: 646-56.

[94] Hoesli AC, Raghuram K, Kiang RLJ, *et al.* Pancreatic cell imobilization in alginate beads produced by emulsion and internal gelation. Biotechnol Bioeng 2010; 108: 424-34.

[95] Hoesli CA, Kiang RLJ, Mocinecova D, *et al.* Reversal of diabetes by ÄTC3 cells encapsulated in alginate beads generated by emulsion and internal gelation. J Biomed Mater Res B 2012; 100: 1017-28.

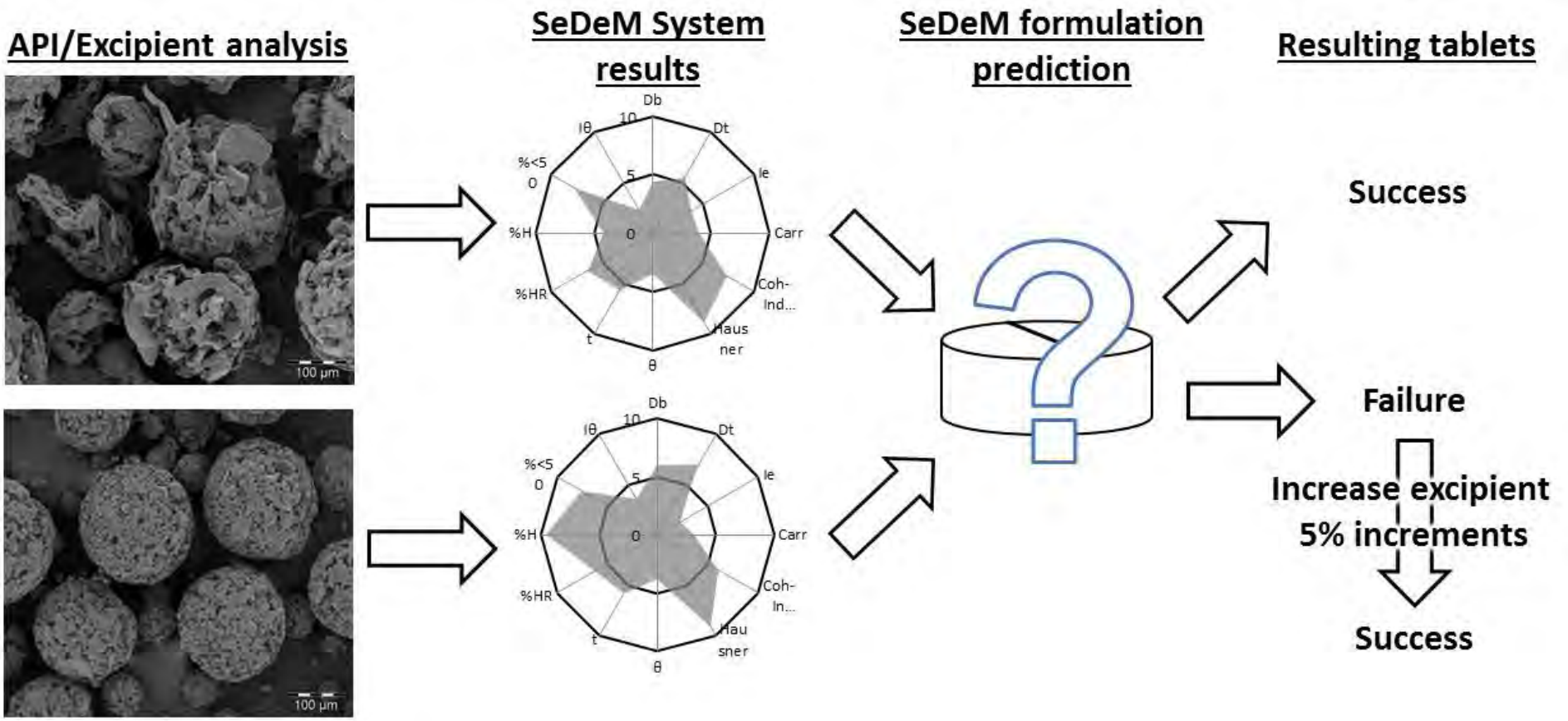
Received: September 28, 2012 **Revised: May 14, 2013** **Accepted: June 17, 2013**

Chapter 3

Research article

This chapter is presented in the form of a research article that was published in the journal titled “Powder Technology” in 2017 (Issue 312 p. 222-236). The complete guidelines for authors is presented in Appendix M. These guidelines state that a submitted manuscript be written in the format of the supplied Microsoft Word template file (i.e. 11 pt Arial font).

Graphical abstract:



Powder Technology 312 (2017) 222–236

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

The SeDeM Expert Diagram System: Its performance and predictability in direct compressible formulations containing novel excipients and different types of active ingredients

Jacques C. Scholtz, Jan H. Steenekamp *, Josias H. Hamman, Louwrens R. Tiedt

North-West University, Centre of Excellence for Pharmaceutical Sciences, Private Bag X6001, Potchefstroom, 2520, South Africa

ARTICLE INFO

Article history:
Received 30 August 2016
Received in revised form 4 February 2017
Accepted 11 February 2017
Available online 21 February 2017

Keywords:
Direct compression
Pre-formulation
SeDeM Diagram Expert System
Formulation prediction
Excipients

ABSTRACT

The SeDeM Expert Diagram System is a galenic pre-formulation system, which evaluates the suitability of excipients and active pharmaceutical ingredients (API's) for direct compression into tablets as well as predicting possible formulations (i.e. ratios of API:excipient) to obtain acceptable direct compressible tablets. In this study, the prediction ability of the SeDeM Expert Diagram System with a special focus on testing the limits of the system was investigated. Three different active pharmaceutical ingredients (API's) in combination with a mix of classic and novel excipients which are currently in use in the wider pharmaceutical community were utilized. The API's and seven excipients were selected based on their physicochemical properties in order to determine the system's ability to predict ratios of API:excipient for acceptable direct compression tablets (e.g. acceptable weight variation as well as sufficient strength to withstand handling). Predicted formulations were tableted and evaluated according to the set criteria. If a tablet formulation failed to meet the criteria, the ratio of excipient to API was increased in 5% increments until a successful formulation was obtained, while the reverse was applied if a formulation was successful. The SeDeM Expert Diagram System proved to be proficient at predicting acceptable tablet formulations, with a few exceptions. The SeDeM system gave successful predictions for only two excipients (FlowLac® 100 and StarLac®) in the case of paracetamol as API. Contrary to predictions by SeDeM for paracetamol, drug loads between 15 and 30% were prepared depending on the excipient. This may be attributed to the ability of the novel excipients to compensate for the elastic properties of paracetamol. With regard to furosemide, none of the predicted formulations rendered acceptable tablets. This could be attributed to the cohesive properties of furosemide forming interactive mixtures with the excipient particles being coated by the relatively small furosemide particles (86.77% < 50 μm) imparting poor flow to the powder particles. In the case of pyridoxine, most of the formulations were predicted acceptable. This work indicates that in cases where the predicted formulation proved to be unsuccessful, by following an increment wise step-up in excipient:API ratio as formulation approach, it is possible to identify an acceptable formulation saving valuable time spent on formulation by a trial and error approach.

1. Introduction

Tablets are popular dosage forms for the administration of active pharmaceutical ingredients (API's), because of relatively low production costs, excellent patient compliance and simplicity of production. Different manufacturing techniques such as wet-granulation, dry-granulation and direct compression of dry powders can be used for tablet manufacturing. Wet granulation remains the most employed technique in spite of it being more time-consuming and therefore more expensive. However, direct compression has recently become popular because it offers the advantage of requiring a smaller number of production steps which is more cost-efficient. Furthermore, direct compression can be applied to thermo-sensitive and moisture-sensitive API's and often produces tablets with faster dissolution times because primary drug particles are released when disintegration takes place [1].

Unfortunately, direct compression as tablet production technique has some disadvantages. The excipients that are used for direct compression have to be able to compensate for poor flow and compression properties, which are often inherent to API's. These challenges often limit the amount of active ingredient to 30% of the tablet formulation [2]. Other problems associated with direct compression include the

Abbreviations: % < 50, Particle size; %H, Hygroscopicity; %HR, Loss on drying; API, Active pharmaceutical ingredient; Carr, Carr's index; Coh, Cohesion index; Da, Bulk density; Dc, Tapped density; Haus, Hausner ratio; Ie, Inter-particle porosity; Iθ, Homogeneity index; t, Powder flow; θ, Angle of repose; MCC, Microcrystalline cellulose; PI, Parameter index; PPI, Parameter profile index; GCI, Good compressibility index; f, Reliability factor; ESEM, Environmental scanning electron microscope; σ_x, Tensile strength; USP, United States Pharmacopoeia.

* Corresponding author.
E-mail address: jan.steenekamp@nwu.ac.za (J.H. Steenekamp).

http://dx.doi.org/10.1016/j.powtec.2017.02.019
0032-5910/

time and cost of experimenting and testing excipient and API combinations. A new system was therefore needed to help decrease both the number of experiments required as well as the time required to render an optimised direct compression tablet formulation. The SeDeM Diagram Expert System was developed to address this need. This system indicates which of the powder properties need to be adjusted in order to facilitate the successful formulation and manufacturing of tablets by direct compression [3–7].

By applying powder assessment techniques which are widely used and accepted within the pharmaceutical industry, SeDeM creates a unique profile for each excipient and API. These profiles can then be used to determine and predict appropriate combinations and ratios of excipient to API for direct compression tablets. This system not only points out specific weaknesses inherent to each API or excipient, but can also indicate if variation between batches occurs [3]. The SeDeM method combines quantitative and experimental results from 12 tests or parameters to determine the specific properties of each pharmaceutical powder. The properties or parameters include bulk density (Da), tapped density (Dc), inter-particle porosity (Ie), Carr's index (Carr), cohesion index (Coh), Hausner ratio (Haus), angle of repose (θ), powder flow (t), loss on drying (%HR), hygroscopicity (%H), particle size (% < 50), and homogeneity index (Iθ). The results of these powder tests are then processed using the equations as presented in Table 1.

The results of tests provide parameters which are converted to radius values to create an irregular shaped polygon with maximum radius values of 10. This graphic representation gives a quick and complete graphical representation of the advantages as well as the shortcomings of each different pharmaceutical ingredient. Overlaying different proposed pharmaceutical powders can show shared weaknesses or indicate areas where an excipient can compensate for an API. The basic shape of a twelve sided polygon as used in this study can be seen in Fig. 1.

Besides creating profiles of the different pharmaceutical ingredients, the SeDeM Systems' goal, is to give an indication of whether a specific pharmaceutical ingredient is suitable for direct compression or not, with each radius value of less than five showing an inadequacy in that area. SeDeM also gives an indication of the overall suitability of the main components, i.e. API and fillers for direct-compression. The SeDeM Expert System can theoretically use the obtained data to predict the amount of required excipient to compensate for API inadequacies. Or stated in another way, SeDeM can shorten pre-formulation times, as a starting formulation can be predicted without preparing numerous different concentration and excipient combinations for a given API by just applying the SeDeM methodologies.

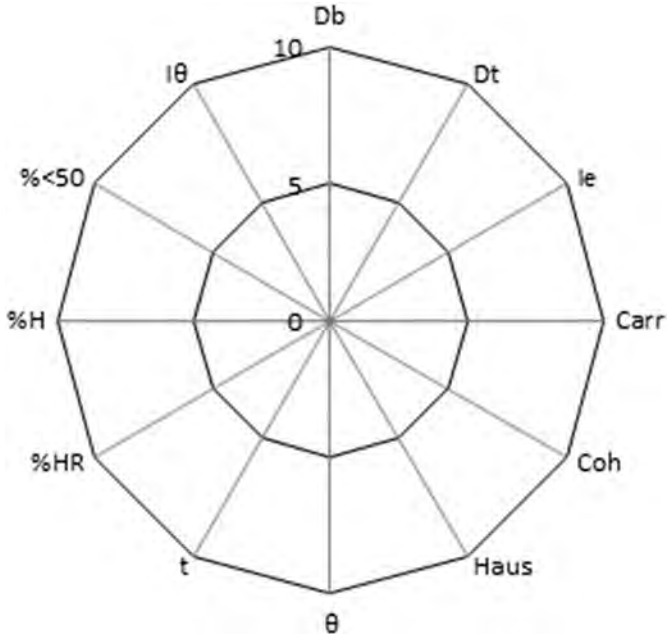


Fig. 1. SeDeM diagram consisting of twelve parameters.

The purpose of this study was to determine if the SeDeM Diagram Expert System is able to identify deficiencies inherent to different pharmaceutical tablet ingredients when applied to a variety of excipients and model API's. The study then continued on to test the ability of the SeDeM Diagram Expert System to predict concentration combinations between API's and excipients, which will deliver an acceptable direct compression tablet formulation. This was done in an effort to identify possible shortcomings and successes of the SeDeM Diagram Expert System. In the event that a formulation did not produce an acceptable tablet, the percentage of API was decreased and the percentage of excipient was increased until an acceptable tablet was compressed. If the SeDeM Expert System predicted an acceptable direct compressible formulation, the percentage API was increased with a corresponding decrease in the percentage of excipients, until the formulation failed to produce acceptable tablets, in order to determine the upper and lower limits of prediction for the SeDeM Expert Diagram System. Furthermore, in the case of unexpected formulation failure an attempt was made to identify a probable cause.

Table 1
Summary of the incidences, parameters and equations used in the SeDeM Diagram Expert System, as well as acceptable ranges of parameter values and equations for converting values into radius values according to the SeDeM Diagram Expert System [3].

Incidence	Parameter	Symbol	Unit	Equation	Acceptable ranges	Equation to convert values to SeDeM radius values
Dimension	Bulk density	Da	g/ml	$Da = m / V_a$	0–1 g/ml	Value × 10
	Tapped density	Dc	g/ml	$Dc = m / V_c$	0–1 g/ml	Value × 10
Compressibility	Inter-particle porosity	Ie	–	$Ie = Dc - Da / Dc \times Da$	0–1.2	(Value × 10) ÷ 1.2
	Carr's index 0–50 (%)	Carr	%	Value ÷ 5		Carr = ((Dc − Da) / Dc) × 100
Cohesion index	Coh	N	Determined by	experiment	0–200 N	Value ÷ 20
Flowability	Hausner ratio	Haus	–	Haus = Dc / Da	3–1	(30 − (10 × Value)) ÷ 2
	Angle of repose	θ	°	Determined by experiment	50–0 (°)	10 − (Value ÷ 5)
	Powder flow	t	*sec*	Determined by experiment	20–0 (s)	10 − (Value ÷ 2)
Lubricity/Stability	Loss on drying	%HR	%	Determined by experiment	20–0 (%)	10 − Value
	Hygroscopicity	%H	%	Determined by experiment	0–50 (%)	10 − (Value ÷ 2)
Lubricity/Dosage	Particles <50 μm	% < 50	%	Determined by experiment	50–0	10 − (Value ÷ 5)
	Homogeneity index	Iθ	–	$I\theta = F_m / (100 + \Delta F^a_{mn})$	$0–2 \times 10^{-2}$	Value × 500

2. Materials and methods

2.1. Materials

The direct compression excipients investigated in this study included: Tablettose® 80, FlowLac® 100, Cellactose® 80, MicroceLac® 100 and StarLac® (Meggle Pharma, Wasserburg, Germany), Avicel® PH200, (FMC Biopolymer, Pennsylvania, USA), and Emcompress®, (JRS Pharma, Rosenberg, Germany). The API's included pyridoxine HCl (Dafeng Hegno Pharmaceuticals, Dafeng, China), paracetamol (Sri Krishna Pharmaceuticals Ltd., Mumbai, India), and furosemide (Adcock Ingram Ltd., Wadeville, South Africa). The furosemide and pyridoxine HCl were purchased. The paracetamol and direct compression excipients were donated.

2.2. Methods

2.2.1. Measurement of SeDeM parameters

The parameters used by the SeDeM Diagram Expert System are predominantly based upon pharmaceutical powder flow characterisation methods (i.e. bulk-and-tapped density determinations, angle of repose, flowability or flow rate, particle size determinations and loss on drying) as described in the United States Pharmacopoeia (USP) and harmonised in the European Pharmacopoeia, with only a few parameters (i.e. inter-particle porosity, cohesion index, hygroscopicity and homogeneity index) that were specifically developed for the SeDeM Diagram Expert System [3,6]. A quick reference of the different parameters, their formulae or equations, and symbols used are given in Table 1. Unless stated otherwise, all determinations were completed in triplicate.

2.2.2. Bulk density (Da)

Bulk density (Da) of the selected excipients and API's were determined according to the method described in the United States Pharmacopoeia [8]. In brief, the method entailed sieving a 100 g sample of powder into a 250 ml graduated cylinder and measuring the volume obtained. Bulk density was calculated with the following formula:

$$Da = m/V_a$$

where:

- m Mass of powder weighed
- V_a Volume of unsettled powder (untapped powder volume)

The average of three determinations with three different powder samples was used.

2.2.3. Tapped density (Dc)

Tapped density (Dc) was determined according to the methods described in the United States Pharmacopoeia [8]. Two powder samples, each with a known weight (approximately 100 g) was poured into graduated 250 ml cylinders and affixed to an Erweka SVM 223 settling apparatus. One sample was tapped for 300 taps (±15 taps) in 1 min from a height of 14 mm (±0.2 mm) according to USP method 1 [8] and the other sample were tapped for 250 taps (±15 taps) in 1 min from a height of 3 mm (±0.2 mm) according to USP method 2 [8]. The samples were left to tap for 1 min increments until the volume decreased by no more than 2% between increments. The average of both methods was used. Tapped density was calculated with the following formula:

$$Dc = m/V_c$$

where:

- m Mass of powder weighed
- V_c Volume of settled powder (tapped powder volume)

2.2.4. Inter-particle porosity (Ie)

Inter-particle porosity is a measure of the porosity or space in between the powder particles. The inter-particle porosity was calculated from the bulk density and tapped density values by using the following equation:

$$Ie = Dc - Da/Dc \times Da$$

2.2.5. Carr's index (Carr)

Carr's index (also known as the compressibility index) is an indirect measure of powder flow. The compressibility as measured by bulk and tapped density differences, is a direct measure of the potential of powder particles to resist flow by interacting with other powder particles. The formula used to determine Carr's index is as follows [8]:

$$Carr = ((Dc - Da)/Dc) \times 100$$

2.2.6. Cohesion index (Coh)

In order to determine the cohesion index, powder was compressed at the maximum compression force on an eccentric tablet press. The maximum pressure is defined as the maximum compression force before capping or breaking of the tablets occurs. If any of the API's cannot be compressed due to powder flow issues or excessive ejection force being required, then a 3.5% *w/w* mixture of the following materials was added [3]:

- Talc, 2.36%;
- Aerosil®, 0.14%; and
- Magnesium stearate, 1%.

2.2.7. Hausner ratio (Haus)

The Hausner ratio, like Carr's index is also an indirect indicator of powder flow. Hausner index is also calculated using tapped and bulk density values. Hausner ratio gives an indication of the resistance of the powder sample to settling because of powder particle interactions. This is defined and explained in the USP [8]. The formula for Hausner ratio is as follows:

$$Hausner = Dc/Da$$

2.2.8. Angle of repose (θ)

The method to determine the angle of repose is described and discussed thoroughly in the United States Pharmacopoeia [9]. In brief, a plugged funnel with an orifice through which the powder can flow freely, was suspended 20 cm above a level table covered with a sheet of paper. An approximate height of the powder cone, using 100 g of powder, was then determined. The height of the funnel was consequently adjusted to ensure that the bottom of the funnel was no closer or further than 5 cm (±1 cm) from the top of the final powder cone. Angle of repose determination was conducted at this determined height. The funnel was filled again with a 100 g sample of powder and the funnel was unplugged, allowing the powder to flow freely from the funnel onto the paper. The height of the powder cone (h) as well as the diameter of the powder cone was measured. The radius (r) was calculated by halving the measured diameter. Angle of repose was calculated using the following formula:

$$\tan\ \theta = h/r$$

2.2.9. Flowability (t)

The methods for powder flow rate determinations are discussed in detail in the United States Pharmacopoeia [9]. To determine the powder flow rate or flowability as SeDeM deems it, a funnel with a 15 mm diameter orifice at the bottom was suspended above a table. The time

required for a 100 g sample of the powder to flow through the 15 mm diameter orifice was recorded in seconds. If the powder sample did not flow freely or did not flow through the 15 mm orifice, the maximum time allowed by the SeDeM System (20 s) was noted [3].

2.2.10. Loss on drying (%HR)

Loss on drying is described in the United States Pharmacopoeia [10]. Briefly, a sample of 1 to 2 g (the precise mass must be known) is placed in a shallow, dried, glass container. The depth of the sample may not exceed 10 mm. Loss on drying for the purposes of the SeDeM System is completed by drying the powder sample at 105 °C (±2 °C) until the weight remains constant. The difference between the starting weight and the weight after drying was determined, followed by determining the percentage of weight loss.

2.2.11. Hygroscopicity (%H)

A sample of the powder, 1 to 2 g (the precise mass must be known) was placed in a shallow, dried, glass container in a climatic chamber for 24 h at a temperature of 22 °C (±2 °C) and a relative humidity of 76% (±2%). The difference between the starting weight and the weight after 24 h was determined, followed by determining the percentage of weight gained [3,6].

2.2.12. Particle size determination

Originally the determination of particle size and size distribution for the SeDeM Diagram Expert System was based on a sieve analysis as described by Perez et al. [3] and Suñé Negre et al. [6], however, powder particle size determination using laser diffraction is an easier, quicker and more accurate method associated with better reproducibility [11]. The particle size of all the materials was determined using a Malvern Mastersizer 2000 instrument fitted with a Hydro 2000SM dispersion unit, using a suitable dispersant in which the sample is insoluble or practically insoluble. The data generated was split into the following different size fractions: the percentage particles between 0 μm and 50 μm, 50 μm to 100 μm, 100 μm to 212 μm, 212 μm to 355 μm and larger than 355 μm. This data was used to determine both the "homogeneity index", as well as the "particle size smaller than 50 μm" parameters.

2.2.13. Particles smaller than 50 μm (% < 50)

This parameter consists only of the percentage particles within the 0 μm and 50 μm fraction, as was determined by means of particle size analysis.

2.2.14. Homogeneity index (Iθ)

The Homogeneity index formula was applied to the data as obtained from the particle size analysis. The SeDeM System defines ranges and this formula determines the relative homogeneity of the particles therein. The equation used for the homogeneity index is:

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

where:

- Iθ Relative homogeneity index.
- F_m The percentage of particles contained in the range with the largest amount of particles
- F_{m-1} The percentage of the particles in the range below the largest range
- F_{m+1} The percentage of the particles in the range above the largest range
- n Order number in a series, in respect to its position to the range with the largest amount of particles
- d_m The mean diameter of the particles in the fraction with the largest amount of particles
- d_{m-1} The mean diameter of the particles in the fraction below the fraction with the largest amount of particles
- d_{m+1} The mean diameter of the particles in the fraction above the fraction with the largest amount of particles

2.2.15. Calculating radius values for polygons

Upon the calculation/determination of the parameter values, the values are then further processed with the equations listed in Table 1 to obtain parameter values between 0 and 10, which are used as the radii of 12 sided polygons which describe the advantages or shortcomings of each component [5,6]. Radius values >5 for each of the tested parameters are deemed acceptable, while values >8 are considered to be ideal. The parameters are then combined into 5 groups or incidences. These incidences are grouped as follows:

- Dimension consists of bulk and tapped density.
- Compressibility is comprised of inter-particle porosity, Carr's index, as well as the cohesion index.
- Flowability is a combination of Hausner ratio, angle of repose as well as powder flow.
- Lubricity/stability is comprised of loss-on-drying and hygroscopicity.
- Lubricity/dosage is a combination of particles <50 μm and the homogeneity index.

It is important to note that parameters that exceed maximum values received the maximum score that pertained to that parameter and parameters that did not reach minimum values, received the minimum value as defined in the limits set by the SeDeM System. In cases where this happened, it was noted and explained. This study specifically aimed to test such occurrences (see the results on the prediction ability of the SeDeM Expert Diagram System).

After all the SeDeM parameters have been measured and the radius values were calculated, the 12 sided polygon was created for each powder and incidence values were calculated to determine the suitability of the pharmaceutical ingredient for direct compression.

The acceptability for direct compression can be further determined by calculating the parameter index (PI), the parameter profile index (PPI), the good compressibility index (GCI) as well as the reliability factor (f). The PI was calculated by dividing the number of radii larger or equal to five by the amount of factors tested. PI values >0.5 are considered acceptable. PPI is a value equal to the average value of all the parameters, where a value of >5 is deemed acceptable. The reliability factor (f) was determined by dividing the polygon area by the circle area of the polygon. Using an infinite number of parameters will give an f value of 1, while using 12 factors gives an f value of 0.952 and using just 8 factors brings reliability down to 0.9. Multiplying the f value with the PPI gives the GCI. A GCI value ≥5 is deemed acceptable for direct compression. This study used all 12 factors as described by Suñé-Negre et al. [6].

2.2.16. Calculating API:excipient ratios for tableting formulations

The SeDeM method was then applied to determine the amount of excipient required to compensate for deficiencies of the different API's. For this determination, the parameters were once again grouped into the "incidences" as mentioned before. The equation for calculating the amount of excipient required to compensate for poor API characteristics is as follows:

$$CP = 100 - ((RE - R)/(RE - RP) \times 100)$$

where:

- CP: The percentage of the excipient needed to correct for API deficiency.
- RE: The incidence value of the excipient used to correct for API deficiency.
- R: The value to which the API's deficient incidence value need to change to, as to ensure sufficient compressibility. As stated earlier,

an incidence value of 5 is the minimum acceptable value.
- RP: The value of the incidence of the API that needs to be corrected, in other words the incidence with the lowest value.

With this equation a basic or starting tablet formulation can theoretically be identified, saving time in the search for a new tablet formulation. From this starting point, the formulation can be optimised with regard to other tablet properties such as dissolution and disintegration [6].

2.2.17. Scanning electron microscopy

Powder samples were affixed to SEM pin stubs using double-sided conductive tape and gently tapped to remove any loose powder. The stubs were then sputter coated under vacuum with a gold/palladium mixture (ratio of 80:20). Scanning electron microscope images of each of the API's and the excipient powder particles were captured using an FEI Quanta 200 environmental scanning electron microscope (ESEM) (FEI Company, Netherlands).

2.2.18. Tableting

The values of the incidences were used to determine the amount of excipient required to compensate for the shortcomings of the selected API's as indicated by the CP values. The respective API's and excipients were mixed for 5 min at 47 rpm with a Turbula mixer type T2C (Willy A Bachofen Maschinenfabrik, Basel); thereafter magnesium stearate (0.5% *w*/*w*) was added to the mixtures and mixed for a further 2 min. Magnesium stearate was added as the compression tests as required for the SeDeM Expert System indicated that the ejection force for tablets prepared from most of the excipients and API's was high, highlighting the need for a lubricant to decrease the ejection force and preventing tablet damage upon ejection. Adding low concentrations of magnesium stearate late in mixing and only mixing for a short time decreases ejection force, without considerably improving flow behaviour or interfering with tablet hardness and binding properties [12].

Compression of the tablet formulations (400 mg per tablet) was done on a single station Korsch® XP1 tablet press (Korsch, Germany) set at maximum compression force with a 10 mm diameter punch and die set (Pam Pharmaceutical & Allied Machinery, India) at a speed of 30 tablets per minute. If the density of the powder mixture was too low to reach a tablet weight of 400 mg, the maximum quantity of powder that could be compressed by applying the maximum compression force was used.

2.2.19. Tablet evaluation

Tablets were evaluated by means of the basic physical tests for conventional tablets, which included uniformity of weight, friability and hardness.

2.2.20. Uniformity of weight

Uniformity of weight was done according to the specifications of the European Pharmacopoeia [13].

2.2.21. Friability

Friability of tablets was determined by the methods as described in the United States pharmacopoeia [14].

2.2.22. Tablet hardness

Tablet hardness was tested with an Erweka TBH 425 TD tablet hardness tester. The apparatus was also used to determine the physical dimensions of the tablets. In order to compare the hardness of the different tablet formulations, it is important to take the geometry of the tablets into account. The tensile strength (σ_x) of tablets was therefore calculated from the dimensions and the hardness values [15] by using the following equation:

$$\sigma_x = 2F/\pi DH$$

where:

- σ_x Tensile strength
- F Tablet hardness or breaking force (N)
- D Diameter of the tablet
- H Height of the tablet

2.2.23. Tablet criteria

The tablet formulations as predicted by the SeDeM Expert Diagram System for each of the selected API's and excipients were evaluated in terms of the following criteria to be classified as acceptable in terms of tablets prepared by direct compression:

- The ability of the powder mixture to flow sufficiently to fill the tablet press die consistently as determined by the uniformity of weight test.
- The ability to create a tablet that can withstand physical stress during handling as determined by the friability test.

Tablets prepared from the formulations had to comply with both of these criteria to be considered successful. If a predicted tablet formulation complied with the criteria, the amount of excipient was decreased in 5% increments until the point of failure was reached. If a predicted tablet formulation did not comply with the criteria, the amount of excipient was increased in 5% increments until a successful formulation was obtained (i.e. compliance with the criteria). The increment size was based on the reliability factor, which in this case was based on a 12 parameter SeDeM diagram. Since the reliability factor is equal to 0.952, it means that a 5% deviation from the predicted formulation is negligible, but a 10% deviation starts to show a significant deviation from predicted figures.

In certain cases, e.g. when paracetamol is formulated with Tablettose® 80, Emcompress®, Cellactose® 80 and MicroceLac® 100, the amount of excipient required, according to the predicted value was >100% of the tablet formulation. Therefore, according to the SeDeM Expert Diagram System, the properties of the API is so poor that these excipients are unable to correct it to sufficient levels for direct compression. In those cases, the tablet formulations were started at an excipient concentration of 94.5%, which was decreased at 5% increments until the tablet did not comply with the criteria. If any of the criteria as stated for tablets were not adhered to, the formulation was considered a failure.

3. Results and discussions

3.1. SeDeM diagram radius values

The 12 parameters for the API's and the excipients were processed, to obtain the radius values that were used to create the polygons (or SeDeM diagrams). The radius values for each of the selected API's and excipients (parameter values) are shown in Table 2, while the incidence values as well as the other direct compression analysis factors, such as PI, PPI and CGI are displayed in Table 3. SeDeM diagrams of the different API's, along with some basic information and SEM micrographs are contained in Table 4 with the same information pertaining to the different excipients showcased in Table 5.

3.1.1. Paracetamol (acetaminophen)

The parameter radius results can be seen in Table 2. It should be noted that the percentage of paracetamol particles smaller than 50 μm (i.e. 52.96%) was higher than the maximum value allowed by the SeDeM Diagram Expert System (the limits can be seen in Table 1), and thus resulted in a radius value of zero. The same applied to the powder flow experiment (t), which showed no flow, even when a bigger orifice was used and therefore a radius value of zero was obtained. This

Table 2
SeDeM polygon radius values for the selected active pharmaceutical ingredients and excipients.

SeDeM		API's			Excipients						
Parameter	Symbol	Paracetamol	Furosemide	Pyridoxine	Tablettose® 80	FlowLac® 100	Avicel® PH200	Emcompress®	Cellactose® 80	MicroceLac® 100	StarLac®
Bulk density	Db	4.25	2.39	6.25	5.93	6.06	3.73	8.83	4.37	4.77	5.92
Tapped density	Dt	6.51	4.10	10.00	7.78	6.87	4.64	10.00	5.44	5.70	7.01
Inter-particle Porosity	Ie	6.82	10.00	5.00	3.34	1.63	4.40	1.81	3.78	2.83	2.18
Carr's index	Carr	6.95	8.37	7.50	4.75	2.37	3.94	3.83	3.96	3.24	3.10
Cohesion index	Coh	0.81	0.00	1.60	7.36	8.77	10.00	6.50	7.39	7.88	6.08
Hausner ratio	Haus	7.33	6.40	7.00	8.44	9.33	8.77	8.82	8.77	9.03	9.08
Angle of repose	θ	1.17	1.88	0.95	3.18	4.09	3.91	3.10	3.44	4.12	3.78
Powder flow	t	0.00	0.00	0.00	6.41	7.39	5.64	8.02	5.62	7.26	5.79
Loss on drying	%HR	9.56	9.84	9.93	9.95	9.45	5.01	7.13	6.44	6.99	6.19
Hygroscopicity	%H	9.99	10.00	9.98	9.98	10.00	10.00	8.47	4.26	9.24	9.65
Particles <50 μm	% < 50	0.00	0.00	0.00	7.23	7.70	8.38	6.64	7.75	7.56	7.59
Homogeneity index	Iθ	5.42	10.00	5.83	1.46	3.63	1.93	2.30	2.25	2.24	3.53

lowered the values of incidences coupled to these two parameters to unacceptable levels for paracetamol. Other parameters with notably low values are the cohesion index and the angle of repose. The cohesion index value of 0.81, can be attributed to plastic deformation, which is often described when paracetamol is involved in tablet compression [16,17]. The angle of repose for paracetamol was 44.1° ± 1.7°, giving the parameter a relatively low and unacceptable SeDeM radius value of 1.17. The low flowability and high angle of repose value may be attributed to the irregular surfaces and shapes of the paracetamol particles as can be seen in the SEM micrographs in Table 4 in addition to the large amount of small particles (i.e. particles <50 μm).

The results of the incidences can be seen in Table 3. The value of the dimension incidence is sufficient for direct compression, as it is above 5 and the lubricity/stability incidence is ideal with a value of 9.77. The values of the compressibility, flowability and lubricity/dosage incidences are all unsatisfactory for direct compression with values of 4.86, 2.84 and 2.71 respectively. The lubricity/dosage incidence was the lowest incidence and was therefore used in the corrective excipient calculations.

An overall view of the suitability of an API and excipient for direct compression is indicated by the values of the PI, PPI and the GCI. Paracetamol exhibited an acceptable PI value of 0.58, but the PPI value of 4.9 and the GCI value of 4.67 were both below a value of 5, which is not ideal for direct compression. These values therefore confirmed that paracetamol is not suited for direct compression. This becomes apparent when the SeDeM Diagram System is used to predict possible formulation combinations (corrective excipient calculations) where SeDeM required >100% of certain formulations to be excipient.

3.1.2. Furosemide

The dimension incidence of furosemide was found to be unacceptable for direct compression (3.25), because of low bulk and tapped density results. The same was found for the flowability incidence, which proved unacceptable for direct compression with a value of 2.65 and was also the incidence used for the corrective excipient calculations. The low value of the flowability incidence can be attributed to a high angle of repose (40.6° ± 3.2°), which led to a SeDeM radius value of 1.88, as well as the powder flow experiment revealing no powder flow through the specified orifice, which resulted in a radius value of zero.

The compressibility incidence for furosemide was acceptable for direct compression (6.12). This was due to a high radius value for Carr's index (8.37) and an inter-particle porosity value exceeding the maximum values of the SeDeM system and as a consequence a radius value of 10 was assigned. The cohesion index experiment delivered no discernible tablets, giving a radius value of zero. The lubricity/stability incidence was ideal for direct compression with a value of 9.92.

In Table 4 the SEM micrograph of the furosemide particles revealed that furosemide consisted of small, sharp needle-like crystals. This was corroborated by the particle size determinations where 86.77% of the furosemide particles were smaller than 50 μm. This exceeded the maximum value allowed by the SeDeM Expert Diagram System by 36.77%, which resulted in a radius value of zero. However, this did not affect the lubricity/dosage incidence as much as expected, as the homogeneity index value of furosemide was above the limits as presented by SeDeM resulting in a radius value of 10. This led to a lubricity/dosage incidence value of 5, which is acceptable for direct compression.

According to the SeDeM Expert Diagram System, furosemide is acceptable as a direct compression API, as the PI (0.5), PPI (5.25) and GCI (5.08) values were all acceptable with respect to the SeDeM System standards.

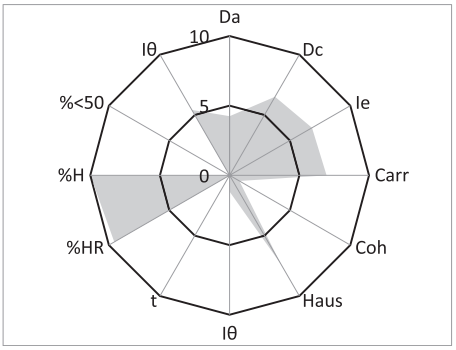
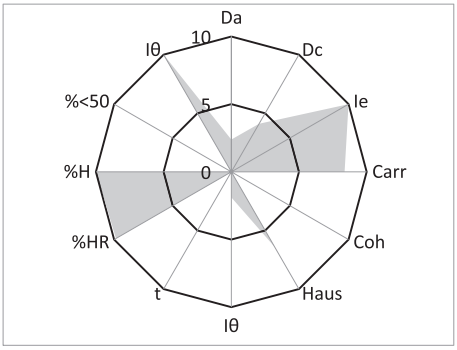
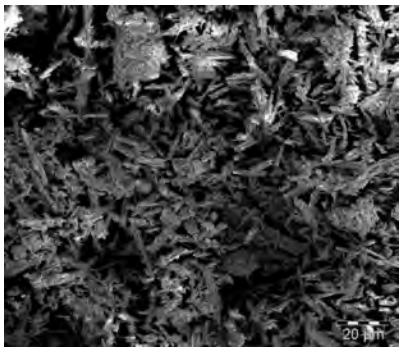
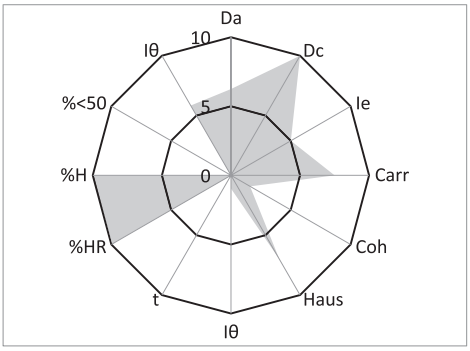
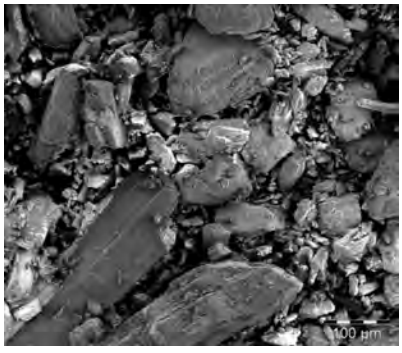
3.1.3. Pyridoxine HCl

Pyridoxine has two parameters, which exceeded the accepted limits of the SeDeM Expert Diagram System, which include the powder flow and particles <50 μm, as can be seen in Table 2. Both these parameters scored a SeDeM radius value of zero. Pyridoxine exhibited no flow, even when a bigger orifice was used and the percentage of particles smaller than 50 μm was 52.95%; the small particles can be seen in the SEM micrograph in Table 4. This lowered both the flowability (2.65) and lubricity/dosage incidences (2.92) under the acceptable value of 5.

Table 3
SeDeM incidence values for the selected API's and excipients.

SeDeM	API's			Excipients						
Incidence	Paracetamol	Furosemide	Pyridoxine	Tablettose® 80	FlowLac® 100	Avicel® PH200	Emcompress®	Cellactose® 80	MicroceLac® 100	StarLac®
Dimension	5.38	3.25	8.12	6.85	6.46	4.19	9.41	4.90	5.24	6.47
Compressibility	4.86	6.12	4.70	5.15	4.25	6.11	4.04	5.04	4.65	3.79
Flowability	2.84	2.76	2.65	6.01	6.93	6.11	6.64	5.94	6.80	6.22
Lubricity/stability	9.77	9.92	9.96	9.97	9.73	7.50	7.80	5.35	8.12	7.92
Lubricity/dosage	2.71	5.00	2.92	4.34	5.67	5.15	4.47	5.00	4.90	5.56
Parameter index (PI)	0.58	0.50	0.67	0.67	0.67	0.50	0.67	0.50	0.58	0.67
Parametric profile index (PPI)	4.90	5.25	5.34	6.32	6.44	5.86	6.29	5.29	5.91	5.83
Good compression index (GCI)	4.67	5.00	5.08	6.01	6.13	5.58	5.98	5.03	5.62	5.55

Table 4
SeDeM diagrams with SEM micrograph of API's.

API (and relevant information)	SeDeM diagram	SEM photomicrograph
Paracetamol • Also known as acetaminophen. • Thermodynamically stable in monoclinic form (the most commercially available form). • Generally thought unsuitable for direct compression because of rigid crystalline structure. • Prone to capping [16,17].		
Furosemide • Low water solubility. • Small average particle size. • Known for poor powder flow properties and therefore issues with die filling when tableting [18].		
Pyridoxine HCl • Highly water soluble. • Reasonable flow attributes [19].		

Another incidence value of pyridoxine, which was deemed unacceptable according to the SeDeM limits, was the compressibility incidence with a value of 4.7, which was due to a low score for the cohesion index parameter of 1.6. As with furosemide, the flowability incidence was the lowest incidence and was used for the corrective excipient calculation experiments; the incidences can be seen in Table 3.

The two remaining incidences, i.e. dimension (8.12) and lubricity/stability (9.92) resulted in acceptable values indicating that the API would be suitable for direct compression.

According to the SeDeM Expert Diagram System, pyridoxine HCl is acceptable as a direct compression API, as the PI value (0.67), PPI (5.34) and GCI (5.08) are all acceptable to the SeDeM System standards.

3.1.4. Tablettose® 80

Tablettose® 80 did not exceed any of the limits described in the SeDeM Expert Diagram System. All the incidences (Table 3) except for one (i.e. lubricity/dosage incidence with a value of 4.34), were deemed acceptable for direct compression. Tablettose® 80 is made by agglomerating alpha-lactose monohydrate particles to form "blackberry" structures [20]; these structures can be clearly seen in the SEM micrographs in Table 5. Some variation in the size of the "blackberry" structures can be seen in the SEM micrographs and this is supported by the homogeneity index. Tablettose® 80 had the lowest homogeneity index (1.46) of all the excipients tested in this study, indicating that Tablettose® 80 exhibited the largest variation in particle size of all the excipients that were tested.

The dimension, compressibility and flowability were considered acceptable for direct compression with values of 6.85, 5.15 and 6.01 respectively and the lubricity/stability incidence was deemed ideal with a value of 9.97.

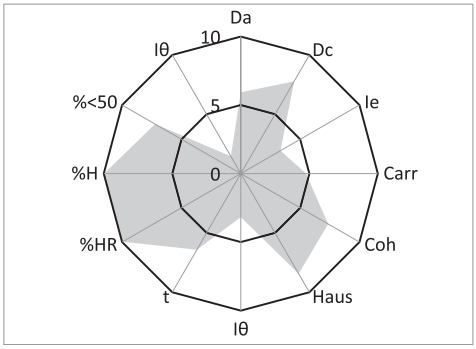
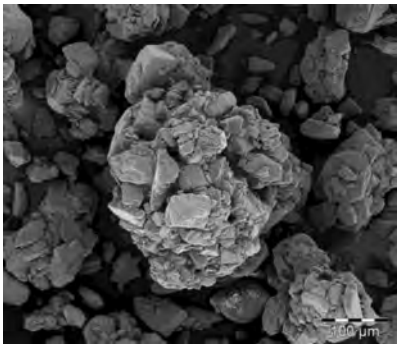
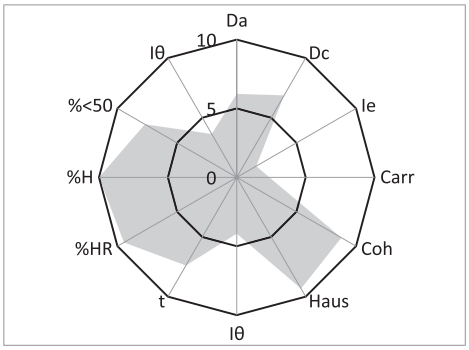
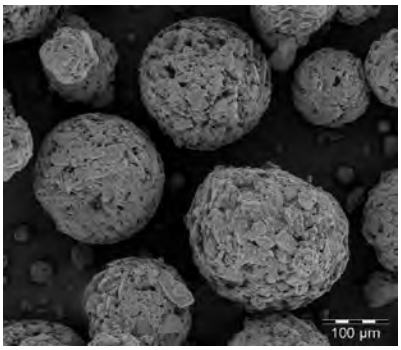
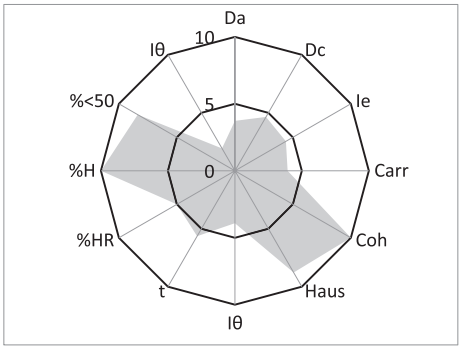
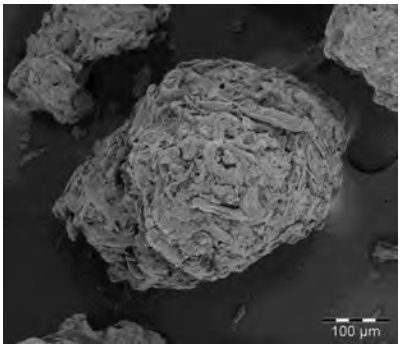
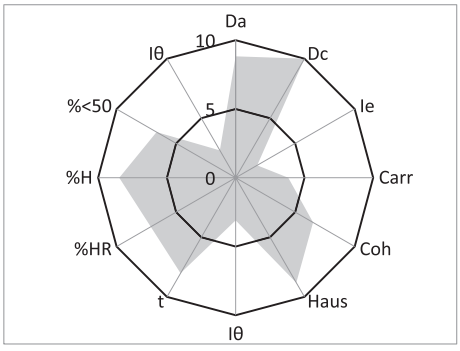
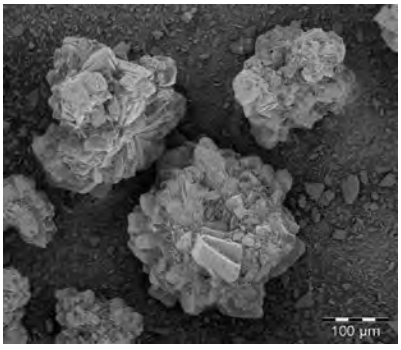
The PI (0.67), PPI (6.32) and GCI (6.01) values identified Tablettose® 80 as an acceptable direct compression excipient.

3.1.5. FlowLac® 100

FlowLac® 100 complied with the criteria for direct compression, except for the compressibility incidence (4.25). This was due to low values for both the inter-particle porosity (1.63) as well as Carr's index (2.37) in spite of an ideal parameter score for compressibility of 8.77.

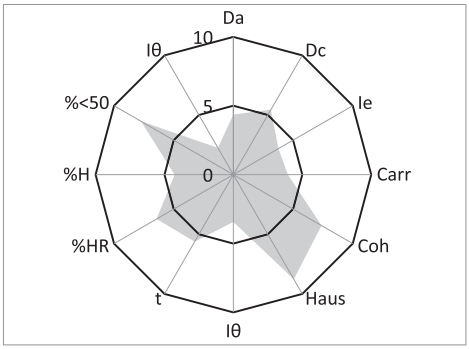
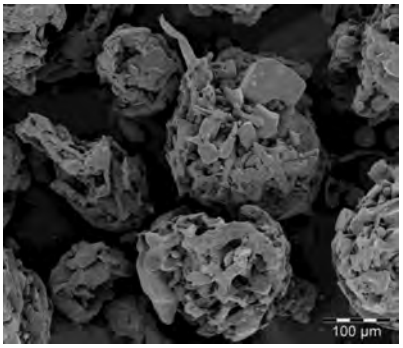
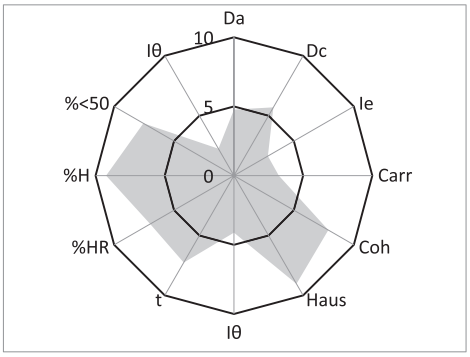
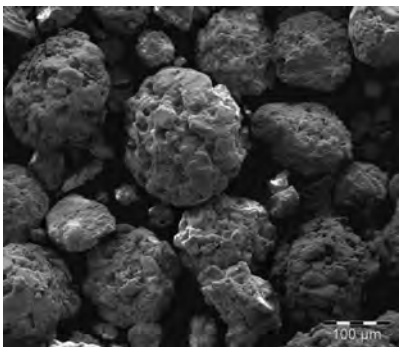
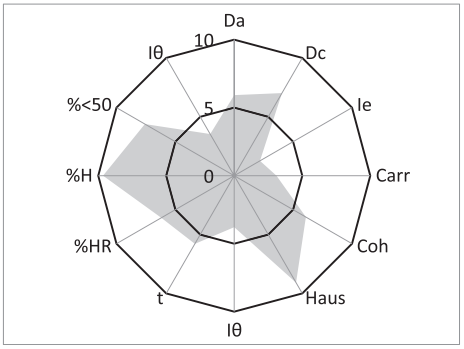
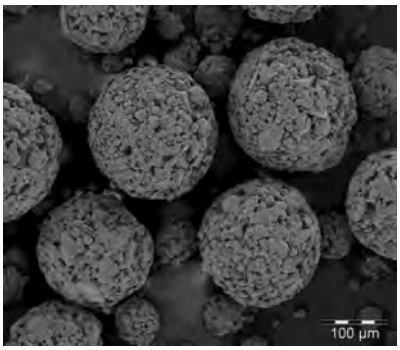
FlowLac® 100 is manufactured by spray drying alpha-lactose monohydrate, which then delivers an amorphous lactose content of

Table 5
SeDeM diagrams with SEM micrograph of excipients.

Excipient (and relevant information)	SeDeM diagram	SEM photomicrograph
Tablettose® 80 • Alpha-lactose monohydrate. • Produced by an agglomeration technique [20]. • Alpha-lactose monohydrate is prone to brittle fracture when compressed [21].		
FlowLac® 100 • Alpha-lactose monohydrate is spray dried to form a combination of amorphous lactose and alpha lactose monohydrate [22]. • Amorphous lactose is prone to plastic deformation during compression [21].		
Avicel® PH200 • Microcrystalline cellulose (MCC). • Low bulk density with high surface area. • High compressibility [23]. • High sensitivity to added lubricants when compacting [24].		
Emcompress® • Calcium hydrogen phosphate dihydrate ($CaHPO_4 \cdot 2H_20$). • Only inorganic excipient used in this study • High density powder with known good flowability. • Brittle fracture binding when compressed. • Low sensitivity to lubricants during compaction [25]. • Incompatible with tetracycline antibiotics and API's sensitive to pH > 7.3 [26].		
Cellactose® 80 • Co-processed excipient: 75% alpha-lactose monohydrate and 25% cellulose powder, spray dried to form a monoparticulate system. • Formulated for high API loads. • Improved adherence capacity, thus easier coating [27].		

(continued on next page)

Table 5 (*continued*)

Excipient (and relevant information)	SeDeM diagram	SEM photomicrograph
MicroceLac® 100 • Co-processed excipient: 75% alpha-lactose monohydrate and 25% MCC, spray dried to form a monoparticulate system. • Formulated for high API loads. • Exhibits both brittle fracture and plastic deformation properties when compressed [28].		
StarLac® • Co processed excipient: 85% alpha-lactose monohydrate and 15% native maize corn starch, spray dried to form a monoparticulate system. • Exhibits both brittle fracture and plastic deformation properties when compressed. • Not as suited to high API loads as other co-processed excipients [29].		
		

between 10 and 15% and forms spherical particles [22]. This spherical nature of the particle structures can be clearly seen in the SEM micrographs in Table 5. This contributed to the relatively good flow properties of this excipient.

The lubricity/stability incidence for FlowLac® was 9.73, with dimension (6.45), flowability (6.93) and lubricity/dosage (5.67) incidences that exhibited acceptable values.

The acceptability of FlowLac® 100 as a direct compression excipient is further supported by the PI of 0.67, PPI of 6.44 and GCI of 6.01.

3.1.6. Avicel® PH200

Avicel® PH200 only had one parameter that was not suited to direct compression, which was the dimension incidence with a value of 4.19 (Table 3). This was due to Avicel® PH200 having a low density. The microcrystalline cellulose (MCC) fibres comprising Avicel® PH200 can be clearly seen in Table 5. The low density inherent to MCC became specifically apparent during the tableting, as it was challenging to obtain tablets with the required weight. Despite this, Avicel® PH200 surpassed the maximum value of the SeDeM System in the cohesion-index parameter experiment, with an average value of 271.8 N ± 13.91 N obtained, giving this parameter a SeDeM radius value of 10, which was also the highest average compressibility value of all tested powders. This resulted in a compressibility incidence with an acceptable value of 6.11.

An interesting parameter to note is the loss on drying, which scored the lowest loss on drying SeDeM score of all the tested powders with a value of 5.01. This indicates that the MCC comprising Avicel® PH200 contained a relatively high amount of moisture with a decrease in weight of 4.99% ± 0.05%. On the other hand, the hygroscopicity parameter value for Avicel® PH200 was 10, because of a very small weight increase of 0.01% ± 0.009%. This resulted in a lubricity incidence value of 7.5.

The rest of the incidences all indicated acceptable values for Avicel® PH200 such as flowability (6.11) and lubricity/dosage (5.15). The same applies to the PI of 0.5, PPI of 5.86 and a CGI of 5.58, which all indicated Avicel® PH200 to be an acceptable excipient for direct compression.

3.1.7. Emcompress®

Emcompress® had the highest value for the dimension incidence of all the excipients that were tested, with a value of 9.41, which is ideal for direct compression. The flowability and lubricity/stability incidences both displayed acceptable values for direct compression; the results

can be seen in Table 3. Despite having an acceptable value for the flowability incidence (6.64), Emcompress® exhibited the lowest value of all the tested excipients for the angle of repose parameter (3.1) which was the result of an angle of repose of 34.5° ± 0.9°. The SEM images (Table 5) revealed that the surface of Emcompress® is irregularly shaped and the particles are jagged, which most probably accounts for the high angle of repose value.

The lubricity/stability incidence was also found to be acceptable for direct compression with a value of 7.8. Unfortunately, the two remaining incidences are unacceptable for direct compression, i.e. compressibility with a value of 4.04 and the lubricity/dosage incidence of 4.47. The overall results as given by the PI value (0.67), PPI (6.29) and GCI (5.98) indicated that Emcompress® is acceptable as a direct compression excipient.

3.1.8. Cellactose® 80

Cellactose® 80 revealed the lowest GCI value (5.03) of the entire range of excipients tested, but Cellactose® 80 had only one incidence parameter that did not comply to acceptable direct compression values with a value of 4.9 for dimension. This excipient is made from a spray-dried mixture of cellulose and lactose [27], with cellulose being known to decrease the density of the particles, however, the resulting particles exhibited acceptable compressibility (5.04), flowability (5.94), lubricity/stability (5.35) and lubricity/dosage (5.0) incidence values.

In Table 5, SEM micrographs of Cellactose® 80 clearly showed long cellulose fibres surrounded by lactose particles. These cellulose fibres could account for the high hygroscopicity of this excipient, in fact, the highest value for hygroscopicity of all the ingredients that were tested with a parameter value of 4.26, which translates to a percentage mass increase of 11.48% ± 6.1%.

Overall, Cellactose® 80 is acceptable for direct compression with values of 0.5 for PI and a PPI of 5.29.

3.1.9. MicroceLac® 100

MicroceLac® 100 has two incidences that are not acceptable for direct compression, i.e. compressibility (4.65) and lubricity/dosage (4.9). The low compressibility value was due to low values attained by the inter-particle porosity and Carr's index parameters, with values of 2.83 and 3.24 respectively. MicroceLac® 100 consists of spray-dried MCC and alpha-lactose monohydrate which are spray dried together [28]. The SEM micrographs showed the mostly spherical structure of the particles due to spray drying (Table 5), however, the MCC fibres are smaller than the cellulose fibres found in Cellactose® 80 and can barely be observed in the particles. The MCC was probably responsible for the overall relatively low density and dimension incidence value (5.23). The low value for the lubricity/dosage incidence is attributed to a low homogeneity index of just 2.24.

The flowability of MicroceLac® 100 was 6.8 and a lubricity/stability incidence value of 8.12 was obtained, which is ideal for direct compression.

Overall, MicroceLac® 100 exhibited a PI (0.58), PPI (5.91) and the GCI (5.62) which identified this excipient as acceptable for direct compression.

3.1.10. StarLac®

StarLac® has only one incidence which was not acceptable for direct compression, namely the compressibility incidence with a value of 3.79. This is the lowest compressibility value of all the different compounds tested in this study. This is due to low parameter values for both Carr's index (3.1) as well as inter-particle porosity (2.18). The compressibility index of StarLac® was also a contributing factor to the low compressibility incidence as StarLac® had the lowest value of any of the tested excipients with a value of 6.08, even though this value is acceptable. The compression index experiments delivered tablets with a hardness of 121.6 N ± 14.95 N.

The remaining incidences all gave acceptable values for direct compression as follows: dimension value of 6.47, flowability value of 6.22, lubricity/stability incidence value of 7.92 and finally lubricity/dosage incidence value of 5.56. StarLac® is a spray-dried combination of lactose and native corn maize starch, which consists of a spherical monoparticulate system [29].

StarLac® is overall classified as an acceptable direct compression excipient with a PI of 0.67, PPI of 5.83 and a GCI of 5.55.

3.2. Tablet formulations predicted by SeDeM Diagram Expert System

When applying the CP equation to calculate the percentage of each selected excipient that was needed to compensate for the deficiencies of each selected API in order to obtain a direct compressible formulation, the lowest incidence for each API was used. As mentioned earlier, paracetamol had lubricity/dosage as the lowest incidence value, while both furosemide and pyridoxine had flowability as the lowest incidence value.

The results obtained from the CP equation calculations for the prediction of the quantities required of the different excipients for each of the selected API's are shown in Table 6.

As explained in the methods, tablets were compressed from formulations containing a relatively large range of excipient concentrations and tested to see if they conformed to the criteria of acceptable physical properties as specified by the Pharmacopoeia.

3.2.1. Paracetamol

The predicted and actual results of paracetamol and excipient combinations can be seen in Table 7. The SeDeM predicted formulations are shaded.

The SeDeM Expert Diagram System predicted that four of the seven excipients investigated in this study would not be able to compensate for paracetamol's insufficient lubricity/dosage incidence (illustrated by predictions requiring >100% excipient). In these cases the tablet formulations were started at an excipient concentration of 94.5%, which was decreased at 5% increments until the tablet did not comply with the criteria. Contrary to the SeDeM System these excipients exceeded the predictions by allowing drug loads of between 15 and 30% in direct compressible tablets. The SeDeM System predicted the percentage of excipient needed for direct compression correctly for two of the excipients, namely FlowLac® 100 and StarLac®.

SeDeM required Tablettose® 80, Emcompress®, Cellactose® 80 and MicroceLac® 100 to be >100% of the tablet formulation in order to be direct compressible, therefore a relatively low drug load of 5% was used as a starting point. Tablettose® 80 reached a paracetamol loading of 15% before the direct compressible tablet formulation failed due to capping. As the amount of paracetamol increased in the formulations a steady decline in the tablet hardness was noted. Emcompress® reached a drug load of 25% before the formulation failed due to capping. Cellactose® 80 and MicroceLac® 100 reached paracetamol loads of 25% and 30% respectively, when failure occurred due to problems with powder flow. The Cellactose® 80 formulation failed due to mass variation,

Table 6
Percentage excipient required for each API as predicted by the SeDeM Expert Diagram System.

Excipient	% Excipient to be included in tablet formulation		
	Paracetamol	Furosemide	Pyridoxine
Tablettose® 80	140.32[a]	68.90	69.93
FlowLac® 100	77.43	53.63	54.84
Avicel® PH200	93.73	66.87	67.94
Emcompress®	130.12[a]	57.67	58.85
Cellactose® 80	100.15[a]	70.43	71.43
MicroceLac® 100	104.50[a]	55.36	56.56
StarLac®	80.34	64.76	65.86

[a] According to the SeDeM prediction, >100% of some excipients was required for paracetamol formulations due to the severity of the deficiency of this API. This refers to exceeding the theoretical amount of the formulation and therefore it can be >100%.

Table 7
Concentration range and results for paracetamol tablets (final tablet weight ± 400 mg per tablet).

Excipient	Excipient concentration (%)	API concentration (%)	Actual dose (mg)	Verdict	Reason for failure
Tablettose® 80	94.50	5.00	20.00	Success	
Tablettose® 80	89.50	10.00	40.00	Success	
Tablettose® 80	84.50	15.00	60.00	Success	
Tablettose® 80	79.50	20.00	80.00	Failure	Friability (capping)
FlowLac® 100	77.43	22.07	88.28	Success	
FlowLac® 100	72.43	27.07	108.28	Failure	Friability (capping)
Avicel® PH200	93.73	5.77	23.08	Success	
Avicel® PH200	88.73	10.77	43.08	Success	
Avicel® PH200	83.73	15.77	63.08	Success	
Avicel® PH200	78.73	20.77	83.08	Success	
Avicel® PH200	73.73	25.77	103.08	Success	
Avicel® PH200	68.73	30.77	123.08	Failure	Friability (capping)
Emcompress®	94.50	5.00	20.00	Success	
Emcompress®	89.50	10.00	40.00	Success	
Emcompress®	84.50	15.00	60.00	Success	
Emcompress®	79.50	20.00	80.00	Success	
Emcompress®	74.50	25.00	100.00	Success	
Emcompress®	69.50	30.00	120.00	Failure	Friability (capping)
Cellactose® 80	94.50	5.00	20.00	Success	
Cellactose® 80	89.50	10.00	40.00	Success	
Cellactose® 80	84.50	15.00	60.00	Success	
Cellactose® 80	79.50	20.00	80.00	Success	
Cellactose® 80	74.50	25.00	100.00	Success	
Cellactose® 80	69.50	30.00	120.00	Failure	Mass variation (flowability)
MicroceLac® 100	94.50	5.00	20.00	Success	
MicroceLac® 100	89.50	10.00	40.00	Success	
MicroceLac® 100	84.50	15.00	60.00	Success	
MicroceLac® 100	79.50	20.00	80.00	Success	
MicroceLac® 100	74.50	25.00	100.00	Success	
MicroceLac® 100	69.50	30.00	120.00	Success	
MicroceLac® 100	64.50	35.00	140.00	Failure	Flowability (poor die filling)
StarLac®	85.34	14.16	56.64	Success	
StarLac®	80.34	19.16	76.64	Success	
StarLac®	75.34	24.16	96.64	Failure	Friability

but no problem with friability was encountered. The MicroceLac® 100 formulation failed due to no filling of the die during the tableting process. In addition, the 30% paracetamol formulation produced relatively soft tablets (51.20 N ± 11.17 N), although the friability of the formulation was 0.56%.

The formulations containing excipients that consisted of cellulose and microcrystalline cellulose were the formulations that reached the highest tensile strength of all the tablet formulations.

Cellactose® 80 and MicroceLac® 100 are both new generation co-processed excipients that exceeded the expectations of the SeDeM Expert Diagram System in overcoming the elastic nature of the paracetamol. The co-processed excipients all exhibited failures in terms of powder flow, but no capping occurred. On the other hand, the conventional, single component excipients all had tablet failures due to capping. StarLac® did not exceed the predictions of the SeDeM Expert Diagram System, but formulation failure was once again due to friability (hardness = 27.8 N ± 5.10 N with friability of 2.70% ± 0.29%), while no sign of capping was present.

3.2.2. Furosemide

The results of tableting experiments of furosemide with different excipients can be seen in Table 8, with the SeDeM predicted formulations indicated by shading.

From Table 8, it is clear that the selected excipients did not perform as predicted by the SeDeM Expert Diagram System for furosemide as API. All of the formulations exhibited insufficient powder flow associated with relatively large mass variation. The failure of the furosemide formulations may be attributed to the particle size and cohesive behaviour of furosemide. Furosemide has very small needle-like particles as clearly visible on the SEM micrograph (Table 4). A total of 86.77% of the furosemide particles were smaller than 50 μm, which led to the particles being extremely static with very poor flow properties.

An interactive mixture is often formed when a powder with very small particles (i.e. furosemide) is mixed with a powder with larger particles (i.e. excipients). The smaller particles tend to form a "coat" on the surface of the larger particles and the entire mixture takes on certain properties of the powder with the smaller particles. To confirm

Table 8
Concentration range and results for furosemide tablets (final tablet weight ± 400 mg per tablet).

Excipient	Excipient concentration (%)	API concentration (%)	Actual dose (mg)	Verdict	Reason for failure
Tablettose® 80	93.90	5.60	22.40	Success	
Tablettose® 80	88.90	10.60	42.40	Failure	Insufficient flow
Tablettose® 80	83.90	15.60	62.40	Failure	Insufficient flow
Tablettose® 80	78.90	20.60	82.40	Failure	Insufficient flow
Tablettose® 80	73.90	25.60	102.40	Failure	Insufficient flow
Tablettose® 80	68.90	30.60	122.40	Failure	Insufficient flow
FlowLac® 100	88.63	10.87	43.48	Success	
FlowLac® 100	83.63	15.87	63.48	Failure	Mass variation
FlowLac® 100	78.63	20.87	83.48	Failure	Insufficient flow
FlowLac® 100	73.63	25.87	103.48	Failure	Insufficient flow
FlowLac® 100	68.63	30.87	123.48	Failure	Insufficient flow
FlowLac® 100	63.63	35.87	143.48	Failure	Insufficient flow
FlowLac® 100	58.63	40.87	163.48	Failure	Insufficient flow
FlowLac® 100	53.63	45.87	183.48	Failure	Insufficient flow
Avicel® PH200	86.87	12.63	50.52	Success	
Avicel® PH200	81.87	17.63	70.52	Failure	Insufficient flow
Avicel® PH200	76.87	22.63	90.52	Failure	Insufficient flow
Avicel® PH200	71.87	27.63	110.52	Failure	Insufficient flow
Avicel® PH200	66.87	32.63	130.52	Failure	Insufficient flow
Emcompress®	92.67	6.83	27.32	Success	
Emcompress®	87.67	11.83	47.32	Failure	Insufficient flow
Emcompress®	82.67	16.83	67.32	Failure	Insufficient flow
Emcompress®	77.67	21.83	87.32	Failure	Insufficient flow
Emcompress®	72.67	26.83	107.32	Failure	Insufficient flow
Emcompress®	67.67	31.83	127.32	Failure	Insufficient flow
Emcompress®	62.67	36.83	147.32	Failure	Insufficient flow
Emcompress®	57.67	41.83	167.32	Failure	Insufficient flow
Cellactose® 80	90.43	9.07	36.28	Success	
Cellactose® 80	85.43	14.07	56.28	Failure	Insufficient flow
Cellactose® 80	80.43	19.07	76.28	Failure	Insufficient flow
Cellactose® 80	75.43	24.07	96.28	Failure	Insufficient flow
Cellactose® 80	70.43	29.07	116.28	Failure	Insufficient flow
MicroceLac® 100	85.36	14.14	56.56	Success	
MicroceLac® 100	80.36	19.14	76.56	Failure	Mass variation
MicroceLac® 100	75.36	24.14	96.56	Failure	Insufficient flow
MicroceLac® 100	70.36	29.14	116.56	Failure	Insufficient flow
MicroceLac® 100	65.36	34.14	136.56	Failure	Insufficient flow
MicroceLac® 100	60.36	39.14	156.56	Failure	Insufficient flow
MicroceLac® 100	55.36	44.14	176.56	Failure	Insufficient flow
StarLac®	94.76	4.74	18.96	Success	
StarLac®	89.76	9.74	38.96	Failure	Insufficient flow
StarLac®	84.76	14.74	58.96	Failure	Insufficient flow
StarLac®	79.76	19.74	78.96	Failure	Insufficient flow
StarLac®	74.76	24.74	98.96	Failure	Insufficient flow
StarLac®	69.76	29.74	118.96	Failure	Insufficient flow
StarLac®	64.76	34.74	138.96	Failure	Insufficient flow

whether this was the case for the furosemide formulations, SEM micrographs were recorded of the unsuccessful powder formulations. The SEM micrographs of mixtures between furosemide and the selected excipients can be seen in Fig. 2. In these micrographs, furosemide's needle-shaped particles can be clearly seen adhering to the surface of larger excipient particles. It is therefore probable that this altered the flow of the powder mixtures to such an extent that the SeDeM Expert Diagram System overestimated the API load in tablets by between 20 and 35% as can be seen in Table 8. Even with relatively low concentrations of furosemide, the flow behaviour of the powder mixtures deteriorated to such an extent that the formulations failed to produce tablets with acceptable properties although the MCC containing excipients (Avicel® PH200 and Microcelac®) were able to accommodate a higher percentage of furosemide in comparison to the other excipients.

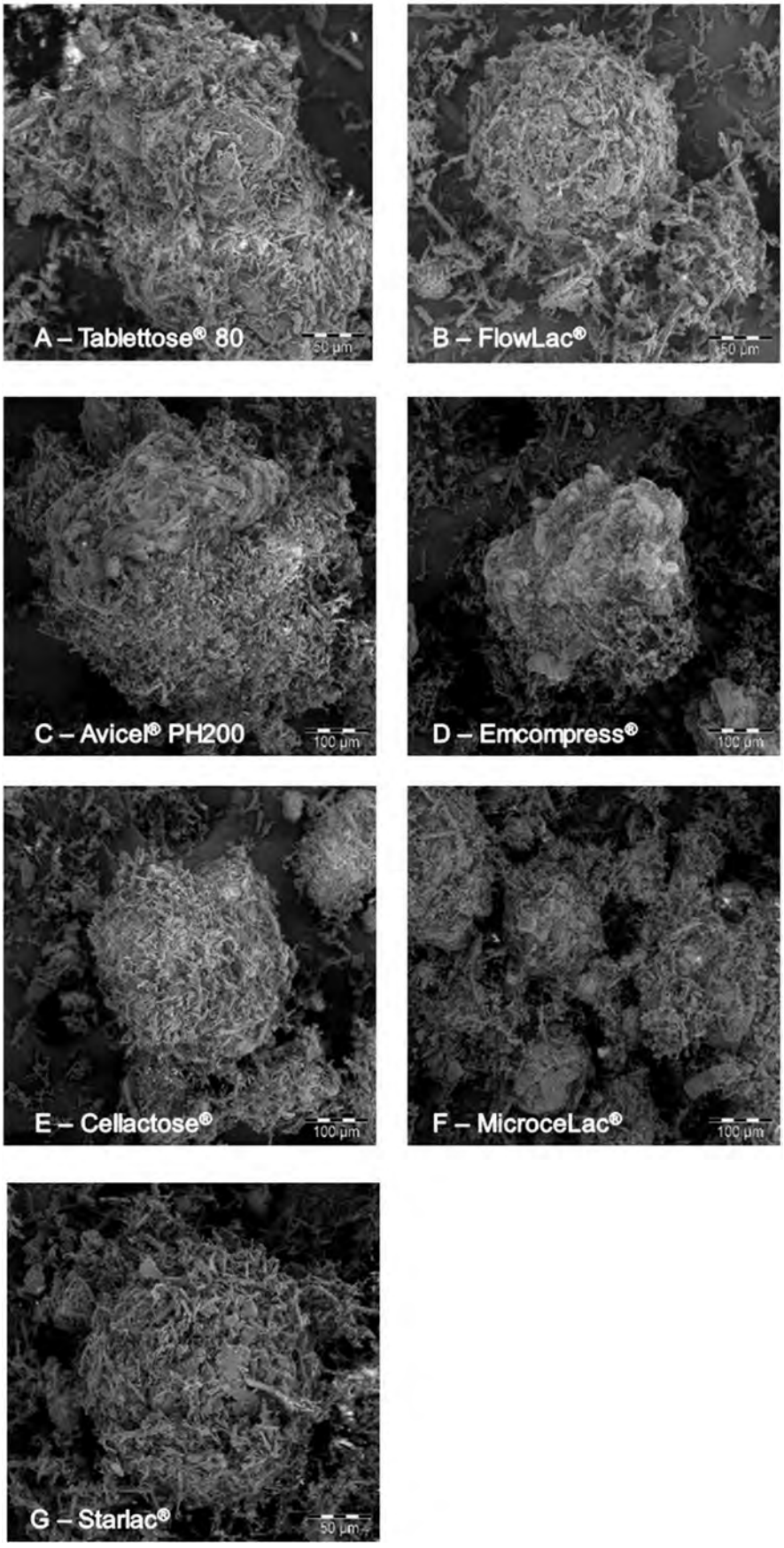


Fig. 2. SEM photomicrographs of powder mixtures of furosemide with (A) Tablettose® 80 (B) FlowLac® 100 (C) Avicel® PH200 (D) Emcompress® (E) Cellactose® 80 (F) MicroceLac® 100 (G) StarLac®.

3.2.3. Pyridoxine hydrochloride

The results obtained for the tablets containing pyridoxine HCl combined with the excipients can be seen in Table 9. As before, the SeDeM predicted formulations are indicated by shading.

As stated earlier in the Methods section of this paper, the reliability factor of the SeDeM Expert Diagram System based on 12 parameters is 0.952, which means that a 5% deviation from the prediction can be considered negligible. From the results and based on the reliability factor, it can be seen that that SeDeM Expert Diagram System predicted three of the pyridoxine containing formulations correctly, specifically FlowLac® 100, MicroceLac® 100 and StarLac® and two other formulations were predicted very closely, namely Tablettose® 80 and Avicel® PH200. Two of the excipients, specifically Emcompress® and Cellactose® 80 varied by 20 and 30% respectively from the SeDeM predictions.

The load of pyridoxine in direct compressible tablets was quite high, with API concentrations of 61.15% and 58.57% reached in the case of Emcompress® and Cellactose® 80.

4. Conclusion

The SeDeM Diagram Expert System attempts to analyse and classify the main components of direct compressible tablet formulations using existing and accessible methods in order to overcome deficiencies of active pharmaceutical ingredients by addition of excipients. Having profiles of excipients ready in a database can save the pharmaceutical industry a lot of time and money as well as to identify inconsistencies between different batches of excipients and API's. The SeDeM diagrams can be produced with relative ease and are specifically useful as a quick reference to prepare direct compressible formulations. The ability to predict the quantities of API and excipients required for successful formulations without physically preparing the tablets is highly advantageous in terms of time efficiency. However, the SeDeM Expert Diagram System also has some shortcomings that the formulator has to be aware of. Some of these shortcomings were identified in this study, where API's with known problems were selected and combined with novel, co-processed excipients that were specifically created for the direct compression manufacturing of tablets.

This study indicated that the SeDeM System does not compensate or compensate to a sufficient extent for certain physicochemical properties such as the elasticity of an API (e.g. paracetamol) or the cohesive behaviour (furosemide) and the consequential formation of active mixtures that can negatively impact on powder flow. In addition, the ability of novel, modern excipients to effectively overcome some deficiencies of API's is not included in the SeDeM System. Furthermore, when the limits that were set for a parameter is surpassed (e.g. particles <50 μm), the SeDeM System becomes ineffective.

Nonetheless, the SeDeM Expert Diagram System revealed itself to be a very valuable and time-saving tool for formulation of direct compression tablets even when API's and excipients with extreme physicochemical properties are involved. Considering the spectrum of API's and excipients evaluated in this study, the value of the SeDeM

Table 9
Concentration range and results for pyridoxine tablets (final tablet weight ± 400 mg per tablet).

Excipient	Excipient concentration (%)	API concentration (%)	Actual dose (mg)	Verdict	Reason for failure
Tablettose® 80	79.93	19.57	78.28	Success	
Tablettose® 80	74.93	24.57	98.28	Failure	Friability
Tablettose® 80	69.93	29.57	118.28	Failure	Friability
FlowLac® 100	59.84	39.66	158.64	Success	
FlowLac® 100	54.84	44.66	178.64	Failure	Friability (capping)
Avicel® PH200	67.94	31.56	125.24	Success	
Avicel® PH200	62.94	36.56	146.24	Success	
Avicel® PH200	57.94	41.56	166.24	Success	
Avicel® PH200	52.94	46.56	186.24	Failure	Friability
Emcompress®	58.85	40.65	162.60	Success	
Emcompress®	53.85	45.65	182.60	Success	
Emcompress®	48.85	50.65	202.60	Success	
Emcompress®	43.85	55.65	222.60	Success	
Emcompress®	38.85	60.65	242.60	Success	
Emcompress®	33.85	65.65	262.60	Failure	Mass variation
Cellactose® 80	71.43	28.07	112.28	Success	
Cellactose® 80	66.43	33.07	132.28	Success	
Cellactose® 80	61.43	38.07	152.28	Success	
Cellactose® 80	56.43	43.07	172.28	Success	
Cellactose® 80	51.43	48.07	192.28	Success	
Cellactose® 80	46.43	53.07	212.28	Success	
Cellactose® 80	41.43	58.07	232.28	Success	
Cellactose® 80	36.43	63.07	252.28	Failure	Friability
MicroceLac® 100	56.56	42.94	171.76	Success	
MicroceLac® 100	51.56	47.94	191.76	Failure	Friability
StarLac®	70.86	28.64	114.56	Success	
StarLac®	65.86	33.64	134.56	Failure	Friability

Expert System lies in the fact that successful formulations (as predicted by the SeDeM Expert System) may be used as a starting point for formulation optimisation highlighting the time and cost benefit of this system. However, in cases where the SeDeM Expert System does not predict success, the approach might be a little more laborious. In these cases, by following an increment wise step-up addition of API as a formulation approach, it is possible to identify an acceptable formulation.

Conflict of interest

None.

Acknowledgements

The financial assistance of the National Research Foundation (NRF) (103479) of South Africa is acknowledged. Opinions expressed and conclusions arrived at are those of the authors and are not necessarily to be attributed to the NRF.

References

[1] G. Alderborn, in: M.E. Aulton, K.M.G. Taylor (Eds.), Tablets and Compaction, fourth ed., Aultons Pharm. Des. Manuf. Med, Churchill Livingstone, Edinburgh 2013, pp. 504–549.
[2] M. Jivraj, L.G. Martini, C.M. Thomson, An overview of the different excipients useful for the direct compression of tablets, Pharm. Sci. Technol. Today 3 (2000) 58–63, http://dx.doi.org/10.1016/S1461-5347(99)00237-0.
[3] P. Pérez, J.M. Suñé-Negre, M. Miñarro, M. Roig, R. Fuster, E. García-Montoya, C. Hernández, R. Ruhí, J.R. Ticó, A new expert systems (SeDeM diagram) for control batch powder formulation and preformulation drug products, Eur. J. Pharm. Biopharm. 64 (2006) 351–359, http://dx.doi.org/10.1016/j.ejpb.2006.06.008.
[4] I. Singh, P. Kumar, Preformulation studies for direct compression suitability of cefuroxime axetil and paracetamol: a graphical representation using SeDeM diagram, Acta Pol. Pharm. Drug Res. 69 (2012) 87–93.
[5] J.M. Suñé-Negre, M. Roig, R. Fuster, C. Hernández, R. Ruhí, E. García-Montoya, P. Pérez-Lozano, M. Miñarro, J.R. Ticó, New classification of directly compressible (DC) excipients in function of the SeDeM Diagram Expert System, Int. J. Pharm. 470 (2014) 15–27, http://dx.doi.org/10.1016/j.ijpharm.2014.04.068.
[6] J.M. Suñé-Negre, E. García, P. Pérez, J.E. Aguilar Diaz, M. Roig, R. Fuster, M. Miñarro, J.R. Ticó Grau, in: P. Vizureanu (Ed.), SeDeM Diagram: A New Expert System for the Formulation of Drugs in Solid Form, Expert Syst. Hum. Mater. Autom, InTech, 2011 (http://www.intechopen.com/books/expert-systems-for-human-materials-and-automation/sedem-diagram-a-new-expert-system-for-the-formulation-of-drugs-in-solid-form (accessed May 12, 2016)).
[7] J.M. Suñé-Negre, P. Pérez-Lozano, M. Miñarro, M. Roig, R. Fuster, C. Hernández, R. Ruhí, E. García-Montoya, J.R. Ticó, Application of the SeDeM Diagram and a new mathematical equation in the design of direct compression tablet formulation, Eur. J. Pharm. Biopharm. 69 (2008) 1029–1039, http://dx.doi.org/10.1016/j.ejpb.2008.01.020.
[8] United States Pharmacopoeia, in: U. S. Pharmacop (Ed.), Bulk Density and Tapped Density of Powders, 39th ed. The United States Pharmacopoeial Convention, Rockville 2016, pp. 456–459 <616 >.
[9] United States Pharmacopoeia, in: U. S. Pharmacop (Ed.), Powder Flow, 39th ed.The United States Pharmacopoeial Convention, Rockville 2016, pp. 1502–1506 <1174 >.
[10] United States Pharmacopoeia, in: U. S. Pharmacop (Ed.), Loss on Drying, 39th ed.The United States Pharmacopoeial Convention, Rockville 2016, pp. 565–566 <731 >.
[11] Malvern Instruments Limited, Top 10 reasons to migrate from sieving to laser diffraction for routine particle size measurements (whitepaper), Malvern.com 2012 http://www.malvern.com/en/pdf/secure/WP121128TenReasonsMigrateFromSieving.pdf (accessed May 13, 2015).
[12] J.-I. Kikuta, N. Kitamori, Effect of mixing time on the lubricating properties of magnesium stearate and the final characteristics of the compressed tablets, Drug Dev. Ind. Pharm. 20 (1994) 343–355, http://dx.doi.org/10.3109/03639049409050187.
[13] Council of Europe, 2.9.5, Uniformity of Mass of Single-dose Preparations, Eur. Pharmacopoeia, seventh ed.Council of Europe, Strasbourg 2011, pp. 265–266.
[14] United States Pharmacopoeia, in: U. S. Pharmacop (Ed.), Friability, 39th ed.The United States Pharmacopoeial Convention, Rockville 2016, pp. 1609–1610 <1216 >.
[15] United States Pharmacopoeia, in: U. S. Pharmacop (Ed.), Tablet Breaking Force, 39th ed.The United States Pharmacopoeial Convention, Rockville 2016, pp. 1610–1613 <1217 >.
[16] P. Di Martino, A.-M. Guyot-Hermann, P. Conflant, M. Drache, J.-C. Guyot, A new pure paracetamol for direct compression: the orthorhombic form, Int. J. Pharm. 128 (1996) 1–8, http://dx.doi.org/10.1016/0378-5173(95)04127-3.
[17] N. Rasenack, B.W. Müller, Crystal habit and tableting behavior, Int. J. Pharm. 244 (2002) 45–57, http://dx.doi.org/10.1016/S0378-5173(02)00296-X.
[18] G.E. Granero, M.R. Longhi, M.J. Mora, H.E. Junginger, K.K. Midha, V.P. Shah, S. Stavchansky, J.B. Dressman, D.M. Barends, Biowaiver monographs for immediate release solid oral dosage forms: furosemide, J. Pharm. Sci. 99 (2010) 2544–2556, http://dx.doi.org/10.1002/jps.22030.
[19] Pubchem, Pyridoxine hydrochloride | $C_{19}H_{35}NO_2 \cdot C_{17}H_{22}N_2O \cdot C_8H_{11}NO_3 \cdot C_4H_6O_4 \cdot 2ClH$ — PubChem, https://pubchem.ncbi.nlm.nih.gov/compound/pyridoxine_hydrochloride#section=Melting-Point 2016 (accessed May 18, 2016).
[20] Meggle Pharma, Technical brochure: Tablettose®, http://www.meggle-pharma.com/en/viewDocuments/upload/86/tablettose.pdf 2014 (accessed April 12, 2014).
[21] J. Ruangchayajatuporn, T. Amornsakchai, N. Sinchaipanid, A. Mitrevej, Compaction behavior and optimization of spray-dried lactose with various amorphous content, J. Drug Delivery Sci. Technol. 21 (2011) 175–181, http://dx.doi.org/10.1016/S1773-2247(11)50019-X.
[22] Meggle Pharma, Technical brochure: FlowLac®, http://www.meggle-pharma.com/en/viewDocuments/upload/87/flowlac.pdf 2014 (accessed April 16, 2014).
[23] G. Thoorens, F. Krier, B. Leclercq, B. Carlin, B. Evrard, Microcrystalline cellulose, a direct compression binder in a quality by design environment—a review, Int. J. Pharm. 473 (2014) 64–72, http://dx.doi.org/10.1016/j.ijpharm.2014.06.055.
[24] J. Wang, H. Wen, D. Desai, Lubrication in tablet formulations, Eur. J. Pharm. Biopharm. 75 (2010) 1–15, http://dx.doi.org/10.1016/j.ejpb.2010.01.007.
[25] P.C. Schmidt, R. Herzog, Calcium phosphates in pharmaceutical tableting: 1. Physicopharmaceutical properties, Pharm. World Sci. 15 (1993) 105–115, http://dx.doi.org/10.1007/BF02113938.
[26] P.C. Schmidt, R. Herzog, Calcium phosphates in pharmaceutical tableting: 2. Comparison of tableting properties, Pharm. World Sci. 15 (1993) 116–122, http://dx.doi.org/10.1007/BF02113939.
[27] Meggle Pharma, Technical brochure: Cellactose® 80, http://www.meggle-pharma.com/en/viewDocuments/upload/89/cellactose80.pdf 2014 (accessed August 15, 2014).
[28] Meggle Pharma, Technical brochure: MicroceLac® 100, http://www.meggle-pharma.com/en/viewDocuments/upload/90/microcelac100.pdf 2014 (accessed September 14, 2014).
[29] Meggle Pharma, Technical brochure: StarLac®, http://www.meggle-pharma.com/en/viewDocuments/upload/91/starlac.pdf 2014 (accessed October 2, 2014).

Chapter 4

Summary and future prospects

This chapter contains final conclusions and remarks on the results obtained from this study and proposals for future research.

4.1. Summary and final conclusions

The patent for the first hand operated device for the production of tablets was awarded in 1843 and thus the age of the tablet dawned. Tablets are the most preferred and widespread dosage form employed for the administration of active pharmaceutical ingredients (API's) (Alderborn, 2013:505). Tablets can be produced by different techniques including wet-granulation and direct compression. Wet granulation is by far the most employed technique, in spite of being more time-consuming and therefore more expensive. Direct compression has the advantage of requiring fewer production steps and can often use fewer excipients. This production technique may even be applied to thermo- and moisture sensitive API's as there are no wetting or drying steps involved in this technique. Direct compression tablets often deliver faster dissolution times, as primary drug particles are released immediately as disintegration transpires (Alderborn, 2013:512).

Unfortunately direct compression is not without disadvantages or shortcomings. The excipients that are suitable for direct compression must possess specific physicochemical properties, as they have to be able to compensate for inadequate flow and compression properties, which are often inherent to API's (Hamman & Steenekamp, 2012:220). This also contributes to limit the amount of active ingredient to 30% of the direct compressible tablet formulation (Jivraj *et al.*, 2000:58). In spite of this, direct compression is becoming increasingly popular with more specifically designed excipients being created for this purpose (Alderborn, 2013:513). Other challenges that may arise include the time and cost of experimenting and testing excipient and API combinations (McCormick, 2005:54). A new system was therefore required to help decrease both the amount of experiments needed as well as decreasing the time taken to obtain an acceptable tablet formulation that can be prepared by direct compression. This need was addressed by the team of Pérez and co-workers with the development of the SeDeM Diagram Expert System (Pérez *et al.*, 2006:351; Suñé Negre *et al.*, 2008:1029; Suñé-Negre *et al.*, 2011:17; Suñé Negre *et al.*, 2014:15).

Three different API's (paracetamol, furosemide and pyridoxine) as well as seven excipients (Tablettose® 80, FlowLac® 100, Avicel® PH200, Emcompress®, Cellactose® 80, MicroceLac® 100 and StarLac®) were used to test the application of the SeDeM Expert Diagram System. The following SeDeM System parameters for each powder was determined individually: 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. The results were used to calculate incidence values. Parameter values were used to

create an irregular 12 sided polygon, which visually represents the perceived strengths and challenges of each pharmaceutical powder for direct compression into tablets.

The parameter values which were calculated were used to determine the ratios of excipient to API at which the SeDeM Expert Diagram System predicted the formulation to deliver acceptable tablets by direct compression. These predicted formulations were prepared and tablets were compressed. The resulting tablets were assessed to determine if they complied with the following criteria:

- The ability of the powder mixture to flow sufficiently to fill the tablet press' die consistently as determined by the uniformity of weight test.
- The ability to create a tablet that can withstand physical stress during handling as determined by the friability test.

Both criteria needed to be met for a formulation to be considered acceptable. In the case of failure, the amount of excipient was increased in 5% w/w increments, until an acceptable formulation was obtained. Where the prediction was found successful, the amount of excipient was decreased in 5% w/w increments until the resulting tablets did not comply with the criteria. In cases where the predicted values did not correspond with results, an attempt was made to identify possible reasons for non-compliance.

The SeDeM Expert Diagram System results indicated that paracetamol was not suitable for direct compression. This was due to overall low values for most of the incidences, especially flowability, compressibility and lubricity/dosage which all presented values unacceptable for direct compression. It led to the SeDeM Expert Diagram System predicting that only three excipients, FlowLac® 100, Avicel® PH200 and StarLac® would be able to compensate for the deficient properties of paracetamol. Of those excipients, FlowLac® 100 and StarLac® produced acceptable tablets within 5 % of the predicted concentrations. Avicel® PH200 exceeded the SeDeM Expert Diagram Systems' prediction (API concentration of 5.77 % w/w) by still delivering acceptable tablets at an API concentration of 25.77 % w/w. Furthermore, tablet formulations were also formulated and investigated for compression by combining paracetamol with the excipients SeDeM deemed incompatible with paracetamol, starting with an API concentration of 5 % w/w and increasing this concentration as mentioned before to determine if these combinations could render acceptable tablets. Acceptable tablets (complied with criteria) at higher than expected API concentrations could be prepared with the remaining excipients, i.e. Tablettose® 80 (API concentration 15 % w/w), Emcompress® (API concentration 25 % w/w), Cellactose® 80 (API concentration 25 % w/w) and MicroceLac® 100 (API concentration 30 % w/w). It needs to be noted that the reason for failure on most of the formulations, i.e. Tablettose® 80, FlowLac® 100, Avicel® PH200 and

Emcompress® was due to capping problems, which is a known problem when direct compression of paracetamol is attempted, because of the elastic deformation properties of paracetamol. In contradiction to this, novel direct compression excipient formulations, i.e. Cellactose® 80, MicroceLac® 100 and StarLac® failed due to problems with powder flow, which lead to the conclusion that these excipients are able to compensate for the elastic deformation properties of paracetamol.

SeDeM overestimated the quantity of furosemide that could be incorporated into any of the formulations. The quantity of furosemide had to be decreased between 20 to 35 % (w/w) in all of the formulations to achieve acceptable tablets from the formulations. The lowest incidence value for furosemide, and therefore, the value used for the predictions made by the SeDeM System was flowability with a value of 2.76. Of the three API's used in this study, furosemide displayed the most parameters that exceeded the limits set in the SeDeM Expert Diagram System with five of the fourteen parameters being exceeded. This contributed to the inability of the SeDeM Expert Diagram System to correctly predict any of the combination concentrations. The powder mixtures as predicted by the SeDeM Expert Diagram System exhibited poor powder flow properties. Furosemide has small powder particles which tend to be cohesive, and as a consequence the furosemide particles coated the surfaces of the excipients, forming interactive powder mixtures. This was confirmed with SEM micrographs of the powder mixtures. Due to the formation of interactive mixtures, the poor flow properties of the API were therefore imparted to the excipients.

Pyridoxine only exceeded three of the parameters, making the SeDeM predictions more accurate for this API. As noted before, pyridoxine was deemed acceptable for direct compression according to the SeDeM Expert Diagram System with acceptable values for the PI (0.67), the PPI (5.34) as well as the GCI (5.08). As was the case with furosemide, the flowability incidence was the lowest and therefore the incidence used for SeDeM predictions.

It needs to be noted that when using the SeDeM Expert Diagram System with 12 parameters (as was used in this case) a reliability factor of 0.952 is achieved. This means a deviation needs to exceed 5 % before it can be considered significant. With this in mind, the SeDeM Expert Diagram System successfully predicted three excipient formulations (FlowLac® 100, MicroceLac® 100 and StarLac®) and predicted two other excipient combinations correct within 10 %, specifically Tablettose® 80 and Avicel® PH200. Emcompress® and Cellactose® 80 exceeded the expectations of the SeDeM Expert Diagram System by 20 and 30 %, respectively.

It was concluded that the SeDeM Expert Diagram System is a valuable time saving system to help a formulating scientist decrease the amount of experiments required to obtain an

acceptable tablet formulation. However, the predictions are sometimes less accurate. The inaccuracy of predictions may be attributed to certain physicochemical properties such as elastic deformation, which is inherent to certain API's such as paracetamol or cohesive behaviour (furosemide) and the consequential formation of interactive mixtures that can negatively impact on powder flow. These physicochemical properties are not sufficiently incorporated in terms of the characterisation tests on which the prediction within in the SeDeM Diagram Expert System is based. Furthermore, the effectiveness of novel co-processed direct compression excipients are also underestimated by the SeDeM Expert Diagram System. However, when the limitations are kept in mind, the SeDeM Expert Diagram System could be a valuable tool for the formulation scientist as powder profiles and possible combinations can be predicted and then optimised for specific uses, reducing the amount of experiments, therefore saving time and money.

Considering the spectrum of API's and excipients evaluated in this study, the value of the SeDeM Expert System lies in the fact that successful formulations (as predicted by the SeDeM Expert System) may be used as a starting point for formulation optimisation, highlighting the time and cost benefit of this system. However, in cases where the SeDeM Expert System does not predict success, the approach might be a little more laborious. In these cases, by following an increment wise step-up addition of API as a formulation approach, it is possible to identify an acceptable formulation.

4.2. Future prospects

The following aspects are recommended for future study:

- By employing tools such as Heckel plots, determine the effect of plastic and elastic properties of API's on SeDeM predictions.
- Test the applicability of the SeDeM Expert Diagram System to the compression of other specialised tablet types such as MUPS (Multiple unit pellet systems) and direct compressible chewing gum drug delivery systems.
- Create new combinations of API's and excipients to further investigate the robustness of the SeDeM Expert Diagram System in terms of predictions. Upon discovering successful formulations (which differ from those predicted), test the entire range of SeDeM parameters to determine if the specific incidences are corrected as predicted.
- Compile a library of the API's and excipients that are available (e.g. especially non-traditional excipients such as chitosan powder) as well as newly developed

excipients (e.g. acrylic solid excipients), in an attempt to find more substances which surpass the limits set by the SeDeM Expert Diagram System. This can then be used to point out any further limitations of the SeDeM expert diagram system.

- Determine if tensile strength could be a better predictor for compressibility (Cohesion index parameter) as used in the SeDeM expert Diagram System as SeDeM defines no specific tablet size.

4.3. References

Alderborn, G. 2013. Tablets and compaction. (*In* Aulton, M.E. & Taylor, K., *ed*. Aulton's Pharmaceutics: The design and manufacture of medicines, 4th ed. London: Churchill Livingstone. p. 504-549).

Hamman, J.H. & Steenekamp, J.H. 2012. Excipients with specialized functions for effective drug delivery. *Expert Opinion Drug Delivery*, 9(2):219-230.

Jivraj, M., Martini, L.G. & Thompson, C.M. 2000. An overview of the different excipients useful for the direct compression of tablets. *Pharmaceutical Science & Technology Today*, 3(2):58-63.

McCormick, D. 2005. Evolution in direct compression. *Pharmaceutical Technology*, 4:52-62.

Pérez, P., Suñé-Negre, J.M., Miñarro, M., Roig, M., Fuster, R., García-Montoya, E., Hernández, C, Ruhí, R. & Ticó, J.R. 2006. A new expert systems (SeDeM Diagram) for control batch powder formulation and preformulation drug products. *European Journal of Pharmaceutics and Biopharmaceutics*, 64:351-359.

Suñé-Negre, J.M., Pérez-Lozano, P., Miñarro, M., Roig, M., Fuster, R., Hernández, C, Ruhí, R., García-Montoya, E. & Ticó-Grau, J.R. 2008. Application of the SeDeM Diagram and a new mathematical equation in the design of direct compression tablet formulation. *European Journal of Pharmaceutics and Biopharmaceutics*, 69:1029-1039.

Suñé-Negre, J.M., Roig, M., Fuster, R., Hernández, C, Ruhí, R., García-Montoya, E., Pérez-Lozano, P., Miñarro, M. & Ticó, J.R. 2014. New classification of directly compressible (DC) excipients in function of the SeDeM Diagram Expert System. *International Journal of Pharmaceutics*, 470:15-27.

Suñé-Negre, J.M., García-Montoya, E., Pérez-Lozano, P., Aguilar-Díaz, J.E., Roig-Carreras, M., Fuster-Garcia, R., Miñarro-Carmona, M. & Ticó-Grau, J.R. 2011. SeDeM Diagram: A

New Expert System for the Formulation of Drugs in Solid Form. (*In* Vizureanu, P., *ed*. Expert Systems for Human, Materials and Automation, Rijeka: InTech. p. 17-34).

Appendix A

Density determination results

This appendix contains raw and calculated density determination data. Methods can be seen in Chapter 3.

Table 1: Density determination results (API's)

Paracetamol								
USP Method 1								
Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
101,86	234	150	0,435299145	0,679066667	35,8974359	1,56	35,8974359	0,8246613
101,7	236	154	0,430932203	0,66038961	34,74576271	1,532467532	34,74576271	0,806293019
101,32	235	150	0,431148936	0,675466667	36,17021277	1,566666667	36,17021277	0,838926174
USP Method 2								
Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
101,38	242	163	0,41892562	0,62196319	32,6446281	1,484662577	32,6446281	0,7792464
100,01	242	158	0,413264463	0,632974684	34,7107438	1,53164557	34,7107438	0,839916008
99,5	238	156	0,418067227	0,637820513	34,45378151	1,525641026	34,45378151	0,824120603

Furosemide								
USP Method 1								
Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
51,36	214	126	0,24	0,407619048	41,12149533	1,698412698	41,12149533	1,713395639
51,04	216	126	0,236296296	0,405079365	41,66666667	1,714285714	41,66666667	1,763322884
51	214	124	0,238317757	0,411290323	42,05607477	1,725806452	42,05607477	1,764705882
USP Method 2								
Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
50,52	212	123	0,238301887	0,410731707	41,98113208	1,723577236	41,98113208	1,761678543
50,36	210	122	0,239809524	0,412786885	41,9047619	1,721311475	41,9047619	1,747418586
49,79	208	120	0,239375	0,414916667	42,30769231	1,733333333	42,30769231	1,767423177

Table 1: Density determination results (API's) (continued)

Pyridoxine								
USP Method 1								
Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
99,8	162	102	0,616049383	0,978431373	37,03703704	1,588235294	37,03703704	0,601202405
99,7	160	101	0,623125	0,987128713	36,875	1,584158416	36,875	0,591775326
101,2	162	102	0,624691358	0,992156863	37,03703704	1,588235294	37,03703704	0,592885375
USP Method 2								
Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
101,37	162	102	0,625740741	0,993823529	37,03703704	1,588235294	37,03703704	0,591891092
101,33	162	100	0,625493827	1,0133	38,27160494	1,62	38,27160494	0,611862232
101,24	160	98	0,63275	1,033061224	38,75	1,632653061	38,75	0,612406164

Table 2: Averages of density determination results (API's)

Paracetamol	Average	STD Dev	% RSD
Mass (g)	100,9616667	0,969297	0,96006438
Bulk volume (ml)	237,8333333	3,48807492	1,46660473
Tapped volume (ml)	155,1666667	4,99666555	3,22019262
Bulk density (g/cm3)	0,424606266	0,00895351	2,10866243
Tapped density (g/cm3)	0,651280222	0,02373098	3,64374298
Carr's Index (%)	34,77042746	1,25323621	3,60431637
Hausner Ratio	1,533513895	0,02916724	1,90198721
Porosity (ε)	34,77042746	1,25323621	3,60431637
Inter-particle porosity (Ie)	0,818860584	0,02295431	2,80320149

Furosemide	Average	STD Dev	% RSD
Mass (g)	50,67833333	0,56823997	1,12126808
Bulk volume (ml)	212,3333333	2,94392029	1,38646167
Tapped volume (ml)	123,5	2,34520788	1,89895375
Bulk density (g/cm3)	0,238683411	0,00137531	0,57620752
Tapped density (g/cm3)	0,410403999	0,00355086	0,86521036
Carr's Index (%)	41,83963717	0,40885924	0,97720551
Hausner Ratio	1,719454485	0,01202405	0,69929421
Porosity (ε)	41,83963717	0,40885924	0,97720551
Inter-particle porosity (Ie)	1,752990785	0,02062325	1,17646074

Pyridoxine	Average	STD Dev	% RSD
Mass (g)	100,7733333	0,79562973	0,78952408
Bulk volume (ml)	161,3333333	1,03279556	0,64016254
Tapped volume (ml)	100,8333333	1,60208198	1,58884163
Bulk density (g/cm3)	0,624641718	0,00536301	0,85857354
Tapped density (g/cm3)	0,999650284	0,0199987	2,00056966
Carr's Index (%)	37,50128601	0,79893596	2,13042284
Hausner Ratio	1,600252893	0,02064955	1,29039286
Porosity (ε)	37,50128601	0,79893596	2,13042284
Inter-particle porosity (Ie)	0,600337099	0,0097919	1,63106766

Table 3: Density determination results (Excipients)

Tablettose® 80

USP Method 1

Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
100,64	171	129	0,588538012	0,780155039	24,56140351	1,325581395	24,56140351	0,417329094
100,61	170	128	0,591823529	0,786015625	24,70588235	1,328125	24,70588235	0,417453533
100,59	169	128	0,595207101	0,785859375	24,26035503	1,3203125	24,26035503	0,407595188

USP Method 2

Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
100,61	170	130	0,591823529	0,773923077	23,52941176	1,307692308	23,52941176	0,397574794
100,58	170	131	0,591647059	0,76778626	22,94117647	1,297709924	22,94117647	0,387751044
100,56	168	130	0,598571429	0,773538462	22,61904762	1,292307692	22,61904762	0,37788385

FlowLac® 100

USP Method 1

Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
100,67	166	148	0,606445783	0,680202703	10,84337349	1,121621622	10,84337349	0,178802026
100,71	168	148	0,599464286	0,680472973	11,9047619	1,135135135	11,9047619	0,198590011
100,68	168	146	0,599285714	0,689589041	13,0952381	1,150684932	13,0952381	0,218514104

USP Method 2

Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
100,64	164	146	0,613658537	0,689315068	10,97560976	1,123287671	10,97560976	0,178855326
100,61	166	145	0,606084337	0,693862069	12,65060241	1,144827586	12,65060241	0,208726767
100,58	165	146	0,609575758	0,68890411	11,51515152	1,130136986	11,51515152	0,188904355

Table 3: Density determination results (Excipients) (continued)

Avicel® PH200								
USP Method 1								
Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
75,89	204	164	0,372009804	0,462743902	19,60784314	1,243902439	19,60784314	0,527078666
75,87	203	164	0,373743842	0,462621951	19,21182266	1,237804878	19,21182266	0,514037169
75,83	202	162	0,37539604	0,46808642	19,8019802	1,24691358	19,8019802	0,527495714
USP Method 2								
Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
75,9	202	162	0,375742574	0,468518519	19,8019802	1,24691358	19,8019802	0,527009223
75,6	204	164	0,370588235	0,46097561	19,60784314	1,243902439	19,60784314	0,529100529
75,5	204	163	0,370098039	0,463190184	20,09803922	1,251533742	20,09803922	0,543046358

Emcompress®								
USP Method 1								
Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
101,56	114	92	0,890877193	1,103913043	19,29824561	1,239130435	19,29824561	0,216620717
101,52	115	92	0,882782609	1,103478261	20	1,25	20	0,226556344
101,45	114	93	0,889912281	1,090860215	18,42105263	1,225806452	18,42105263	0,206998521
USP Method 2								
Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
101,58	116	94	0,875689655	1,080638298	18,96551724	1,234042553	18,96551724	0,216578067
101,57	116	94	0,875603448	1,080531915	18,96551724	1,234042553	18,96551724	0,21659939
101,56	115	93	0,883130435	1,092043011	19,13043478	1,23655914	19,13043478	0,216620717

Table 3: Density determination results (Excipients) (continued)

Cellactose® 80

USP Method 1

Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
100,43	230	184	0,436652174	0,545815217	20	1,25	20	0,458030469
100,4	231	185	0,434632035	0,542702703	19,91341991	1,248648649	19,91341991	0,458167331
100,49	231	184	0,435021645	0,546141304	20,34632035	1,255434783	20,34632035	0,46770823

USP Method 2

Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
100,41	230	184	0,436565217	0,545706522	20	1,25	20	0,458121701
100,38	230	184	0,436434783	0,545543478	20	1,25	20	0,458258617
100,43	228	186	0,440482456	0,539946237	18,42105263	1,225806452	18,42105263	0,418201733

MicroceLac® 100

USP Method 1

Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
100,27	210	176	0,47747619	0,569715909	16,19047619	1,193181818	16,19047619	0,339084472
100,24	210	175	0,477333333	0,5728	16,66666667	1,2	16,66666667	0,349162011
100,23	210	175	0,477285714	0,572742857	16,66666667	1,2	16,66666667	0,349196847

USP Method 2

Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
101,07	212	178	0,476745283	0,567808989	16,03773585	1,191011236	16,03773585	0,336400514
101,06	212	178	0,476698113	0,567752809	16,03773585	1,191011236	16,03773585	0,336433802
100,98	211	178	0,478578199	0,567303371	15,63981043	1,185393258	15,63981043	0,326797386

Table 3: Density determination results (Excipients) (continued)

StarLac®								
USP Method 1								
Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
101,17	171	144	0,591637427	0,702569444	15,78947368	1,1875	15,78947368	0,266877533
101,16	170	142	0,595058824	0,712394366	16,47058824	1,197183099	16,47058824	0,276789245
101,16	170	142	0,595058824	0,712394366	16,47058824	1,197183099	16,47058824	0,276789245
USP Method 2								
Mass (g)	Bulk volur	Tapped vo	Bulk density (g/	Tapped density	Carr's Index (%	Hausner Ratio	Porosity (ε)	Inter-particle porosity (Ie)
101,16	170	146	0,595058824	0,692876712	14,11764706	1,164383562	14,11764706	0,237247924
101,21	172	146	0,588430233	0,693219178	15,11627907	1,178082192	15,11627907	0,256891612
101,19	172	146	0,588313953	0,693082192	15,11627907	1,178082192	15,11627907	0,256942386

Table 4: Averages of density determination results (Excipients)

Tablettose® 80	Average	STD Dev	% RSD
Mass (g)	100,5983333	0,02786874	0,02770298
Bulk volume (ml)	169,6666667	1,03279556	0,60872037
Tapped volume (ml)	129,3333333	1,21106014	0,93638671
Bulk density (g/cm3)	0,59293511	0,00347548	0,58614843
Tapped density (g/cm3)	0,777879639	0,00736783	0,94716807
Carr's Index (%)	23,76954612	0,87317405	3,67349906
Hausner Ratio	1,311954803	0,01499403	1,14287709
Porosity (ε)	23,76954612	0,87317405	3,67349906
Inter-particle porosity (Ie)	0,400931251	0,0161397	4,02555282

FlowLac® 100	Average	STD Dev	% RSD
Mass (g)	100,6483333	0,04792355	0,04761485
Bulk volume (ml)	166,1666667	1,60208198	0,96414161
Tapped volume (ml)	146,5	1,22474487	0,83600333
Bulk density (g/cm3)	0,605752402	0,00564047	0,93115083
Tapped density (g/cm3)	0,687057661	0,00550566	0,80133945
Carr's Index (%)	11,83078953	0,90358679	7,63758659
Hausner Ratio	1,134282322	0,0116562	1,02762774
Porosity (ε)	11,83078953	0,90358679	7,63758659
Inter-particle porosity (Ie)	0,195398765	0,01620773	8,29469576

Avicel® PH200	Average	STD Dev	% RSD
Mass (g)	75,765	0,17120164	0,22596401
Bulk volume (ml)	203,1666667	0,98319208	0,48393376
Tapped volume (ml)	163,1666667	0,98319208	0,6025692
Bulk density (g/cm3)	0,372929756	0,00240852	0,64583796
Tapped density (g/cm3)	0,464356098	0,0031507	0,67850937
Carr's Index (%)	19,68825142	0,2945199	1,49591699
Hausner Ratio	1,245161776	0,00456148	0,36633616
Porosity (ε)	19,68825142	0,2945199	1,49591699
Inter-particle porosity (Ie)	0,527961276	0,00921564	1,74551519

Emcompress®	Average	STD Dev	% RSD
Mass (g)	101,54	0,04857983	0,04784305
Bulk volume (ml)	115	0,89442719	0,77776277
Tapped volume (ml)	93	0,89442719	0,96174967
Bulk density (g/cm3)	0,88299927	0,0066037	0,74787136
Tapped density (g/cm3)	1,09191079	0,0103492	0,94780622
Carr's Index (%)	19,13012792	0,51805834	2,70807566
Hausner Ratio	1,236596855	0,00794414	0,64241921
Porosity (ε)	19,13012792	0,51805834	2,70807566
Inter-particle porosity (Ie)	0,216662292	0,00618539	2,85485286

Table 4: Averages of density determination results (Excipients) (continued)

Cellactose® 80	Average	STD Dev	% RSD
Mass (g)	100,4233333	0,03777124	0,03761202
Bulk volume (ml)	230	1,09544512	0,47628048
Tapped volume (ml)	184,5	0,83666003	0,45347427
Bulk density (g/cm3)	0,436631385	0,00207185	0,47450852
Tapped density (g/cm3)	0,544309244	0,00247859	0,45536347
Carr's Index (%)	19,78013215	0,68270894	3,45148824
Hausner Ratio	1,246648314	0,0104813	0,84075817
Porosity (ε)	19,78013215	0,68270894	3,45148824
Inter-particle porosity (Ie)	0,453081347	0,01751059	3,86477805

MicroceLac® 100	Average	STD Dev	% RSD
Mass (g)	100,6416667	0,43402381	0,43125658
Bulk volume (ml)	210,8333333	0,98319208	0,46633616
Tapped volume (ml)	176,6666667	1,50554531	0,85219546
Bulk density (g/cm3)	0,477352806	0,00068109	0,14268005
Tapped density (g/cm3)	0,569687322	0,00252901	0,44393031
Carr's Index (%)	16,20651527	0,40046554	2,4710157
Hausner Ratio	1,193432925	0,00570406	0,47795381
Porosity (ε)	16,20651527	0,40046554	2,4710157
Inter-particle porosity (Ie)	0,339512505	0,00857811	2,52659608

StarLac®	Average	STD Dev	% RSD
Mass (g)	101,175	0,02073644	0,02049562
Bulk volume (ml)	170,8333333	0,98319208	0,57552707
Tapped volume (ml)	144,3333333	1,96638416	1,36239087
Bulk density (g/cm3)	0,592259681	0,00329017	0,55552902
Tapped density (g/cm3)	0,701089377	0,00950052	1,35510775
Carr's Index (%)	15,51347589	0,91347377	5,88825982
Hausner Ratio	1,18373569	0,01276138	1,07806024
Porosity (ε)	15,51347589	0,91347377	5,88825982
Inter-particle porosity (Ie)	0,261922991	0,01500359	5,72824492

Appendix B

Cohesion index results

This appendix contains raw and calculated cohesion index data.
Methods can be seen in Chapter 3.

Table 1: Cohesion index determination results (API'S)

Cohesion Index			10mm tablet Diameter						
	Paracetamol			Furosemide			Pyridoxine		
	Thickness (mm)	Diameter (mm)	Hardness (N)	Thickness (mm)	Diameter (mm)	Hardness (N)	Thickness (mm)	Diameter (mm)	Hardness (N)
	3,35	9,14	22	N/A	N/A	N/A	4,45	9,99	38
	3,31	9,95	13	N/A	N/A	N/A	4,43	10,01	39
	3,36	10,01	15	N/A	N/A	N/A	4,28	9,97	28
	3,35	9,9	16	N/A	N/A	N/A	4,34	10	29
	3,36	10,04	13	N/A	N/A	N/A	4,69	10,09	34
	3,49	9,84	18	N/A	N/A	N/A	4,33	10,01	34
	3,56	10,04	15	N/A	N/A	N/A	4,29	10,07	31
	3,25	10,02	15	N/A	N/A	N/A	4,29	10,07	23
	3,32	9,95	18	N/A	N/A	N/A	4,37	10,05	34
	3,34	9,9	16	N/A	N/A	N/A	4,42	10,05	29
Average	3,369	9,879	16,1	N/A	N/A	N/A	4,389	10,031	31,9
STD Dev	0,089993827	0,268222544	2,685351208	N/A	N/A	N/A	0,122333787	0,040124805	4,863697725
% RSD (STD/AV	2,671232619	2,715077887	16,67920005	N/A	N/A	N/A	2,787281555	0,400008028	15,24670133
All API's exhibited flow and ejection problems									
Thus add mixture:									
Talc	2,36%								
Aerosil	0,14%								
MgSt	1%								

Table 2: Cohesion index determination results (Excipients)

Cohesion Index			10mm tablet Diameter						
	Tablettose® 80*			FlowLac® 100*			Avicel® PH200		
	Thickness (mm)	Diameter (mm)	Hardness (N)	Thickness (mm)	Diameter (mm)	Hardness (N)	Thickness (mm)	Diameter (mm)	Hardness (N)
	4,14	10,02	150	4,62	10,02	178	2,85	9,77	290
	4,12	10,09	180	4,6	10,08	176	2,82	9,73	298
	4,13	10,02	158	4,53	10,01	181	2,84	9,69	273
	4,12	10,14	151	4,59	10,02	174	2,83	9,74	269
	4,1	10,08	127	4,53	10,12	188	2,84	9,74	270
	4,16	10,06	161	4,52	10,14	185	2,85	9,7	257
	4,1	10,02	139	4,58	10	166	2,81	9,75	259
	4,09	10,04	130	4,62	10	174	2,82	9,76	255
	4,09	10,06	131	4,61	10,05	166	2,81	9,72	269
	4,12	10,06	144	4,58	10,08	165	2,81	9,73	278
Average	4,117	10,059	147,1	4,578	10,052	175,3	2,828	9,733	271,8
STD Dev	0,022632327	0,037844712	16,49545392	0,038239014	0,050728033	8,014570065	0,016193277	0,024966644	13,91082712
% RSD (STD/AV	0,549728611	0,376227378	11,21376881	0,835277728	0,504656118	4,571916752	0,572605271	0,256515405	5,118037939
Excipients with ejection problems receive 1%. Excipients with added MgSt Indicated with (*)									

Cohesion Index			10mm tablet Diameter						
	Emcompress®*			Cellactose® 80			MicroceLac® 100		
	Thickness (mm)	Diameter (mm)	Hardness (N)	Thickness (mm)	Diameter (mm)	Hardness (N)	Thickness (mm)	Diameter (mm)	Hardness (N)
	4,63	10,03	159	309	9,97	150	3,69	10,06	157
	4,59	10,02	131	3,11	9,91	155	3,8	10,11	213
	4,51	10,02	78	3,08	9,95	149	3,65	9,95	177
	4,59	10,04	132	3,08	9,96	147	3,69	10,03	162
	4,63	10,04	158	3,11	10,05	149	3,64	10,09	170
	4,59	10,04	144	3,06	10,02	142	3,65	10,1	134
	4,57	10,18	115	3,09	9,98	168	3,8	9,98	151
	4,6	10,12	124	3,06	10,01	142	3,73	10,02	111
	4,62	10,47	131	3,12	9,96	148	3,69	9,95	129
	4,6	10,22	128	3,11	9,98	127	3,67	9,94	171
Average	4,593	10,118	130	33,682	9,979	147,7	3,701	10,023	157,5
STD Dev	0,034976182	0,142735186	23,08438626	96,73688689	0,039567102	10,37143513	0,058395205	0,065667513	28,6521281
% RSD (STD/AV(	0,761510611	1,410705535	17,7572202	287,2064809	0,396503677	7,021960143	1,577822353	0,65516824	18,19182736

Excipients with ejection problems receive 1%. Excipients with added MgSt Indicated with (*)

Cohesion Index			
	StarLac®*		
	Thickness (mm)	Diameter (mm)	Hardness (N)
	4,53	10	153
	4,55	10,09	102
	4,55	10,08	105
	4,56	10,07	108
	4,46	10,05	130
	4,55	10,24	126
	4,52	10,23	116
	4,56	10,14	128
	4,48	10,16	126
	4,52	10,17	122
Average	4,528	10,123	121,6
STD Dev	0,034253954	0,078322694	14,95326051
% RSD (STD/AV(	0,756491907	0,773710306	12,29708924

Excipients with ejection problems receive 1%. Excipients with added MgSt Indicated with (*)

Appendix C

Angle of repose results

This appendix contains raw and calculated angle of repose data.
Methods can be seen in Chapter 3.

Table 1: Angle of repose determination results (API's)

Angle of Repose											
Paracetamol				Furosemide				Pyridoxine			
Height	Diameter	Angle		Height	Diameter	Angle		Height	Diameter	Angle	
4,7	10,6	41,56637		4	9,3	40,70261		5	9,6	46,16914	
4,9	10,4	43,29865		3,6	8,5	40,26656		4,7	9,5	44,69685	
5,2	10,1	45,83841		3,3	6,4	45,8814		4,7	9,6	44,39691	
5,3	10,5	45,27154		3,5	8,9	38,18565		4,7	9,4	45	
4,9	9,9	44,70916		3,5	9	37,87498		4,8	9,3	45,90938	

Summary	Angle (AVG)	ST Deviation	%RSD
Paracetamol	44,13682659	1,719036451	3,894789417
Furosemide	40,58224195	3,212015568	7,914830263
Pyridoxine	45,23445583	0,770491802	1,703329437

Table 2: Angle of repose determination results (Excipients)

Angle of Repose											
Tablettose® 80				FlowLac® 100				Avicel® PH200			
Height	Diameter	Angle		Height	Diameter	Angle		Height	Diameter	Angle	
3,5	10,1	34,72464		3,2	11	30,19162		3,2	10,7	30,88495	
3,5	10,6	33,43987		3,1	11	29,40719		3,1	10,7	30,08969	
3,5	10,3	34,20048		3,1	11,1	29,18592		3,1	10,5	30,56084	
3,5	10,3	34,20048		3,1	10,9	29,63154		3,1	10,6	30,32361	
3,5	10,4	33,94359		3,1	11	29,40719		3,1	10,6	30,32361	

Emcompress®				Cellactose® 80				MicroceLac® 100			
Height	Diameter	Angle		Height	Diameter	Angle		Height	Diameter	Angle	
3,6	9,9	36,02737		3,4	10,5	32,92786		3,3	10,6	31,90811	
3,5	10,4	33,94359		3,4	10,4	33,17851		3,2	11	30,19162	
3,5	10,3	34,20048		3,4	10,5	32,92786		3,3	10,7	31,66722	
3,4	10	34,2157		3,4	10,4	33,17851		3,3	10,9	31,1951	
3,5	10,3	34,20048		3,3	10,6	31,90811		3,2	10,9	30,41958	

StarLac®			
Height	Diameter	Angle	
3,1	11,1	29,18592	
3,1	11	29,40719	
3,1	11,2	28,96766	
3,2	11	30,19162	
3,1	11,1	29,18592	

Table 2: Angle of repose determination results (Excipients) (continued)

Summary	Angle (AVG)	ST Deviation	%RSD
Tablettose® 80	34,10181326	0,46652781	1,368043999
FlowLac® 100	29,56469072	0,384251347	1,299696826
Avicel® PH200	30,43653691	0,3009705	0,988846073
Emcompress®	34,51752616	0,851641624	2,467273059
Cellactose® 80	32,82417111	0,527207714	1,606156975
MicroceLac® 100	31,0763247	0,753182085	2,423652385
StarLac®	29,38766086	0,475536201	1,618149208

Appendix D

Flowability

This appendix contains raw and calculated flowability data.
Methods can be seen in Chapter 3.

Table 1: Flowability determination results (API's and excipients)

Powder flow determination	RH%	39%
15mm Orifice Diameter	Temp	22 °C

API's exhibited no flow through a 15mm diameter orifice.

Tablettose® 80				FlowLac® 100				Avicel® PH200			
Mass (g)	Time (sec)	Flowrate (g/sec)	Powder flow (t^n)	Mass (g)	Time (sec)	Flowrate (g/sec)	Powder flow (t^n)	Mass (g)	Time (sec)	Flowrate (g/sec)	Powder flow (t^n)
100,58	7	14,4	6,959634122	100,43	5,3	18,9	5,277307577	100,28	8,7	11,5	8,675708018
100,62	7,6	13,2	7,553170344	100,35	5,3	18,9	5,281514699	100,21	8,7	11,5	8,681768287
100,59	7,3	13,8	7,257182623	100,35	5,2	19,3	5,181863478	100,21	8,8	11,4	8,781558727
100,54	7	14,4	6,962403024	100,31	5,2	19,3	5,183929818	100,2	8,7	11,5	8,682634731
100,54	7,2	14	7,161328824	100,28	5,2	19,3	5,185480654	100,22	8,8	11,4	8,780682499
	Average	SEM	%RDS		Average	SEM	%RDS		Average	SEM	%RDS
	7,178744	0,245694704	3,422530611		5,222019	0,052428207	1,003983407		8,72047	0,055430909	0,635641272

Emcompress®				Cellactose® 80				MicroceLac® 100			
Mass (g)	Time (sec)	Flowrate (g/sec)	Powder flow (t^n)	Mass (g)	Time (sec)	Flowrate (g/sec)	Powder flow (t^n)	Mass (g)	Time (sec)	Flowrate (g/sec)	Powder flow (t^n)
100,77	4	25,2	3,969435348	100,71	8,8	11,4	8,737960481	100,43	8,3	12,1	8,26446281
100,76	4,1	24,6	4,068671232	100,65	8,7	11,6	8,643815201	100	8,5	11,6	8,5
100,75	4	25,2	3,969829297	100,61	8,8	11,4	8,746645463	100,01	8,3	11,6	8,299170083
100,75	3,9	25,8	3,870967742	100,59	8,9	11,3	8,847797992	100,22	8,5	11,8	8,48134105
100,75	4	25,2	3,970223325	100,56	8,9	11,3	8,85043755	100,14	8,6	11,6	8,587976832
	Average	SEM	%RDS		Average	SEM	%RDS		Average	SEM	%RDS
	3,969825	0,055430909	1,396305979		8,765331	0,086470101	0,986501226		8,42659	0,138702448	1,646009185

StarLac®			
Mass (g)	Time (sec)	Flowrate (g/sec)	Powder flow (t^n)
100,75	5,5	18,3	5,459057072
100,65	5,5	18,3	5,464480874
100,62	5,6	18	5,565493938
100,63	5,5	18,3	5,465566928
100,57	5,5	18,3	5,468827682
	Average	SEM	%RDS
	5,484685	0,045310145	0,826121146

Summary	Average (t^n)	SEM	%RDS
Tablettose® 80	7,178743787	0,245694704	3,422530611
FlowLac® 100	5,222019245	0,052428207	1,003983407
Emcompress®	3,969825389	0,055430909	1,396305979
Avicel® PH200	8,720470452	0,055430909	0,635641272
Cellactose® 80	8,765331337	0,086470101	0,986501226
MicroceLac® 100	8,426590155	0,138702448	1,646009185
StarLac®	5,484685299	0,045310145	0,826121146

Appendix E

Loss on drying

This appendix contains loss on drying data. Methods can be seen in Chapter 3.

Table 1: Loss on drying determination results (API's)

Paracetamol			Furosemide			Pyridoxine		
Container (g)	Cont + PWDR (g)	After Drying (g)	Container (g)	Cont + PWDR (g)	After Drying (g)	Container (g)	Cont + PWDR (g)	After Drying (g)
196,9583	199,4487	199,4371	197,3374	199,8481	199,8436	197,0751	199,8579	199,8561
197,4316	199,8293	199,8173	197,289	199,5515	199,5477	197,4773	200,095	200,093
197,4873	199,7493	199,7411	197,1244	199,7203	199,7166	197,3669	199,8333	199,8314
	PWDR	Hum Mass		PWDR	Hum Mass		PWDR	Hum Mass
	2,4904	-0,0116		2,5107	-0,0045		2,7828	-0,0018
	2,3977	-0,012		2,2625	-0,0038		2,6177	-0,002
	2,262	-0,0082		2,5959	-0,0037		2,4664	-0,0019
	%MASS Dec	0,465788628		%MASS Dec	0,179232883		%MASS Dec	0,064683053
	%MASS Dec	0,500479626		%MASS Dec	0,167955801		%MASS Dec	0,076402949
	%MASS Dec	0,362511052		%MASS Dec	0,142532455		%MASS Dec	0,077035355
Average % decrease mass		0,442926436	Average % decrease mass		0,16324038	Average % decrease mass		0,072707119
STD Dev		0,071769365	STD Dev		0,018799116	STD Dev		0,006956235
% RSD (STD/AVG)		16,20345034	% RSD (STD/AVG)		11,51621668	% RSD (STD/AVG)		9,567475014

Table 2: Loss on drying determination results (Excipients)

Tablettose® 80			FlowLac® 100			Avicel® PH200		
Container (g)	Cont + PWDR (g)	After Drying (g)	Container (g)	Cont + PWDR (g)	After Drying (g)	Container (g)	Cont + PWDR (g)	After Drying (g)
197,3224	200,2804	200,2795	197,4121	199,8702	199,8594	197,3871	199,7508	199,6338
197,2735	199,5778	199,5776	197,4631	199,9113	199,8971	197,11	199,9194	199,7775
197,0899	199,5632	199,5608	197,1945	199,7491	199,7332	197,2557	199,6337	199,5153
	PWDR	Hum Mass		PWDR	Hum Mass		PWDR	Hum Mass
	2,958	-0,0009		2,4581	-0,0108		2,3637	-0,117
	2,3043	-0,0002		2,4482	-0,0142		2,8094	-0,1419
	2,4733	-0,0024		2,5546	-0,0159		2,378	-0,1184
	%MASS Dec	0,030425963		%MASS Dec	0,439363736		%MASS Dec	4,949866734
	%MASS Dec	0,008679425		%MASS Dec	0,580017972		%MASS Dec	5,050900548
	%MASS Dec	0,097036348		%MASS Dec	0,622406639		%MASS Dec	4,978973928
Average % decrease mass		0,045380579	Average % decrease mass		0,547262783	Average % decrease mass		4,99324707
STD Dev		0,046037668	STD Dev		0,095816767	STD Dev		0,052007209
% RSD (STD/AVG)		101,4479512	% RSD (STD/AVG)		17,50836535	% RSD (STD/AVG)		1,041550892

Table 2: Loss on drying determination results (Excipients) (continued)

Emcompress®			Cellactose® 80			MicroceLac® 100		
Container (g)	Cont + PWDR (g)	After Drying (g)	Container (g)	Cont + PWDR (g)	After Drying (g)	Container (g)	Cont + PWDR (g)	After Drying (g)
197,2332	200,4005	200,3088	197,0384	199,404	199,3207	197,245	199,5153	199,448
197,2659	199,751	199,6772	197,2231	199,9033	199,8029	197,0268	199,9186	199,8301
197,136	200,0852	200,0041	197,0078	199,3058	199,2273	197,4687	199,9605	199,8858
	PWDR	Hum Mass		PWDR	Hum Mass		PWDR	Hum Mass
	3,1673	-0,0917		2,3656	-0,0833		2,2703	-0,0673
	2,4851	-0,0738		2,6802	-0,1004		2,8918	-0,0885
	2,9492	-0,0811		2,298	-0,0785		2,4918	-0,0747
	%MASS Dec	2,895210432		%MASS Dec	3,521305377		%MASS Dec	2,964365943
	%MASS Dec	2,969699408		%MASS Dec	3,745989105		%MASS Dec	3,060377619
	%MASS Dec	2,749898277		%MASS Dec	3,416013925		%MASS Dec	2,997832892
Average % decrease mass		2,871602706	Average % decrease mass		3,561102803	Average % decrease mass		3,007525485
STD Dev		0,111786081	STD Dev		0,168549047	STD Dev		0,04873418
% RSD (STD/AVG)		3,89281151	% RSD (STD/AVG)		4,733057599	% RSD (STD/AVG)		1,620407875

Table 2: Loss on drying determination results (Excipients) (continued)

StarLac®		
Container (g)	Cont + PWDR (g)	After Drying (g)
197,4495	199,9542	199,8537
197,1199	199,8427	199,7408
197,3073	199,6161	199,5314
	PWDR	Hum Mass
	2,5047	-0,1005
	2,7228	-0,1019
	2,3088	-0,0847
	%MASS Dec	4,012456582
	%MASS Dec	3,742470986
	%MASS Dec	3,668572419
Average % decrease mass		3,807833329
STD Dev		0,181020044
% RSD (STD/AVG)		4,753885696

Appendix F

Hygroscopicity determination

This appendix contains hygroscopicity determination data.
Methods can be seen in Chapter 3.

Table 1: Hygroscopicity determination results (API's)

Paracetamol			Furosemide			Pyridoxine		
Container (g)	Cont + PWDR (g)	Hum + Time (g)	Container (g)	Cont + PWDR (g)	Hum + Time (g)	Container (g)	Cont + PWDR (g)	Hum + Time (g)
196,9587	199,4797	199,4799	197,3374	199,5434	199,5434	197,0728	199,6778	199,6789
197,4314	199,5568	199,5569	197,2899	199,5201	199,5204	197,4775	200,2279	200,2286
197,4856	199,6201	199,6208	197,1252	199,6145	199,6147	197,3659	200,3108	200,3116
	PWDR (g)	Hum Mass (g)		PWDR (g)	Hum Mass (g)		PWDR (g)	Hum Mass (g)
	2,521	0,0002		2,206	0		2,605	0,0011
	2,1254	0,0001		2,2302	0,0003		2,7504	0,0007
	2,1345	0,0007		2,4893	0,0002		2,9449	0,0008
	%MASS Inc	0,00793336		%MASS Inc	0		%MASS Inc	0,042226488
	%MASS Inc	0,004704997		%MASS Inc	0,013451708		%MASS Inc	0,025450844
	%MASS Inc	0,032794565		%MASS Inc	0,008034387		%MASS Inc	0,027165608
Average % mass increase		0,015144307	Average % mass increase		0,007162032	Average % mass increase		0,031614313
STD Dev		0,015370566	STD Dev		0,006768151	STD Dev		0,009230319
% RSD (STD/AVG)		101,4940164	% RSD (STD/AVG)		94,50043087	% RSD (STD/AVG)		29,1966457

Table 2: Hygroscopicity determination results (Excipients)

Tablettose® 80			FlowLac® 100			Avicel® PH200		
Container (g)	Cont + PWDR (g)	Hum + Time (g)	Container (g)	Cont + PWDR (g)	Hum + Time (g)	Container (g)	Cont + PWDR (g)	Hum + Time (g)
197,3234	199,3452	199,346	197,4114	199,5623	199,5623	197,3843	199,5623	199,5623
197,2732	199,4289	199,4305	197,4561	199,6695	199,6695	197,1077	199,6695	199,6695
197,0842	199,2223	199,2229	197,1917	199,2577	199,258	197,2523	199,2577	199,258
	PWDR (g)	Hum Mass (g)		PWDR (g)	Hum Mass (g)		PWDR (g)	Hum Mass (g)
	2,0218	0,0008		2,1509	0		2,178	0
	2,1557	0,0016		2,2134	0		2,5618	0
	2,1381	0,0006		2,066	0,0003		2,0054	0,0003
	%MASS Inc	0,039568701		%MASS Inc	0		%MASS Inc	0
	%MASS Inc	0,07422183		%MASS Inc	0		%MASS Inc	0
	%MASS Inc	0,028062298		%MASS Inc	0,014520813		%MASS Inc	0,014959609
Average % mass increase		0,047284277	Average % mass increase		0,004840271	Average % mass increase		0,004986536
STD Dev		0,02402755	STD Dev		0,008383595	STD Dev		0,008636934
% RSD (STD/AVG)		50,8150958	% RSD (STD/AVG)		173,2050808	% RSD (STD/AVG)		173,2050808

Table 2: Hygroscopicity determination results (Excipients) (continued)

Emcompress®			Cellactose® 80			MicroceLac® 100		
Container (g)	Cont + PWDR (g)	Hum + Time (g)	Container (g)	Cont + PWDR (g)	Hum + Time (g)	Container (g)	Cont + PWDR (g)	Hum + Time (g)
197,2345	199,4609	199,5255	197,2345	199,4609	199,5623	197,2409	199,5986	199,6345
197,2646	199,3649	199,436	197,2646	199,3649	199,6361	197,0235	199,797	199,8405
197,1381	199,3112	199,3746	197,1381	199,3112	199,68	197,4636	199,7385	199,7719
	PWDR (g)	Hum Mass (g)		PWDR (g)	Hum Mass (g)		PWDR (g)	Hum Mass (g)
	2,2264	0,0646		2,2264	0,1014		2,3577	0,0359
	2,1003	0,0711		2,1003	0,2712		2,7735	0,0435
	2,1731	0,0634		2,1731	0,3688		2,2749	0,0334
	%MASS Inc	2,901545095		%MASS Inc	4,554437657		%MASS Inc	1,522670399
	%MASS Inc	3,385230681		%MASS Inc	12,91244108		%MASS Inc	1,56841536
	%MASS Inc	2,917491142		%MASS Inc	16,97114721		%MASS Inc	1,468196404
Average % mass increase		3,068088973	Average % mass increase		11,47934198	Average % mass increase		1,519760721
STD Dev		0,274768478	STD Dev		6,331192525	STD Dev		0,050172796
% RSD (STD/AVG)		8,955688072	% RSD (STD/AVG)		55,15292196	% RSD (STD/AVG)		3,301361523

Table 2: Hygroscopicity determination results (Excipients) (continued)

StarLac®		
Container (g)	Cont + PWDR (g)	Hum + Time (g)
197,4307	199,8615	199,8786
197,1176	199,974	199,9949
197,3028	199,7266	199,7434
	PWDR (g)	Hum Mass (g)
	2,4308	0,0171
	2,8564	0,0209
	2,4238	0,0168
	%MASS Inc	0,703472108
	%MASS Inc	0,731690239
	%MASS Inc	0,693126496
Average % mass increase		0,709429614
STD Dev		0,019960198
% RSD (STD/AVG)		2,813555767

Appendix G

Particle size determination

This appendix contains raw and calculated flowability data.

Methods can be seen in Chapter 3.

Table 1: Size determination results for paracetamol

Paracetamol				
Sieve size	Vol % on sieve			
2000				
1700	0		0	
1400	0		0	
1180	0,03		0	
1000	0,12		0	
850	0,25		0	
710	0,38		0	
600	0,44		0,19	
500	0,51		0,46	
425	0,46		0,49	
355	0,53	2,72	0,53	1,67
300	0,57		0,53	
250	0,84		0,82	
212	1,13	2,54	1,24	2,59
180	1,66		1,97	
150	2,73		3,27	
125	3,9		4,52	
106	4,64	12,93	5,13	14,89
90	5,59		5,92	
75	7,21		7,32	
63	7,63		7,46	
53	8,02	28,45	7,59	28,29
45	7,75		7,16	
38	7,87		7,18	
0	37,73	53,35	38,22	52,56
Total	99,99	99,99	100	100

Paracetamol			
Sieve size	Average % Particles	STD DEV	%RSD
> 355µm	2,195	0,525	23,91799544
355µm - 212µm	2,565	0,025	0,974658869
212µm - 100µm	13,91	0,98	7,045291157
100µm - 50µm	28,37	0,08	0,281988016
< 50µm	52,955	0,395	0,745916344
Total	99,995		

Table 2: Size determination results for furosemide

Furosemide				
Sieve size	Vol % on sieve			
2000				
1700	0,14		0,24	
1400	0,35		0,58	
1180	0,42		0,68	
1000	0,44		0,71	
850	0,38		0,66	
710	0,26		0,62	
600	0,01		0,49	
500	0		0,5	
425	0		0,47	
355	0,03	2,03	0,56	5,51
300	0,18		0,53	
250	0,32		0,54	
212	0,34	0,84	0,43	1,5
180	0,34		0,37	
150	0,38		0,38	
125	0,46		0,43	
106	0,61	1,79	0,56	1,74
90	0,89		0,81	
75	1,44		1,31	
63	1,93		1,77	
53	2,55	6,81	2,36	6,25
45	3,09		2,9	
38	3,97		3,75	
0	81,46	88,52	78,37	85,02
Total	99,99	99,99	100,02	100,02

Furosemide			
Sieve size	Average % Particles	STD DEV	%RSD
> 355µm	3,77	1,74	46,15384615
355µm - 212µm	1,17	0,33	28,20512821
212µm - 100µm	1,765	0,025	1,416430595
100µm - 50µm	6,53	0,28	4,287901991
< 50µm	86,77	1,75	2,016826092
Total	100,005		

Table 3: Size determination results for pyridoxine

Pyridoxine				
Sieve size	Vol % on sieve			
2000				
1700	0		0	
1400	0		0	
1180	0		0	
1000	0		0	
850	0		0	
710	0		0	
600	0		0	
500	0		0	
425	0		0	
355	0,05	0,05	0	0
300	0,45		0,22	
250	1,5		1,37	
212	2,09	4,04	1,95	3,54
180	2,79		2,49	
150	3,99		3,38	
125	5		4,17	
106	5,4	17,18	4,6	14,64
90	6,06		5,39	
75	7,3		6,89	
63	7,2		7,24	
53	7,06	27,62	7,52	27,04
45	6,43		7,15	
38	6,28		7,18	
0	38,39	51,1	40,46	54,79
Total	99,99	99,99	100,01	100,01

Pyridoxine			
Sieve size	Average % Particles	STD DEV	%RSD
> 355µm	0,025	0,025	100
355µm - 212µm	3,79	0,25	6,596306069
212µm - 100µm	15,91	1,27	7,982401006
100µm - 50µm	27,33	0,29	1,061105013
< 50µm	52,945	1,845	3,484748324
Total	100		

Table 4: Size determination results for Tablettose® 80

Tablettose® 80				
Sieve size	Vol % on sieve			
2000				
1700	0		0	
1400	0		0	
1180	0		0	
1000	0		0	
850	0		0,07	
710	0,37		0,58	
600	1,37		1,49	
500	2,95		2,8	
425	4,13		3,66	
355	6,19	15,01	5,32	13,92
300	7,08		6,06	
250	8,58		7,48	
212	8,08	23,74	7,3	20,84
180	7,89		7,45	
150	8,26		8,22	
125	7,44		7,86	
106	5,95	29,54	6,62	30,15
90	5,2		6	
75	5,05		5,95	
63	4,19		4,93	
53	3,59	18,03	4,15	21,03
45	2,92		3,27	
38	2,54		2,75	
0	8,22	13,68	8,02	14,04
Total	100	100	99,98	99,98

Tablettose® 80			
Sieve size	Average % Particles	STD DEV	%RSD
> 355µm	14,465	0,545	3,767715175
355µm - 212µm	22,29	1,45	6,505159264
212µm - 100µm	29,845	0,305	1,021946725
100µm - 50µm	19,53	1,5	7,680491551
< 50µm	13,86	0,18	1,298701299
Total	99,99		

Table 5: Size determination results for FlowLac® 100

FlowLac® 100				
Sieve size	Vol % on sieve			
2000				
1700	0		0	
1400	0		0	
1180	0		0	
1000	0		0	
850	0		0	
710	0		0	
600	0		0	
500	0		0	
425	0,03		0,01	
355	0,82	0,85	0,51	0,52
300	2,27		1,83	
250	4,79		4,14	
212	6,71	13,77	6,07	12,04
180	8,78		8,23	
150	11,61		11,24	
125	12,43		12,44	
106	10,92	43,74	11,25	43,16
90	9,75		10,31	
75	9,01		9,76	
63	6,63		7,32	
53	4,83	30,22	5,36	32,75
45	3,28		3,58	
38	2,42		2,53	
0	5,74	11,44	5,43	11,54
Total	100,02	100,02	100,01	100,01

FlowLac® 100			
Sieve size	Average % Particles	STD DEV	%RSD
> 355µm	0,685	0,165	24,08759124
355µm - 212µm	12,905	0,865	6,702828361
212µm - 100µm	43,45	0,29	0,667433832
100µm - 50µm	31,485	1,265	4,017786247
< 50µm	11,49	0,05	0,43516101
Total	100,015		

Table 6: Size determination results for Avicel® PH200

Avicel® PH200				
Sieve size	Vol % on sieve			
2000				
1700	0		0	
1400	0		0	
1180	0		0	
1000	0		0	
850	0		0	
710	0		0	
600	0		0,13	
500	1,8		1,59	
425	3,71		3,4	
355	6,65	12,16	6,35	11,47
300	8,41		8,29	
250	10,85		10,9	
212	10,51	29,77	10,68	29,87
180	10,23		10,45	
150	10,33		10,59	
125	8,67		8,88	
106	6,28	35,51	6,4	36,32
90	4,89		4,94	
75	4,15		4,14	
63	3,01		2,96	
53	2,33	14,38	2,27	14,31
45	1,79		1,73	
38	1,52		1,48	
0	4,88	8,19	4,82	8,03
Total	100,01	100,01	100	100

Avicel® PH200			
Sieve size	Average % Particles	STD DEV	%RSD
> 355µm	11,815	0,345	2,920016928
355µm - 212µm	29,82	0,05	0,167672703
212µm - 100µm	35,915	0,405	1,127662537
100µm - 50µm	14,345	0,035	0,243987452
< 50µm	8,11	0,08	0,986436498
Total	100,005		

Table 7: Size determination results for Emcompress®

Emcompress®				
Sieve size	Vol % on sieve			
2000				
1700	0		0	
1400	0		0	
1180	0		0	
1000	0		0	
850	0		0	
710	0		0	
600	0		0	
500	0,36		0,36	
425	1,72		1,68	
355	4,79	6,87	4,65	6,69
300	8,15		7,89	
250	12,76		12,35	
212	13,74	34,65	13,33	33,57
180	13,7		13,34	
150	12,98		12,7	
125	9		8,86	
106	4,56	40,24	4,53	39,43
90	1,97		1,98	
75	0,51		0,53	
63	0,01		0,01	
53	0	2,49	0	2,52
45	0		0	
38	0,02		0,02	
0	15,75	15,77	17,78	17,8
Total	100,02	100,02	100,01	100,01

Emcompress®			
Sieve size	Average % Particles	STD DEV	%RSD
> 355µm	6,78	0,09	1,327433628
355µm - 212µm	34,11	0,54	1,583113456
212µm - 100µm	39,835	0,405	1,016693862
100µm - 50µm	2,505	0,015	0,598802395
< 50µm	16,785	1,015	6,047065833
Total	100,015		

Table 8: Size determination results for Cellactose® 80

Cellactose® 80				
Sieve size	Vol % on sieve			
2000				
1700	0		0	
1400	0		0	
1180	0		0	
1000	0		0	
850	0		0	
710	0		0	
600	0		0	
500	0,7		0,53	
425	2,18		2,15	
355	4,71	7,59	4,86	7,54
300	6,79		7,15	
250	9,65		10,25	
212	10,03	26,47	10,68	28,08
180	10,25		10,9	
150	10,7		11,33	
125	9,17		9,59	
106	6,71	36,83	6,87	38,69
90	5,3		5,25	
75	4,67		4,39	
63	3,66		3,22	
53	3,15	16,78	2,61	15,47
45	2,67		2,14	
38	2,46		1,95	
0	7,2	12,33	6,13	10,22
Total	100	100	100	100

Cellactose® 80			
Sieve size	Average % Particles	STD DEV	%RSD
> 355µm	7,565	0,025	0,330469266
355µm - 212µm	27,275	0,805	2,951420715
212µm - 100µm	37,76	0,93	2,462923729
100µm - 50µm	16,125	0,655	4,062015504
< 50µm	11,275	1,055	9,356984479
Total	100		

Table 9: Size determination results for MicroceLac® 100

MicroceLac® 100				
Sieve size	Vol % on sieve			
2000				
1700	0		0	
1400	0		0	
1180	0		0	
1000	0		0	
850	0		0	
710	0		0	
600	0		0	
500	0,04		0,03	
425	1,14		1,21	
355	3,51	10,26	3,11	4,35
300	5,57		5,04	
250	8,44		7,83	
212	9,29	27,76	8,85	21,72
180	10,03		9,79	
150	11,08		11,12	
125	10,05		10,37	
106	7,72	35,12	8,15	39,43
90	6,27		6,73	
75	5,53		5,99	
63	4,18		4,51	
53	3,39	15,83	3,61	20,84
45	2,73		2,84	
38	2,44		2,49	
0	8,33	10,77	8,31	13,64
Total	99,74	99,74	99,98	99,98

MicroceLac® 100			
Sieve size	Average % Particles	STD DEV	%RSD
> 355µm	7,305	2,955	0
355µm - 212µm	24,74	3,02	12,2069523
212µm - 100µm	37,275	2,155	5,781354795
100µm - 50µm	18,335	2,505	13,66239433
< 50µm	12,205	1,435	11,75747644
Total	99,86		

Table 10: Size determination results for StarLac®

	StarLac®			
Sieve size	Vol % on sieve			
2000				
1700	0		0	
1400	0		0	
1180	0		0	
1000	0		0	
850	0		0	
710	0		0	
600	0		0	
500	0		0	
425	0,08		0,04	
355	1,83	1,91	1,25	1,29
300	4,05		3,36	
250	7,53		6,6	
212	9,42	21	8,55	18,51
180	11,07		10,32	
150	13		12,45	
125	12,19		12,05	
106	9,37	45,63	9,58	44,4
90	7,37		7,83	
75	6,05		6,69	
63	4,09		4,7	
53	2,95	20,46	3,45	22,67
45	2,17		2,53	
38	1,86		2,13	
0	6,99	11,02	8,45	13,11
Total	100,02	100,02	99,98	99,98

StarLac®			
Sieve size	Average % Particles	STD DEV	%RSD
> 355µm	1,6	0,31	19,375
355µm - 212µm	19,755	1,245	6,302201974
212µm - 100µm	45,015	0,615	1,366211263
100µm - 50µm	21,565	1,105	5,124043589
< 50µm	12,065	1,045	8,661417323
Total	100		

Table 11: Homogeneity index analysis results paracetamol

Homogeneity index	Iθ				
Paracetamol					
Sieve size	AVG Size				
355-500	427	2.195	Fm+4	402	882.39
212-355	283	2.565	Fm+3	258	661.77
100-212	156	13.91	Fm+2	131	1822.21
50-100	75	28.37	Fm+1	50	1418.5
0-50	25	52.955	Fm	0	0
	Paracetamol				
	Iθ	0.010841			
	%< 50µm	52.955			

Table 12: Homogeneity index analysis results furosemide

Homogeneity index	Iθ				
Furosemide					
Sieve size	AVG Size				
355-500	427	3.77	Fm+4	402	1515.54
212-355	283	1.17	Fm+3	258	301.86
100-212	156	1.765	Fm+2	131	231.215
50-100	75	6.53	Fm+1	50	326.5
0-50	25	86.77	Fm	0	0
	Furosemide				
	Iθ	0.035057			
	%< 50µm	86.77			

Table 13: Homogeneity index analysis results pyridoxine

Homogeneity index	Iθ				
Pyridoxine					
Sieve size	AVG Size				
355-500	427	0.025	Fm+4	402	10.05
212-355	283	3.79	Fm+3	258	977.82
100-212	156	15.91	Fm+2	131	2084.21
50-100	75	27.33	Fm+1	50	1366.5
0-50	25	52.945	Fm	0	0
	Pyridoxine				
	Iθ	0.011666			
	%< 50µm	52.945			

Table 14: Homogeneity index analysis results Tablettose® 80

Homogeneity index	Iθ				
	Tablettose® 80				
Sieve sizes	AVG Size				
355-500	427	14.465	Fm+2	271	3920.015
212-355	283	22.29	Fm+1	127	2830.83
100-212	156	29.845	Fm	0	0
50-100	75	19.53	Fm-1	81	1581.93
0-50	25	13.86	Fm-2	131	1815.66

Tablettose® 80	
Iθ	0.002912
%< 50µm	13.86

Table 15: Homogeneity index analysis results FlowLac® 100

Homogeneity index	Iθ				
	FlowLac® 100				
Sieve size	AVG Size				
355-500	427	0.685	Fm+2	271	185.635
212-355	283	12.905	Fm+1	127	1638.935
100-212	156	43.45	Fm	0	0
50-100	75	31.485	Fm-1	81	2550.285
0-50	25	11.49	Fm-2	131	1505.19

FlowLac® 100	
Iθ	0.007266
%< 50µm	11.49

Table 16: Homogeneity index analysis results Avicel® PH200

Homogeneity index	Iθ				
	Avicel® PH200				
Sieve size	AVG Size				
355-500	427	11.815	Fm+2	271	3201.865
212-355	283	29.82	Fm+1	127	3787.14
100-212	156	35.915	Fm	0	0
50-100	75	14.345	Fm-1	81	1161.945
0-50	25	8.11	Fm-2	131	1062.41

Avicel® PH200	
Iθ	0.003856
%< 50µm	8.11

Table 17: Homogeneity index analysis results Emcompress®

Homogeneity index	Iθ				
	Emcompress®				
Sieve size	AVG Size				
355-500	427	6.78	Fm+2	271	1837.38
212-355	283	34.11	Fm+1	127	4331.97
100-212	156	39.835	Fm	0	0
50-100	75	2.505	Fm-1	81	202.905
0-50	25	16.785	Fm-2	131	2198.835
	Emcompress®				
	Iθ	0.004594			
	%< 50µm	16.785			

Table 18: Homogeneity index analysis results Cellactose® 80

Homogeneity index	Iθ				
	Cellactose® 80				
Sieve size	AVG Size				
355-500	427	7.565	Fm+2	271	2050.115
212-355	283	27.275	Fm+1	127	3463.925
100-212	156	37.76	Fm	0	0
50-100	75	16.125	Fm-1	81	1306.125
0-50	25	11.275	Fm-2	131	1477.025
	Cellactose® 80				
	Iθ	0.004497			
	%< 50µm	11.275			

Table 19: Homogeneity index analysis results MicroceLac® 100

Homogeneity index	Iθ				
	MicroceLac® 100				
Sieve size	AVG Size				
355-500	427	7.305	Fm+2	271	1979.655
212-355	283	24.74	Fm+1	127	3141.98
100-212	156	37.275	Fm	0	0
50-100	75	18.335	Fm-1	81	1485.135
0-50	25	12.205	Fm-2	131	1598.855
	MicroceLac® 100				
	Iθ	0.004488			
	%< 50µm	12.205			

Table 20: Homogeneity index analysis results StarLac®

Homogeneity index	Iθ				
	StarLac®				
Sieve size	AVG Size				
355-500	427	1.6	Fm+2	271	433.6
212-355	283	19.755	Fm+1	127	2508.885
100-212	156	45.015	Fm	0	0
50-100	75	21.565	Fm-1	81	1746.765
0-50	25	12.065	Fm-2	131	1580.515
	StarLac®				
	Iθ	0.007067			
	%< 50µm	12.065			

Appendix H

SeDeM Expert Diagram System determination results

This appendix contains raw and calculated data which was used to create SeDeM Diagrams of each different pharmaceutical powder. Methods can be seen in Chapter 3.

Table 1: SeDeM determination results paracetamol

Paracetamol		Raw data	SeDem Calculation	Incidence
Bulk Density	Db	0.424606266	4.246062657	Dimension
Tapped Density	Dt	0.651280222	6.512802217	5.379432437
Inter-particle Porosity	Ie	0.818860584	6.8238382	Compressibility
Carr's Index	Carr	34.77042746	6.954085493	
Cohesion Index	Coh-Index	16.1	0.805	4.860974564
Hausner Ratio	Hausner	1.533513895	7.332430524	Flowability
Angle Of Repose	θ	44.13682659	1.172634683	
Powder Flow	t	20	0	2.835021736
Loss on Drying	%HR	0.442926436	9.557073564	Lubricity/Stability
Higroscopicity	%H	0.015144307	9.992427846	9.774750705
Particles < 50µm	%<50	50	0	Lubricity/Dosage
Homogeneity Index	Iθ	0.010840616	5.420308012	2.710154006

Paracetamol			
Parameter Index	IP	0.583333333	Acceptable
Paramatric Profile Index	IPP	4.9013886	Fail
Good Compression Index	IGC	4.666121947	Fail

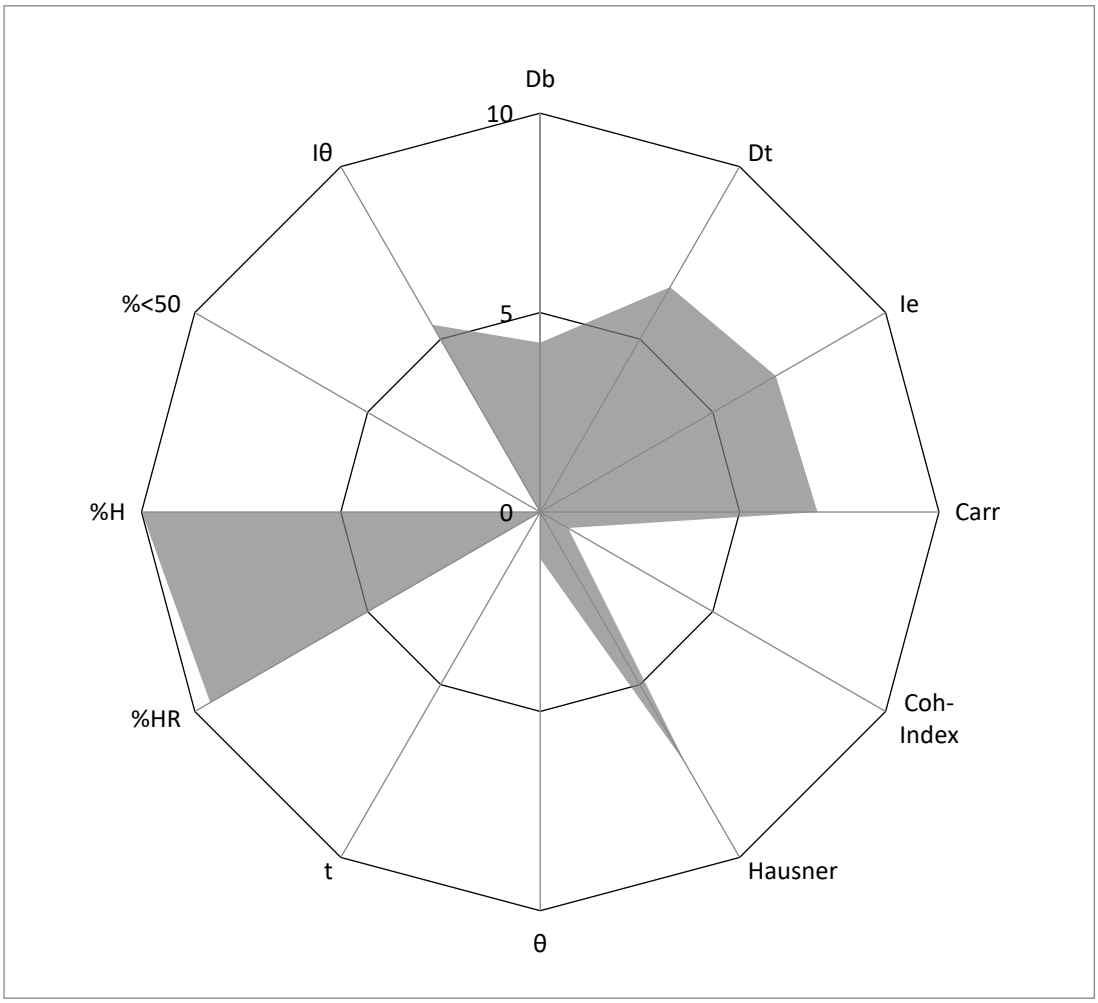


Figure 1: SeDeM Diagram for paracetamol

Table 2: SeDeM determination results furosemide

Furosemide		Raw data	SeDem Calculation	Incidence
Bulk Density	Db	0.238683411	2.386834107	Dimension
Tapped Density	Dt	0.410403999	4.104039991	3.245437049
Inter-particle Porosity	Ie	1.752990785	10	Compressibility
Carr's Index	Carr	41.83963717	8.367927435	
Cohesion Index	Coh-Index	0	0	6.122642478
Hausner Ratio	Hausner	1.719454485	6.402727576	Flowability
Angle Of Repose	θ	40.58224195	1.883551609	
Powder Flow	t	20	0	2.762093062
Loss on Drying	%HR	0.16324038	9.83675962	Lubricity/Stability
Higroscopicity	%H	0.007162032	9.996418984	9.916589302
Particles < 50µm	%<50	50	0	Lubricity/Dosage
Homogeneity Index	Iθ	0.02	10	5

Furosemide			
Parameter Index	IP	0.5	Acceptable
Paramatric Profile Index	IPP	5.248188277	Acceptable
Good Compression Index	IGC	4.99627524	Fail

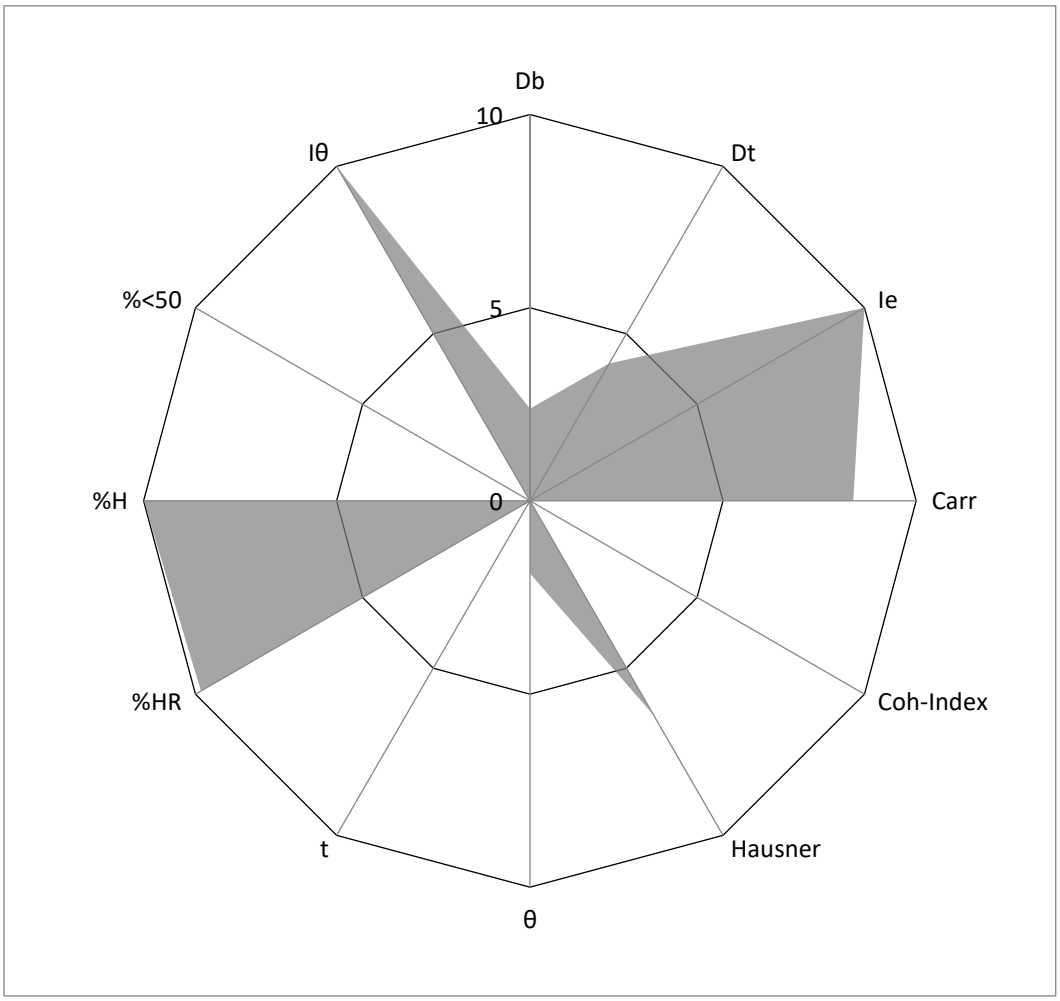


Figure 2: SeDeM Diagram for furosemide

Table 3: SeDeM determination results pyridoxine

Pyridoxine		Raw data	SeDem Calculation	Incidence
Bulk Density	Db	0.624641718	6.246417181	Dimension
Tapped Density	Dt	0.999650284	9.996502837	8.121460009
Inter-particle Porosity	Ie	0.600337099	5.002809159	Compressibility
Carr's Index	Carr	37.50128601	7.500257202	
Cohesion Index	Coh-Index	31.9	1.595	4.699355453
Hausner Ratio	Hausner	1.600252893	6.998735534	Flowability
Angle Of Repose	θ	45.23445583	0.953108834	
Powder Flow	t	20	0	2.650614789
Loss on Drying	%HR	0.072707119	9.927292881	Lubricity/Stability
Higroscopicity	%H	0.031614313	9.984192843	9.955742862
Particles < 50µm	%<50	50	0	Lubricity/Dosage
Homogeneity Index	Iθ	0.011665543	5.832771484	2.916385742

Pyridoxine			
Parameter Index	IP	0.666666667	Acceptable
Paramatric Profile Index	IPP	5.336423996	Acceptable
Good Compression Index	IGC	5.080275644	Acceptable

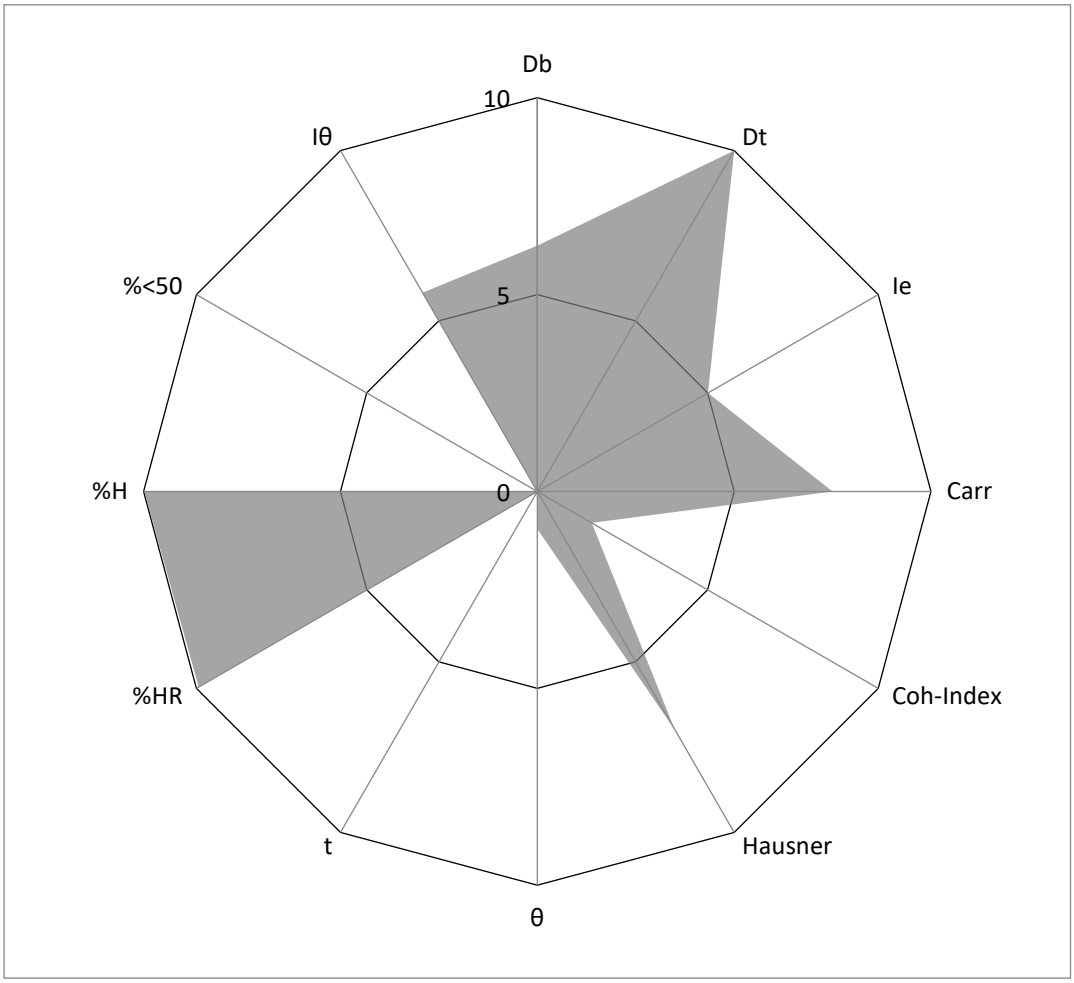


Figure 3: SeDeM Diagram for pyridoxine

Table 4: SeDeM determination results Tablettose® 80

Tablettose® 80		Raw data	SeDem Calculation	Incidence
Bulk Density	Db	0.59293511	5.9293511	Dimension
Tapped Density	Dt	0.777879639	7.77879639	6.854073745
Inter-particle Porosity	Ie	0.400931251	3.341093755	Compressibility
Carr's Index	Carr	23.76954612	4.753909225	
Cohesion Index	Coh-Index	147.1	7.355	5.150000993
Hausner Ratio	Hausner	1.311954803	8.440225984	Flowability
Angle Of Repose	θ	34.10181326	3.179637347	
Powder Flow	t	7.178743787	6.410628106	6.010163813
Loss on Drying	%HR	0.045380579	9.954619421	Lubricity/Stability
Higroscopicity	%H	0.047284277	9.976357862	9.965488641
Particles < 50µm	%<50	13.86	7.228	Lubricity/Dosage
Homogeneity Index	Iθ	0.002912152	1.456075976	4.342037988

Tablettose® 80			
Parameter Index	IP	0.666666667	Acceptable
Paramatric Profile Index	IPP	6.316974597	Acceptable
Good Compression Index	IGC	6.013759817	Acceptable

Figure 4: SeDeM Diagram for Tablettose® 80

Table 5: SeDeM determination results FlowLac® 100

FlowLac® 100		Raw data	SeDem Calculation	Incidence
Bulk Density	Db	0.605752402	6.057524024	Dimension
Tapped Density	Dt	0.687057661	6.870576606	6.464050315
Inter-particle Porosity	Ie	0.195398765	1.62832304	Compressibility
Carr's Index	Carr	11.83078953	2.366157906	
Cohesion Index	Coh-Index	175.3	8.765	4.253160315
Hausner Ratio	Hausner	1.134282322	9.32858839	Flowability
Angle Of Repose	θ	29.56469072	4.087061857	
Powder Flow	t	5.222019245	7.388990377	6.934880208
Loss on Drying	%HR	0.547262783	9.452737217	Lubricity/Stability
Higroscopicity	%H	0.004840271	9.997579864	9.725158541
Particles < 50µm	%<50	11.49	7.702	Lubricity/Dosage
Homogeneity Index	Iθ	0.007265832	3.632915806	5.667457903

FlowLac® 100			
Parameter Index	IP	0.666666667	Acceptable
Paramatric Profile Index	IPP	6.439787924	Acceptable
Good Compression Index	IGC	6.130678104	Acceptable

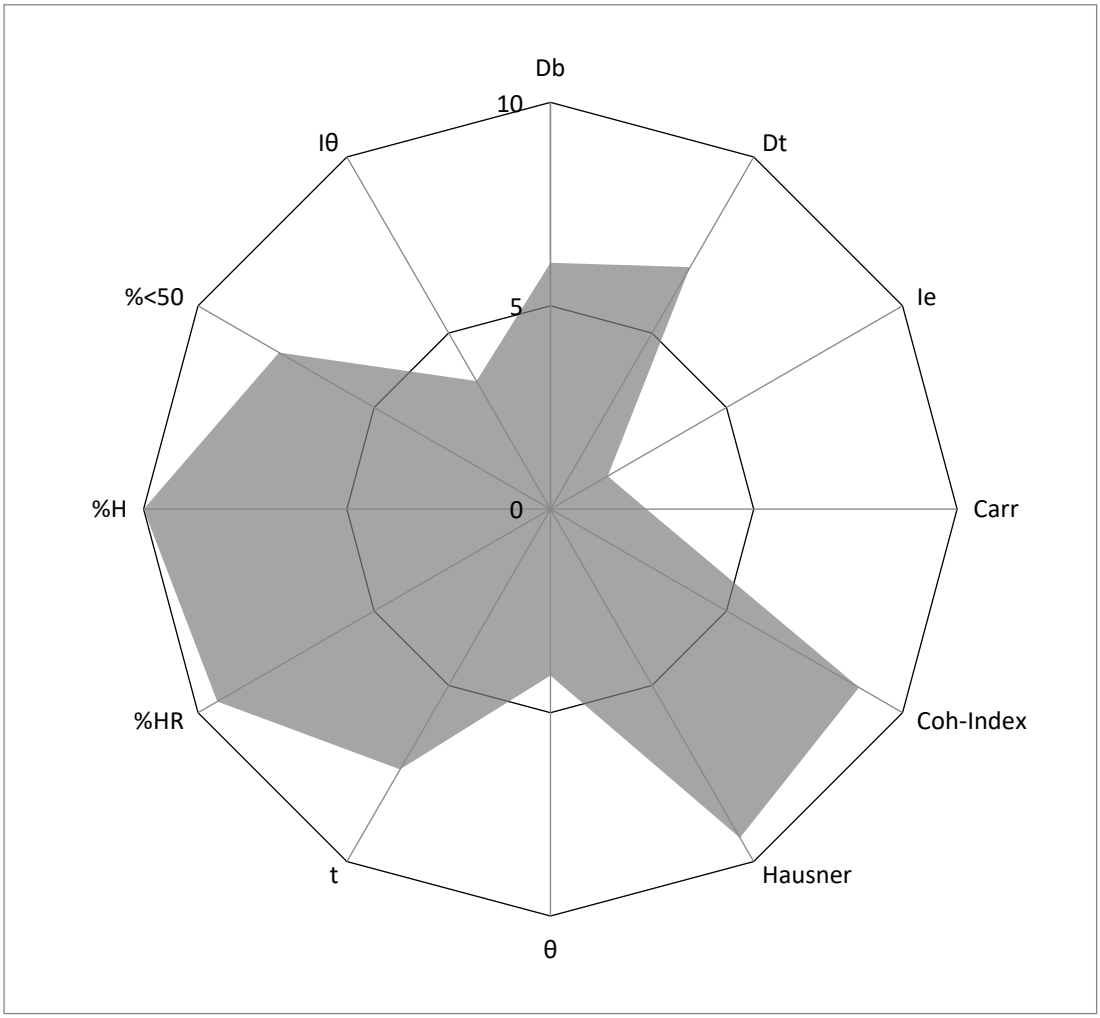


Figure 5: SeDeM Diagram for Flowlac® 100

Table 6: SeDeM determination results Avicel® PH200

Avicel® PH200		Raw data	SeDem Calculation	Incidence
Bulk Density	Db	0.372929756	3.729297558	Dimension
Tapped Density	Dt	0.464356098	4.643560976	4.186429267
Inter-particle Porosity	Ie	0.527961276	4.399677304	Compressibility
Carr's Index	Carr	19.68825142	3.937650285	
Cohesion Index	Coh-Index	200	10	6.11244253
Hausner Ratio	Hausner	1.245161776	8.774191118	Flowability
Angle Of Repose	θ	30.43653691	3.912692618	
Powder Flow	t	8.720470452	5.639764774	6.108882836
Loss on Drying	%HR	4.99324707	5.00675293	Lubricity/Stability
Higroscopicity	%H	0.004986536	9.997506732	7.502129831
Particles < 50µm	%<50	8.11	8.378	Lubricity/Dosage
Homogeneity Index	Iθ	0.003856288	1.928144085	5.153072043

Avicel® PH200			
Parameter Index	IP	0.5	Acceptable
Paramatric Profile Index	IPP	5.862269865	Acceptable
Good Compression Index	IGC	5.580880911	Acceptable

Figure 6: SeDeM Diagram for Avicel® PH200

Table 7: SeDeM determination results Emcompress®

Emcompress®		Raw data	SeDem Calculation	Incidence
Bulk Density	Db	0.88299927	8.829992701	Dimension
Tapped Density	Dt	1	10	9.414996351
Inter-particle Porosity	Ie	0.216662292	1.805519104	Compressibility
Carr's Index	Carr	19.13012792	3.826025584	
Cohesion Index	Coh-Index	130	6.5	4.043848229
Hausner Ratio	Hausner	1.236596855	8.817015723	Flowability
Angle Of Repose	θ	34.51752616	3.096494768	
Powder Flow	t	3.969825389	8.015087306	6.642865932
Loss on Drying	%HR	2.871602706	7.128397294	Lubricity/Stability
Higroscopicity	%H	3.068088973	8.465955514	7.797176404
Particles < 50µm	%<50	16.785	6.643	Lubricity/Dosage
Homogeneity Index	Iθ	0.004594001	2.297000723	4.470000362

Emcompress®			
Parameter Index	IP	0.666666667	Acceptable
Paramatric Profile Index	IPP	6.28537406	Acceptable
Good Compression Index	IGC	5.983676105	Acceptable

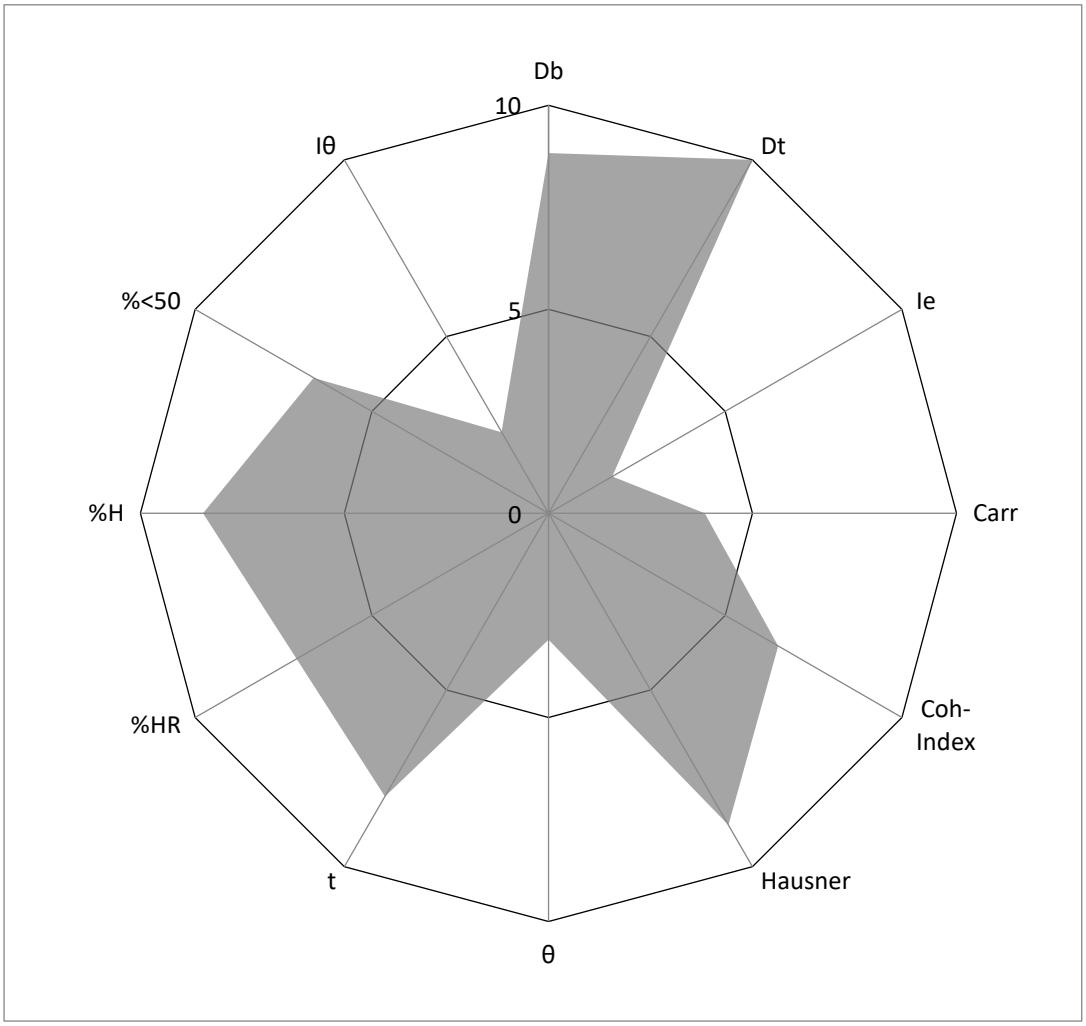


Figure 7: SeDeM Diagram for Emcompress®

Table 8: SeDeM determination results Cellactose® 80

Cellactose® 80		Raw data	SeDem Calculation	Incidence
Bulk Density	Db	0.436631385	4.36631385	Dimension
Tapped Density	Dt	0.544309244	5.443092435	4.904703142
Inter-particle Porosity	Ie	0.453081347	3.775677889	Compressibility
Carr's Index	Carr	19.78013215	3.95602643	
Cohesion Index	Coh-Index	147.7	7.385	5.03890144
Hausner Ratio	Hausner	1.246648314	8.766758431	Flowability
Angle Of Repose	θ	32.82417111	3.435165778	
Powder Flow	t	8.765331337	5.617334331	5.939752847
Loss on Drying	%HR	3.561102803	6.438897197	Lubricity/Stability
Higroscopicity	%H	11.47934198	4.260329009	5.349613103
Particles < 50µm	%<50	11.275	7.745	Lubricity/Dosage
Homogeneity Index	Iθ	0.004496742	2.248371181	4.996685591

Cellactose® 80			
Parameter Index	IP	0.5	Acceptable
Paramatric Profile Index	IPP	5.286497211	Acceptable
Good Compression Index	IGC	5.032745345	Acceptable

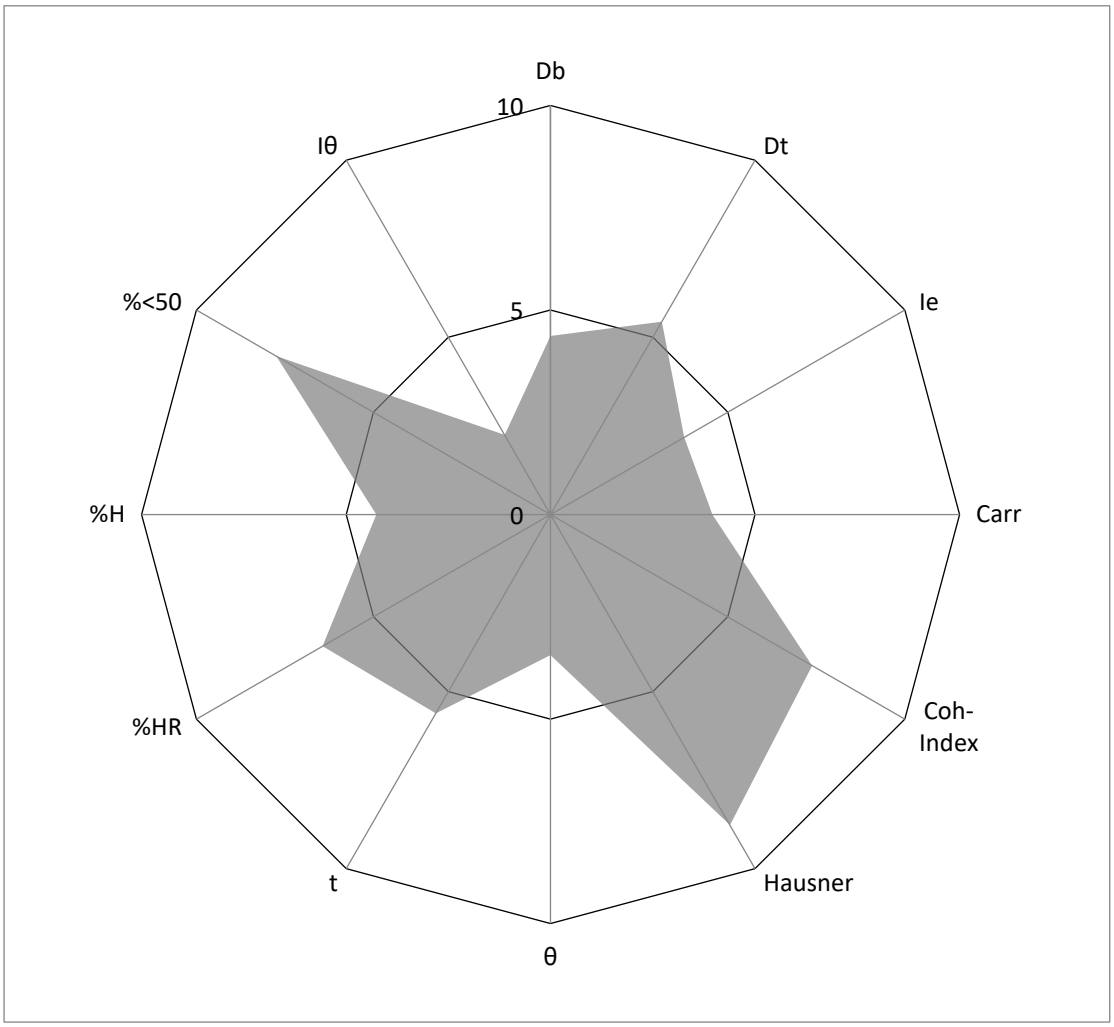


Figure 8: SeDeM Diagram for Cellactose® 80

Table 9: SeDeM determination results MicroceLac® 100

MicroceLac® 100		Raw data	SeDem Calculation	Incidence
Bulk Density	Db	0.477352806	4.773528056	Dimension
Tapped Density	Dt	0.569687322	5.696873225	5.23520064
Inter-particle Porosity	Ie	0.339512505	2.829270878	Compressibility
Carr's Index	Carr	16.20651527	3.241303055	
Cohesion Index	Coh-Index	157.5	7.875	4.648524644
Hausner Ratio	Hausner	1.193432925	9.032835376	Flowability
Angle Of Repose	θ	29.38766086	4.122467828	
Powder Flow	t	5.484685299	7.257657351	6.804320185
Loss on Drying	%HR	3.007525485	6.992474515	Lubricity/Stability
Higroscopicity	%H	1.519760721	9.240119639	8.116297077
Particles < 50µm	%<50	12.205	7.559	Lubricity/Dosage
Homogeneity Index	Iθ	0.004487922	2.243961171	4.901480585

MicroceLac® 100			
Parameter Index	IP	0.583333333	Acceptable
Paramatric Profile Index	IPP	5.905374258	Acceptable
Good Compression Index	IGC	5.621916293	Acceptable

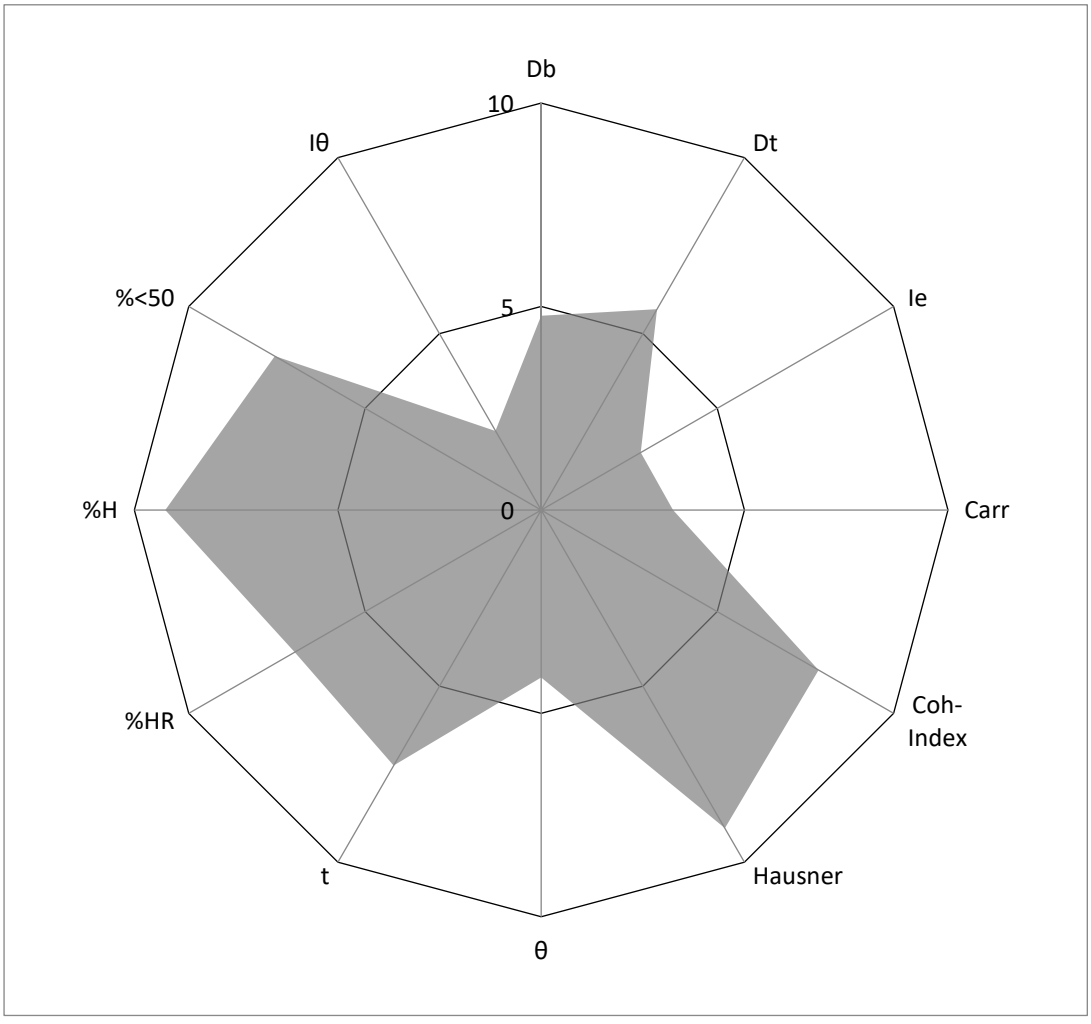


Figure 9: SeDeM Diagram for MicroceLac® 100

Table 10: SeDeM determination results StarLac®

StarLac®		Raw data	SeDem Calculation	Incidence
Bulk Density	Db	0.592259681	5.922596806	Dimension
Tapped Density	Dt	0.701089377	7.010893765	6.466745285
Inter-particle Porosity	Ie	0.261922991	2.182691588	Compressibility
Carr's Index	Carr	15.51347589	3.102695178	
Cohesion Index	Coh-Index	121.6	6.08	3.788462256
Hausner Ratio	Hausner	1.18373569	9.081321548	Flowability
Angle Of Repose	θ	31.0763247	3.784735059	
Powder Flow	t	8.426590155	5.786704922	6.217587177
Loss on Drying	%HR	3.807833329	6.192166671	Lubricity/Stability
Higroscopicity	%H	0.709429614	9.645285193	7.918725932
Particles < 50µm	%<50	12.065	7.587	Lubricity/Dosage
Homogeneity Index	Iθ	0.00706698	3.533489854	5.560244927

StarLac®			
Parameter Index	IP	0.666666667	Acceptable
Paramatric Profile Index	IPP	5.825798382	Acceptable
Good Compression Index	IGC	5.54616006	Acceptable

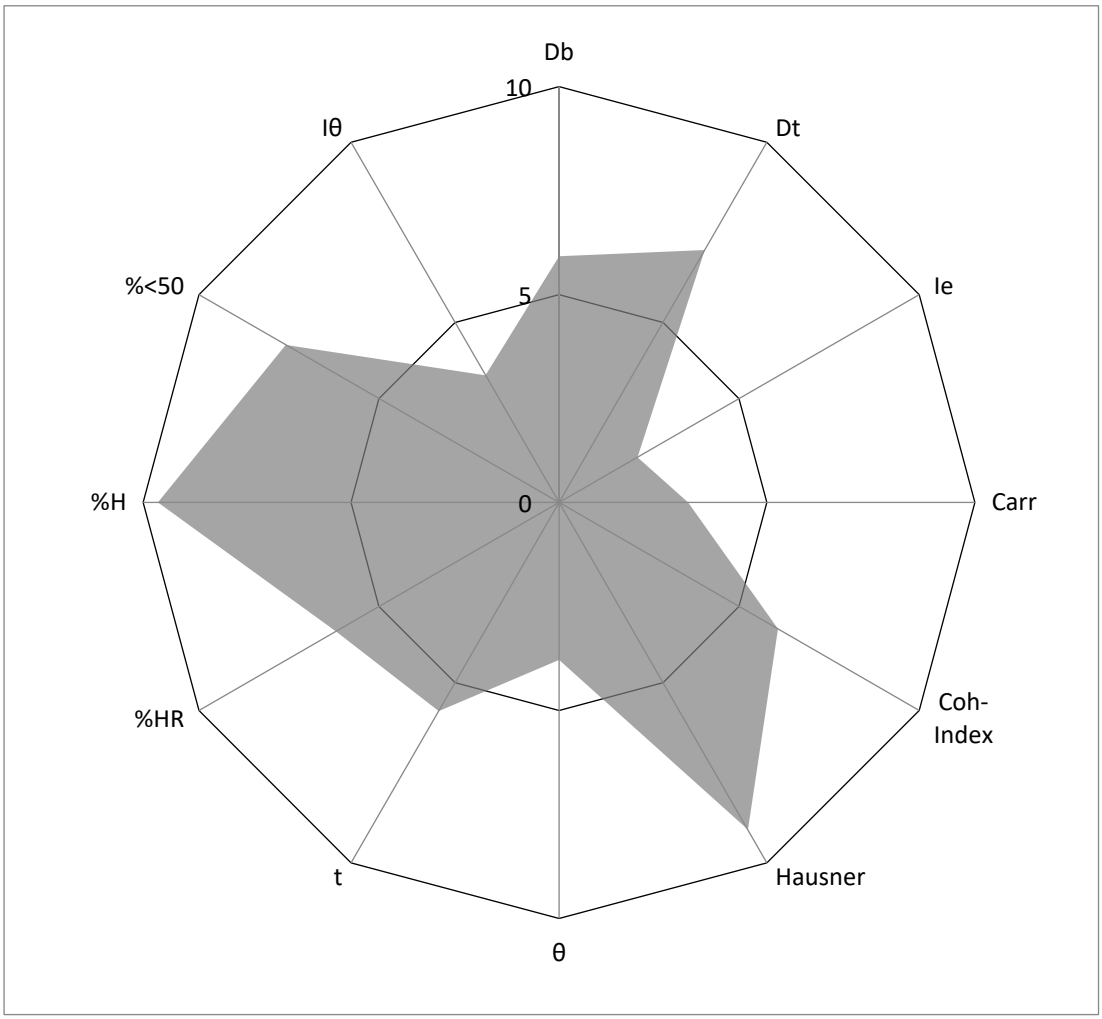


Figure 10: SeDeM Diagram for StarLac®

Appendix I

Tableting results for paracetamol formulations

This appendix contains raw and calculated results of formulations of paracetamol combined with different excipients (in different concentrations). Methods can be seen in Chapter 3. Tablet formulations are indicated with the API, API concentration and lastly the excipient.

Tableting results (Paracetamol)

Table 1: Formulations of paracetamol (5 % w/w) with Tablettose® 80

Formula: Paracetamol 05 Tablettose® 80

Uniformity of Weight		
Tab No.	Weight (g)	
1	394.4	Pass
2	396	Pass
3	397	Pass
4	393.6	Pass
5	382.4	Pass
6	401.1	Pass
7	394.1	Pass
8	379.7	Pass
9	393.7	Pass
10	391.7	Pass
11	393.9	Pass
12	394.8	Pass
13	392.8	Pass
14	393.2	Pass
15	393.1	Pass
16	397	Pass
17	396	Pass
18	396.7	Pass
19	394.4	Pass
20	388.5	Pass
Average	393.205	
STD Dev	4.865396073	
% RSD (ST	1.237368821	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	3.81	10.04	70	1.164982696
2	3.8	10.03	75	1.252728208
3	3.83	10.03	84	1.392065602
4	3.82	10.05	77	1.276854535
5	3.83	10.06	73	1.206163629
6	3.83	10.06	66	1.090504103
7	3.81	10.06	73	1.212495196
8	3.8	10.05	80	1.333584231
9	3.82	10.05	80	1.326602115
10	3.81	10.06	77	1.278933289
Average	3.816	10.049	75.5	1.25349136
STD Dev	0.011737878	0.01197219	5.275730597	0.088490936
% RSD (STI	0.307596381	0.119138123	6.987722645	7.059556942

Friability	(Enough tablets to be near as possible to 6.5g)			
Weight (g)	6.6612			
Before		Broken?		
Cracked?	6.6333			
After	0.420605129			Pass

Table 2: Formulations of paracetamol (10 % w/w) with Tablettose® 80

Formula: Paracetamol 10 Tablettose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	386.7	Pass		1	3.75	10.04	83	1.403438011
2	389.6	Pass		2	3.76	10.06	73	1.228618803
3	385.5	Pass		3	3.73	10.07	78	1.322015123
4	388.9	Pass		4	3.69	10.06	68	1.166177583
5	383.7	Pass		5	3.75	10.08	82	1.381027019
6	386.9	Pass		6	3.77	10.08	73	1.222928597
7	386.3	Pass		7	3.71	10.05	83	1.417157906
8	389.5	Pass		8	3.76	10.05	71	1.196147027
9	379.4	Pass		9	3.73	10.07	70	1.186423829
10	369.7	Pass		10	3.72	10.07	76	1.29157998
11	389.7	Pass		Average	3.737	10.063	75.7	1.281551388
12	379.7	Pass		STD Dev	0.025407785	0.013374935	5.578729445	0.09473444
13	382.8	Pass		% RSD (STI	0.679897922	0.132912005	7.369523706	7.392168651
14	380.8	Pass						
15	385.3	Pass						
16	386.7	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	387.6	Pass		Weight (g)	6.5323			
18	386.3	Pass		Before		Broken?		
19	382.3	Pass		Cracked?	6.5001			
20	385.6	Pass		After	0.495376994			Pass
Average	384.65							
STD Dev	4.709955861							
% RSD (ST	1.224478321							

Table 3: Formulations of paracetamol (15 % w/w) with Tablettose® 80

Formula: Paracetamol 15 Tablettose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	374.5	Pass		1	3.73	10.03	82	1.395353386
2	379.9	Pass		2	3.67	10.06	63	1.086317129
3	384.6	Pass		3	3.72	10.05	74	1.260093702
4	384.5	Pass		4	3.67	10.05	58	1.00109661
5	384.1	Pass		5	3.77	10.04	56	0.941874604
6	380.7	Pass		6	3.72	10.06	67	1.139761558
7	381.1	Pass		7	3.72	10.07	78	1.325568927
8	380.4	Pass		8	3.74	10.05	72	1.219480768
9	381	Pass		9	3.7	10.05	61	1.044340624
10	374.5	Pass		10	3.67	10.04	67	1.157591019
11	378.6	Pass		Average	3.711	10.05	67.8	1.157147833
12	384.5	Pass		STD Dev	0.033482997	0.011547005	8.612652192	0.144656789
13	385.7	Pass		% RSD (STI	0.902263469	0.114895576	12.70302683	12.50115021
14	380.5	Pass						
15	371.4	Pass						
16	385.9	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	382.8	Pass		Weight (g)	6.4607			
18	362.4	Pass		Before		Broken?		
19	369.4	Pass		Cracked?	6.4285			
20	361.4	Pass		After	0.500894454			Pass
Average	378.395							
STD Dev	7.28989748							
% RSD (ST	1.926531133							

Table 4: Formulations of paracetamol (20 % w/w) with Tablettose® 80

Formula: Paracetamol 20 Tablettose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	377.2	Pass		1	3.39	9.62	38	0.741803622
2	364.1	Pass		2	3.72	9.63	53	0.941860894
3	378.1	Pass		3	3.8	9.63	45	0.782857566
4	376	Pass		4	3.8	9.64	39	0.677772743
5	372.4	Pass		5	3.8	9.63	55	0.956825914
6	376.8	Pass		6	3.77	9.61	54	0.948875307
7	377.8	Pass		7	3.78	9.63	40	0.699555261
8	374.9	Pass		8	3.73	9.63	57	1.010229066
9	378.9	Pass		9	3.72	9.62	49	0.871682227
10	375.5	Pass		10	3.72	9.61	52	0.926013118
11	371	Pass		Average	3.723	9.625	48.2	0.855747572
12	372.4	Pass		STD Dev	0.12211561	0.009718253	7.161626134	0.120059271
13	377	Pass		% RSD (STD	3.280032502	0.100968864	14.85814551	14.02975305
14	372.2	Pass						
15	377.2	Pass						
16	378.6	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	377	Pass		Weight (g)	6.376	6.382	6.371	
18	374.1	Pass		Cracked?	Yes	Broken?	Yes	
19	376.2	Pass		After (g)	5.9023	5.8053	5.9375	
20	378.9	Pass		Diff %	8.025684902	9.934025804	7.301052632	Fail, redo
Average	375.315			Average	8.420254446	Fail		
STD Dev	3.549985174			STD Dev	1.360110575			
% RSD (ST	0.945868184			% RSD (STD	16.15284411			

Table 5: Formulations of paracetamol (17 % w/w) with FlowLac® 100

Formula: Paracetamol 17 FlowLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	391.8	Pass		1	3.95	10.07	80	1.280393745
2	387.9	Pass		2	3.94	10.05	85	1.366585364
3	391	Pass		3	3.93	10.03	93	1.501998808
4	390	Pass		4	3.93	10.1	72	1.154778515
5	387.4	Pass		5	3.93	10.07	94	1.512118949
6	387.2	Pass		6	3.95	10.05	94	1.507456606
7	388.1	Pass		7	3.9	10.06	81	1.31432435
8	384.6	Pass		8	3.92	10.05	89	1.438195749
9	382.4	Pass		9	3.9	10.05	83	1.34811688
10	387.6	Pass		10	3.92	10.06	91	1.469053011
11	386.3	Pass		Average	3.927	10.059	86.2	1.389302198
12	389.3	Pass		STD Dev	0.017669811	0.018529256	7.284687136	0.117941646
13	388.8	Pass		% RSD (STI	0.449956991	0.184205748	8.450913151	8.489272272
14	386.9	Pass						
15	389.5	Pass						
16	387.6	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	384.3	Pass		Weight (g)	6.5808			
18	384.4	Pass		Before		Broken?		
19	390.6	Pass		Cracked?	6.5515			
20	384.9	Pass		After	0.447225826			Pass
Average	387.53							
STD Dev	2.502440914							
% RSD (ST	0.645741211							

Table 6: Formulations of paracetamol (22 % w/w) with FlowLac® 100

Formula: Paracetamol 22 FlowLac® 100

Uniformity of Weight		
Tab No.	Weight (g)	
1	379.9	Pass
2	403.2	Pass
3	376.9	Pass
4	377.9	Pass
5	403.9	Pass
6	389.3	Pass
7	387.3	Pass
8	399.5	Pass
9	381.2	Pass
10	393.2	Pass
11	385.6	Pass
12	374.7	Pass
13	403.6	Pass
14	385.9	Pass
15	397.1	Pass
16	406.4	Pass
17	396.6	Pass
18	384.3	Pass
19	392.7	Pass
20	373.6	Pass
Average	389.64	
STD Dev	10.50685991	
% RSD (ST	2.696555773	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	3.8	10.02	116	1.939486648
2	3.95	10.01	153	2.463430877
3	4	10.09	61	0.962185484
4	3.85	10.03	148	2.439945781
5	3.87	10.03	132	2.164921513
6	3.96	10.07	124	1.979598662
7	3.9	10.04	148	2.406265357
8	3.77	10.02	106	1.786392622
9	3.83	10.16	118	1.930499299
10	3.85	10.03	122	2.011306657
Average	3.878	10.05	122.8	2.00840329
STD Dev	0.073756356	0.045704364	26.74903944	0.438632764
% RSD (STD	1.901917371	0.454769791	21.78260541	21.83987478

Friability	17 tabs			
Weight (g)	6.6237			
Before		Broken?		
Cracked?	6.5981			
After	0.387990482			Pass

Table 7: Formulations of paracetamol (27 % w/w) with FlowLac® 100

Formula: Paracetamol 27 FlowLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (m	Diameter (m	Hardness (N)	Tens Str (σt)
1	393.2	Pass		1	4.01	10.06	70	1.104678266
2	400.4	Pass		2	3.52	10.08	53	0.950939302
3	401.4	Pass		3	4	10.09	49	0.772903093
4	404.9	Pass		4	3.94	10.11	63	1.006869754
5	385.7	Pass		5	3.94	10.13	65	1.036782868
6	398.8	Pass		6	3.88	10.18	53	0.854233284
7	376.5	Fail		7	3.85	10.23	50	0.808190543
8	396.6	Pass		8	3.95	10.12	83	1.321845227
9	401.6	Pass		9	3.94	10.12	61	0.973942289
10	396.2	Pass		10	3.98	10.14	54	0.851829852
11	400.8	Pass		Average	3.901	10.126	60.1	0.968221448
12	395.2	Pass		STD Dev	0.142630058	0.049486249	10.64007101	0.163467787
13	396.6	Pass		% RSD (STD	3.656243466	0.488704814	17.70394511	16.88330571
14	398.8	Pass						
15	396.3	Pass						
16	399.1	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	403.4	Pass		Weight (g)	6.647	6.603	6.597	
18	398.6	Pass		Cracked?	Yes	Broken?	Yes	Fail
19	396	Pass		After (g)				
20	393.6	Pass		Diff %				
Average	396.685			Average		Fail		
STD Dev	6.328654551			STD Dev				
% RSD (ST	1.595385394			% RSD (STD				

Table 8: Formulations of paracetamol (5 % w/w) with Avicel® PH200

Formula: Paracetamol 05 Avicel® PH200

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (m	Diameter (m	Hardness (N)	Tens Str (σt)
1	374.6	Pass		1	4.71	10	184	2.487007179
2	374.4	Pass		2	4.7	10.03	201	2.714422143
3	376.3	Pass		3	4.68	10.03	183	2.481900843
4	374	Pass		4	4.69	10.02	184	2.492627498
5	376.8	Pass		5	4.7	10.01	185	2.503340444
6	374.6	Pass		6	4.69	10	184	2.497612753
7	374.4	Pass		7	4.69	9.99	190	2.581638285
8	373.7	Pass		8	4.66	9.99	188	2.570908187
9	374.8	Pass		9	4.69	10.02	181	2.451986832
10	377	Pass		10	4.68	10.04	182	2.465880039
11	372.1	Pass		Average	4.689	10.013	186.2	2.52473242
12	375.5	Pass		STD Dev	0.013703203	0.017669811	5.846176338	0.078591596
13	373.7	Pass		% RSD (STD	0.292241484	0.176468701	3.139729505	3.112868317
14	373.9	Pass						
15	373.1	Pass						
16	377	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	373.2	Pass		Weight (g)	6.3715			
18	374.4	Pass		Before		Broken?		
19	375.1	Pass		Cracked?	6.366			
20	377.4	Pass		After	0.086396481			Pass
Average	374.8							
STD Dev	1.458910913							
% RSD (ST	0.38925051							

Table 9: Formulations of paracetamol (10 % w/w) with Avicel® PH200

Formula: Paracetamol 10 Avicel® PH200

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	377.9	Pass		1	3.53	9.98	265	4.7887344
2	373.2	Pass		2	3.53	9.98	245	4.427320483
3	374.5	Pass		3	3.52	9.98	253	4.584874363
4	375.7	Pass		4	3.53	9.98	263	4.752593008
5	376.5	Pass		5	3.53	9.98	251	4.535744658
6	372.4	Pass		6	3.57	9.98	254	4.538528659
7	373	Pass		7	3.58	9.98	250	4.454577957
8	375.6	Pass		8	3.55	9.98	257	4.618004502
9	376.9	Pass		9	3.53	9.98	246	4.445391179
10	370.4	Pass		10	3.5	9.98	259	4.72042717
11	362	Pass		Average	3.537	9.98	254.3	4.586619638
12	372.3	Pass		STD Dev	0.023593784	1.87244E-15	6.717307662	0.131211347
13	374.8	Pass		% RSD (STI	0.667056389	1.8762E-14	2.641489446	2.860741834
14	370.5	Pass						
15	377.5	Pass						
16	374.9	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	374	Pass		Weight (g)	6.7248			
18	372.1	Pass		Before	2 Caps	Broken?	2 cracked	
19	375.7	Pass		Cracked?	6.7188			
20	377.6	Pass		After	0.089301661			Pass
Average	373.875							
STD Dev	3.588853357							
% RSD (ST	0.959907284							

Table 10: Formulations of paracetamol (15 % w/w) with Avicel® PH200

Formula: Paracetamol 15 Avicel® PH200

Uniformity of Weight		
Tab No.	Weight (g)	
1	335.9	Pass
2	329.7	Pass
3	335.3	Pass
4	328.3	Pass
5	330.9	Pass
6	325.2	Pass
7	344.7	Pass
8	331.8	Pass
9	342.9	Pass
10	323.9	Pass
11	325.9	Pass
12	324.7	Pass
13	325.7	Pass
14	328.6	Pass
15	337.9	Pass
16	327.7	Pass
17	333.7	Pass
18	329.4	Pass
19	333.7	Pass
20	331.7	Pass
Average	331.38	
STD Dev	5.795969562	
% RSD (ST	1.749040244	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	3.49	9.99	142	2.592850951
2	3.49	10	154	2.80915315
3	3.49	9.99	146	2.665889006
4	3.49	10	148	2.699705625
5	3.48	10	139	2.542820355
6	3.51	9.99	146	2.650698755
7	3.48	9.99	138	2.527053737
8	3.48	9.99	144	2.636925639
9	3.48	9.99	149	2.728485557
10	3.48	9.99	149	2.728485557
Average	3.487	9.993	145.5	2.658206833
STD Dev	0.009486833	0.004830459	4.904646323	0.088027761
% RSD (STI	0.27206289	0.048338426	3.370890944	3.311546702

Friability	20 tabs			
Weight (g)	6.6239			
Before		Broken?		
Cracked?	6.6055			
After	0.278555749			Pass

Table 11: Formulations of paracetamol (20 % w/w) with Avicel® PH200

Formula: Paracetamol 20 Avicel® PH200

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	332.2	Pass		1	3.48	9.99	115	2.105878114
2	320.6	Pass		2	3.49	10	127	2.316639286
3	318.2	Pass		3	3.49	9.99	124	2.264179703
4	318.9	Pass		4	3.53	10	141	2.542872179
5	317.6	Pass		5	3.5	9.99	138	2.51261343
6	330.2	Pass		6	3.48	9.99	114	2.087566131
7	324.4	Pass		7	3.48	9.99	131	2.398869852
8	320.9	Pass		8	3.47	9.99	126	2.313959242
9	324	Pass		9	3.64	9.99	134	2.345946207
10	310.1	Pass		10	3.44	9.99	98	1.815441537
11	312.7	Pass		Average	3.5	9.992	124.8	2.270396568
12	322.5	Pass		STD Dev	0.054160256	0.00421637	12.8996124	0.217735113
13	320.4	Pass		% RSD (STD	1.547435887	0.04219746	10.33622788	9.590179795
14	322	Pass						
15	317.4	Pass						
16	323.8	Pass		**Friability**	20 tabs			
17	322.1	Pass		Weight (g)	6.449			
18	320.8	Pass		Before		Broken?		
19	336.2	Pass		Cracked?	6.4247			
20	323.5	Pass		After	0.378227777			Pass
Average	321.925							
STD Dev	6.018207024							
% RSD (ST	1.869443822							

Table 12: Formulations of paracetamol (25 % w/w) with Avicel® PH200

Formula: Paracetamol 25 Avicel® PH200

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	316.4	Pass		1	3.49	10	79	1.441059084
2	323	Pass		2	3.49	10.02	85	1.547411785
3	315.9	Pass		3	3.49	10.01	85	1.548957651
4	322	Pass		4	3.48	10.01	78	1.425480905
5	319.5	Pass		5	3.48	10.01	81	1.480307094
6	315.5	Pass		6	3.48	10.01	81	1.480307094
7	313.5	Pass		7	3.49	10	87	1.586989117
8	318.1	Pass		8	3.49	10	83	1.5140241
9	315.2	Pass		9	3.46	10.01	85	1.56238792
10	315.8	Pass		10	3.46	10.01	78	1.433720679
11	313.5	Pass		Average	3.481	10.008	82.2	1.502064543
12	316.6	Pass		STD Dev	0.01197219	0.006324555	3.259175083	0.058170092
13	314.9	Pass		% RSD (STI	0.343929618	0.063194997	3.964933191	3.872675941
14	318.5	Pass						
15	315.2	Pass						
16	320.4	Pass		**Friability**	21 tabs			
17	318.7	Pass		Weight (g)	6.6605			
18	313.7	Pass		Before		Broken?		
19	317.4	Pass		Cracked?	6.6419			
20	315.5	Pass		After	0.28004035			Pass
Average	316.965							
STD Dev	2.707159125							
% RSD (ST	0.854087715							

Table 13: Formulations of paracetamol (30 % w/w) with Avicel® PH200

Formula: Paracetamol 30 Avicel® PH200

Uniformity of Weight		
Tab No.	Weight (g)	
1	311.5	Pass
2	301.9	Pass
3	306.8	Pass
4	310.5	Pass
5	306.3	Pass
6	301.3	Pass
7	309.9	Pass
8	305.1	Pass
9	308.1	Pass
10	301.3	Pass
11	302.4	Pass
12	330.8	Fail
13	313.8	Pass
14	314.4	Pass
15	304.8	Pass
16	303.5	Pass
17	311	Pass
18	305.3	Pass
19	302.7	Pass
20	301	Pass
Average	307.62	
STD Dev	6.915398531	
% RSD (ST	2.24803281	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	3.46	10.01	62	1.13962413
2	3.47	10	66	1.210861815
3	3.46	10.01	61	1.121243095
4	3.47	10.01	53	0.971387343
5	3.48	10.01	61	1.11479917
6	3.49	10.01	58	1.056935809
7	3.48	10.01	63	1.151349962
8	3.48	10.01	67	1.224451547
9	3.44	10.01	53	0.979858744
10	3.46	10.01	59	1.084481027
Average	3.469	10.009	60.3	1.105499264
STD Dev	0.014491377	0.003162278	4.738729319	0.085260246
% RSD (STI	0.417739312	0.031594342	7.858589252	7.712374704

Friability	(Enough tablets to be near as possible to 6.5g)			
Weight (g)	6.4568	6.3937	6.3676	
Cracked?	No	Broken?	Chipping	
After (g)	6.3518	6.3175	6.3082	
Diff %	1.653074719	1.206173328	0.941631527	Fail, redo
Average	1.266959858	Fail		
STD Dev	0.359595753			
% RSD (STI	28.38256876			

Table 14: Formulations of paracetamol (5 % w/w) with Emcompress®

Formula: Paracetamol 05 Emcompress®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	387.5	Pass		1	2.73	9.98	93	2.173050821
2	391	Pass		2	2.72	10.01	87	2.034212853
3	391.6	Pass		3	2.72	10	92	2.153272759
4	394.7	Pass		4	2.74	10.02	94	2.179664707
5	388.4	Pass		5	2.73	10.03	98	2.278466348
6	392.5	Pass		6	2.73	10.02	91	2.117830247
7	390.1	Pass		7	2.72	10.02	90	2.102257966
8	390	Pass		8	2.74	10.04	94	2.175322746
9	389.8	Pass		9	2.72	10.02	90	2.102257966
10	397.7	Pass		10	2.73	10.03	105	2.441213944
11	389.6	Pass		Average	2.728	10.017	93.4	2.175755036
12	391.5	Pass		STD Dev	0.007888106	0.017029386	5.03763613	0.113401642
13	389.1	Pass		% RSD (STI	0.28915346	0.170004855	5.3936147	5.212059291
14	390.5	Pass						
15	391	Pass						
16	391.1	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	397.9	Pass		Weight (g)	6.6662			
18	397.1	Pass		Before		Broken?		
19	391.2	Pass		Cracked?	6.6481			
20	394.2	Pass		After	0.272258239			Pass
Average	391.825							
STD Dev	3.000153505							
% RSD (ST	0.765687106							

Table 15: Formulations of paracetamol (10 % w/w) with Emcompress®

Formula: Paracetamol 10 Emcompress®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	377.7	Pass		1	2.69	10.02	79	1.865895051
2	369.9	Pass		2	2.68	10.02	85	2.015099676
3	372.5	Pass		3	2.66	10.02	72	1.719741855
4	369	Pass		4	2.7	10.03	89	2.092210766
5	369.9	Pass		5	2.67	10.03	84	1.996858148
6	369.8	Pass		6	2.69	10.03	86	2.029202371
7	370.9	Pass		7	2.7	10.03	86	2.021686807
8	369	Pass		8	2.68	10.03	80	1.894673509
9	380.9	Pass		9	2.69	10.03	90	2.123583877
10	369	Pass		10	2.64	10.03	84	2.019549717
11	367.3	Pass		Average	2.68	10.027	83.5	1.977850178
12	370.9	Pass		STD Dev	0.018856181	0.004830459	5.296749527	0.119459546
13	384.1	Pass		% RSD (STI	0.703588837	0.048174518	6.343412608	6.039868292
14	368.4	Pass						
15	374.6	Pass						
16	374.4	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	371.6	Pass		Weight (g)	6.3401			
18	376.2	Pass		Before		Broken?		
19	370.4	Pass		Cracked?	6.315			
20	370.4	Pass		After	0.39746635			Pass
Average	372.345							
STD Dev	4.410212431							
% RSD (ST	1.184442501							

Table 16: Formulations of paracetamol (15 % w/w) with Emcompress®

Formula: Paracetamol 15 Emcompress®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	384.8	Pass		1	2.79	10.03	81	1.842722784
2	382.7	Pass		2	2.76	10.03	76	1.747767664
3	377.4	Pass		3	2.82	10.03	81	1.82311935
4	387.2	Pass		4	2.73	10.03	79	1.836722872
5	379.2	Pass		5	2.79	10.04	94	2.136338467
6	375.8	Pass		6	2.75	10.03	82	1.892606592
7	366.6	Pass		7	2.79	10.03	84	1.910971776
8	378.2	Pass		8	2.79	10.03	92	2.092969088
9	380.7	Pass		9	2.77	10.04	84	1.922852305
10	370	Pass		10	2.8	10.02	104	2.35986799
11	383.2	Pass		Average	2.779	10.031	85.7	1.956593889
12	372.1	Pass		STD Dev	0.026436507	0.005676462	8.472832401	0.185475392
13	370.7	Pass		% RSD (STD	0.951295673	0.056589195	9.886618904	9.479503785
14	377	Pass						
15	387.1	Pass						
16	381.1	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	384.1	Pass		Weight (g)	6.45			
18	386	Pass		Before		Broken?		
19	384.7	Pass		Cracked?	6.43			
20	385.9	Pass		After	0.311041991			Pass
Average	379.725							
STD Dev	6.149272529							
% RSD (ST	1.619401548							

Table 17: Formulations of paracetamol (20 % w/w) with Emcompress®

Formula: Paracetamol 20 Emcompress®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	396.7	Pass		1	2.89	10.03	76	1.669148358
2	398	Pass		2	2.98	10.03	61	1.299250106
3	392.9	Pass		3	2.91	10.04	81	1.76497452
4	401.5	Pass		4	2.98	10.04	92	1.957573032
5	400.8	Pass		5	2.92	10.04	73	1.585208597
6	394.6	Pass		6	2.82	10.02	67	1.509517304
7	385.9	Pass		7	2.9	10.04	81	1.771060639
8	386.4	Pass		8	2.9	10.04	77	1.683600854
9	385.9	Pass		9	2.93	10.04	89	1.926055496
10	374.5	Pass		10	2.83	10.03	73	1.63725232
11	393.7	Pass		Average	2.906	10.035	77	1.680364123
12	397.2	Pass		STD Dev	0.052957006	0.007071068	9.368979548	0.193815436
13	398.2	Pass		% RSD (STD	1.822333297	0.070464054	12.16750591	11.53413318
14	392.3	Pass						
15	397.1	Pass						
16	393.2	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	394	Pass		Weight (g)	6.6813			
18	389.7	Pass		Before		Broken?		
19	383.2	Pass		Cracked?	6.6625			
20	393.3	Pass		After	0.28217636			Pass
Average	392.455							
STD Dev	6.591739248							
% RSD (ST	1.67961658							

Table 18: Formulations of paracetamol (25 % w/w) with Emcompress®

Formula: Paracetamol 25 Emcompress®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	374.4	Pass		1	2.82	10.04	94	2.113611462
2	376	Pass		2	2.91	10.03	106	2.312022553
3	373.3	Pass		3	2.82	10.03	85	1.913149935
4	366.4	Pass		4	2.87	10.03	100	2.211552702
5	366.1	Pass		5	2.89	10.04	105	2.303763358
6	356.1	Pass		6	2.83	10.04	80	1.792462017
7	377.5	Pass		7	2.85	10.04	97	2.158108545
8	370.2	Pass		8	2.86	10.03	99	2.19709255
9	367.9	Pass		9	2.84	10.04	90	2.009419348
10	338.6	Fail		10	2.84	10.04	94	2.098726874
11	353.7	Pass		Average	2.853	10.036	95	2.110990935
12	378.2	Pass		STD Dev	0.029832868	0.005163978	8.286535263	0.166131454
13	372.6	Pass		% RSD (STD	1.045666589	0.051454542	8.722668698	7.869832649
14	361.8	Pass						
15	373.3	Pass						
16	376.8	Pass		**Friability**	(Enough tablets	18 tabs		
17	373.8	Pass		Weight (g)	6.6337			
18	370.7	Pass		Before		Broken?		
19	372.7	Pass		Cracked?	6.606			
20	376.1	Pass		After	0.419315774			Pass
Average	368.81							
STD Dev	9.812607358							
% RSD (ST	2.66061315							

Table 19: Formulations of paracetamol (30 % w/w) with Emcompress®

Formula: Paracetamol 30 Emcompress®

Uniformity of Weight		
Tab No.	Weight (g)	
1	380.7	Pass
2	375.4	Pass
3	379.5	Pass
4	389.1	Pass
5	361.4	Pass
6	375.7	Pass
7	376.3	Pass
8	340.8	Fail
9	384.4	Pass
10	378.3	Pass
11	370.4	Pass
12	374.2	Pass
13	380	Pass
14	382.7	Pass
15	357.6	Pass
16	377.5	Pass
17	387.9	Pass
18	372.6	Pass
19	381.1	Pass
20	393.9	Pass
Average	375.975	
STD Dev	11.85530638	
% RSD (ST	3.153216673	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	3.02	10.04	100	2.099614035
2	3.04	10.02	76	1.588372686
3	3.01	10.04	105	2.211918972
4	2.98	10.04	95	2.021406935
5	2.98	10.06	93	1.974916902
6	2.96	10.05	93	1.990239304
7	3.06	10.08	57	1.17644877
8	3.04	10.04	61	1.272338479
9	2.82	10.02	67	1.509517304
10	2.94	10.04	94	2.027341606
Average	2.985	10.043	84.1	1.787211499
STD Dev	0.069482212	0.017669811	17.29129518	0.368436884
% RSD (STI	2.327712293	0.175941562	20.56039855	20.61518093

Friability	(Enough tablets to be near as possible to 6.5g)			
Weight (g)	6.4151	6.4335	6.4396	
Cracked?	Chipped	Broken?	Capped	
After (g)	6.1201	6.0201	6.1891	
Diff %	4.820182677	6.866995565	4.047438238	Fail, redo
Average	5.24487216	Fail		
STD Dev	1.456964909			
% RSD (STI	27.77884503			

Table 20: Formulations of paracetamol (35 % w/w) with Emcompress®

Formula: Paracetamol 35 Emcompress®

Uniformity of Weight				Tablet Hardness					
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)	
1	367.3	Pass		1	3.05	10.02	80	1.666489375	
2	376.7	Pass		2	3.01	10.04	77	1.622073913	
3	385.7	Pass		3	3.02	10.04	63	1.322756842	
4	377.7	Pass		4	3.09	10.05	45	0.922503655	
5	378	Pass		5	2.96	10.04	72	1.542365121	
6	376.7	Pass		6	3.1	10.05	51	1.042131548	
7	373.8	Pass		7	3.04	10.05	76	1.583631275	
8	363.8	Pass		8	3.01	10.05	73	1.536280173	
9	362.4	Pass		9	3.07	10.05	73	1.506255154	
10	371.7	Pass		10	2.9	10.05	64	1.39796416	
11	380	Pass		Average	3.025	10.044	67.4	1.414245122	
12	364.9	Pass		STD Dev	0.060598863	0.009660918	11.59693446	0.250377078	
13	356.1	Pass		% RSD (STD	2.003268205	0.09618596	17.20613421	17.70393787	
14	363.9	Pass							
15	384.8	Pass							
16	373.6	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)				
17	377.8	Pass		Weight (g)	6.3292	6.3941	6.4182		
18	374.8	Pass		Cracked?	No	Broken?	No		
19	374.2	Pass		After (g)	4.3352	5.4213	4.5228		
20	365.4	Pass		Diff %	45.99557114	17.94403556	41.90766782	Fail, redo	
Average	372.465			Average	35.28242484	Fail			
STD Dev	7.84710976			STD Dev	15.15396138				
% RSD (ST	2.106804602			% RSD (STD	42.95045322				

Table 21: Formulations of paracetamol (5 % w/w) with Cellactose® 80

Formula: Paracetamol 05 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	384.9	Pass		1	3.68	10	204	3.529087869
2	386.8	Pass		2	3.7	10.01	207	3.558071466
3	386	Pass		3	3.71	10.01	205	3.514196136
4	381.9	Pass		4	3.7	10	223	3.836924574
5	387.6	Pass		5	3.71	10	216	3.706465521
6	386.3	Pass		6	3.73	10	226	3.857267253
7	385.9	Pass		7	3.7	10.02	209	3.58886369
8	384.5	Pass		8	3.7	10.02	217	3.726236462
9	385.8	Pass		9	3.69	10.02	221	3.805207192
10	384.3	Pass		10	3.69	10.02	227	3.908515985
11	386	Pass		Average	3.701	10.01	215.5	3.703083615
12	386.4	Pass		STD Dev	0.013703203	0.00942809	8.746427842	0.147155581
13	386.7	Pass		% RSD (STI	0.370256774	0.094186717	4.058667212	3.973866018
14	382	Pass						
15	385.7	Pass						
16	389.9	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	385.3	Pass		Weight (g)	6.5553			
18	383.8	Pass		Before		Broken?		
19	387.2	Pass		Cracked?	6.5506			
20	388.2	Pass		After	0.071749153			Pass
Average	385.76							
STD Dev	1.904399339							
% RSD (ST	0.493674652							

Table 22: Formulations of paracetamol (10 % w/w) with Cellactose® 80

Formula: Paracetamol 10 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	383.4	Pass		1	3.71	10	172	2.951444767
2	380.6	Pass		2	3.68	9.99	158	2.736049202
3	385	Pass		3	3.71	10	176	3.020083017
4	381.2	Pass		4	3.73	10.01	179	3.052040165
5	382.8	Pass		5	3.71	10.02	175	2.996929595
6	380.8	Pass		6	3.71	10.01	177	3.034208371
7	381.7	Pass		7	3.72	9.99	178	3.049240625
8	382.1	Pass		8	3.73	9.99	177	3.023981078
9	382.1	Pass		9	3.7	10.02	178	3.056544195
10	380.6	Pass		10	3.71	10.02	174	2.979804283
11	378.7	Pass		Average	3.711	10.005	174.4	2.99003253
12	382.9	Pass		STD Dev	0.014491377	0.012692955	6.131883887	0.09541146
13	381.9	Pass		% RSD (STI	0.390497891	0.126866119	3.515988467	3.190984011
14	382	Pass						
15	381.8	Pass						
16	381.4	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	380.8	Pass		Weight (g)	6.4952			
18	385.9	Pass		Before		Broken?		
19	385	Pass		Cracked?	6.4889			
20	382.1	Pass		After	0.097088875			Pass
Average	382.14							
STD Dev	1.702753189							
% RSD (ST	0.445583605							

Table 23: Formulations of paracetamol (15 % w/w) with Cellactose® 80

Formula: Paracetamol 15 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	377.5	Pass		1	3.65	10.02	175	3.046194191
2	373.6	Pass		2	3.62	10.02	164	2.878377021
3	375.9	Pass		3	3.63	10.01	172	3.013476905
4	376.2	Pass		4	3.65	10.02	176	3.063601015
5	376.8	Pass		5	3.65	10.02	183	3.185448783
6	374.6	Pass		6	3.63	10.02	179	3.132988548
7	375.4	Pass		7	3.63	10.02	176	3.08048036
8	379.1	Pass		8	3.61	10.02	176	3.097546733
9	375.7	Pass		9	3.6	10.02	175	3.088502444
10	377.5	Pass		10	3.62	10.02	179	3.141643212
11	377	Pass		Average	3.629	10.019	175.5	3.072825921
12	376.9	Pass		STD Dev	0.017288403	0.003162278	5.016638981	0.084381252
13	378.5	Pass		% RSD (STD	0.476395792	0.031562807	2.85848375	2.746047253
14	380	Pass						
15	378.6	Pass						
16	376.8	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	376	Pass		Weight (g)	6.4149			
18	381.2	Pass		Before		Broken?		
19	376.9	Pass		Cracked?	6.409			
20	378.9	Pass		After	0.092058043			Pass
Average	377.155							
STD Dev	1.835462082							
% RSD (ST	0.486659883							

Table 24: Formulations of paracetamol (20 % w/w) with Cellactose® 80

Formula: Paracetamol 20 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	390.4	Pass		1	3.81	10.02	133	2.21788522
2	389.1	Pass		2	3.81	10.03	129	2.149037157
3	391.4	Pass		3	3.84	10.01	142	2.351815052
4	385.3	Pass		4	3.81	10.02	147	2.451346822
5	388.9	Pass		5	3.81	10.03	141	2.34894759
6	389.9	Pass		6	3.83	10.01	144	2.391166202
7	385.8	Pass		7	3.78	10.03	132	2.216467264
8	389.3	Pass		8	3.83	10.02	143	2.37219106
9	386.1	Pass		9	3.81	10.03	142	2.365606793
10	389.5	Pass		10	3.81	10.02	134	2.234561048
11	386.4	Pass		Average	3.814	10.022	138.7	2.309902421
12	391	Pass		STD Dev	0.016465452	0.007888106	6.1110101	0.097539517
13	384.3	Pass		% RSD (STD	0.431710856	0.078707906	4.405919322	4.222668271
14	389.4	Pass						
15	388.7	Pass						
16	390.5	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	388.3	Pass		Weight (g)	6.5996			
18	389.2	Pass		Before		Broken?		
19	386.2	Pass		Cracked?	6.5901			
20	370.8	Pass		After	0.144155627			Pass
Average	387.525							
STD Dev	4.428837913							
% RSD (ST	1.142852181							

Table 25: Formulations of paracetamol (25 % w/w) with Cellactose® 80

Formula: Paracetamol 25 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	371.7	Pass		1	3.67	10.03	110	1.902417406
2	376.5	Pass		2	3.66	10.02	112	1.944237604
3	363.3	Pass		3	3.72	10.03	125	2.132781
4	369.4	Pass		4	3.65	10.03	108	1.878062673
5	358.5	Pass		5	3.69	10.03	119	2.04691489
6	365.8	Pass		6	3.63	10.03	113	1.97583652
7	367.6	Pass		7	3.64	10.02	105	1.832737714
8	369.7	Pass		8	3.64	10.03	108	1.883222186
9	364.6	Pass		9	3.65	10.02	111	1.932157459
10	367.2	Pass		10	3.65	10.03	117	2.034567895
11	365.9	Pass		Average	3.66	10.027	112.8	1.956293535
12	371.2	Pass		STD Dev	0.027080128	0.004830459	5.996295152	0.092029538
13	373	Pass		% RSD (STI	0.739894208	0.048174518	5.315864497	4.704280634
14	360.9	Pass						
15	361.4	Pass						
16	370	Pass		**Friability**	(Enough tablets	18 tabs		
17	366.8	Pass		Weight (g)	6.6001			
18	373.7	Pass		Ammount		Broken?		
19	363.1	Pass		Cracked?	6.5878			
20	358	Pass		After	0.186708765			Pass
Average	366.915							
STD Dev	5.090473559							
% RSD (ST	1.387371342							

Table 26: Formulations of paracetamol (30 % w/w) with Cellactose® 80

Formula: Paracetamol 30 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	348	Pass		1	3.65	10.03	98	1.704167981
2	358.4	Pass		2	3.51	10.02	57	1.031763454
3	351.4	Pass		3	3.68	10.03	104	1.79376155
4	362	Pass		4	3.64	10.04	94	1.637468221
5	353.3	Pass		5	3.67	10.03	105	1.815943888
6	353.4	Pass		6	3.62	10.03	89	1.560488693
7	351	Pass		7	3.63	10.06	92	1.603848508
8	348.1	Pass		8	3.62	10.04	88	1.541418304
9	351.4	Pass		9	3.67	10.04	105	1.814135179
10	369.9	Fail		10	3.66	10.04	105	1.819091832
11	326.6	Fail		Average	3.635	10.036	93.7	1.632208761
12	368.6	Pass		STD Dev	0.048819395	0.010749677	14.57585523	0.23753637
13	356.1	Pass		% RSD (STI	1.343037003	0.10711117	15.55587537	14.55306302
14	366.2	Pass						
15	320.5	Fail						
16	352.6	Pass		**Friability**	(Enough tablets	18 tabs		
17	367.8	Pass		Weight (g)	6.3225			
18	360	Pass		Before		Broken?		
19	320.4	Fail		Cracked?	6.3098			
20	357.4	Pass		After	0.201274208			Pass
Average	352.155							
STD Dev	14.45612145							
% RSD (ST	4.105045065							

Table 27: Formulations of paracetamol (35 % w/w) with Cellactose® 80

Formula: Paracetamol 35 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	351.2	Pass		1	3.42	10.02	23	0.427281541
2	324.4	Pass		2	3.48	10.04	45	0.819935481
3	348.5	Pass		3	3.56	10.06	69	1.226538642
4	352.6	Pass		4	3.61	10.05	74	1.298489909
5	345.5	Pass		5	3.68	10.04	94	1.619669653
6	348.4	Pass		6	3.62	10.05	78	1.364897673
7	303.8	Complete Fail		7	3.55	10.04	66	1.178859351
8	351.6	Pass		8	3.64	10.05	85	1.479216026
9	347.2	Pass		9	3.44	10.04	35	0.645143033
10	316.6	Fail		10	3.64	10.03	76	1.325230427
11	351.4	Pass		Average	3.564	10.042	64.5	1.138526174
12	345	Pass		STD Dev	0.090455637	0.011352924	22.82907503	0.382887914
13	350.4	Pass		% RSD (STD	2.538036946	0.113054414	35.39391477	33.63013719
14	332.2	Pass						
15	356.7	Fail						
16	348.9	Pass		**Friability**	(Enough tablets	19 tabs		
17	305.4	Fail		Weight (g)		6.478		
18	333.3	Pass		Ammount		Broken?		
19	330.8	Pass		Cracked?		6.4583		
20	308.4	Fail		After		0.305033832		Pass
Average	337.615							
STD Dev	17.22691514							
% RSD (ST	5.102532512							

Table 28: Formulations of paracetamol (5 % w/w) with MicroceLac® 100

Formula: Paracetamol 05 MicroceLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	387.5	Pass		1	3.64	10	337	5.893979761
2	386.5	Pass		2	3.63	10	310	5.436697781
3	385.6	Pass		3	3.63	10.01	355	6.219676169
4	387.9	Pass		4	3.63	10	329	5.769914741
5	386.9	Pass		5	3.63	10.01	329	5.764150591
6	387.3	Pass		6	3.63	9.98	326	5.728759055
7	388.2	Pass		7	3.62	10	329	5.785853732
8	387.8	Pass		8	3.62	10.01	330	5.797642272
9	386.2	Pass		9	3.62	10	327	5.750681369
10	388.3	Pass		10	3.6	10.01	330	5.829851395
11	386.7	Pass		Average	3.625	10.002	330.2	5.797720687
12	387.9	Pass		STD Dev	0.010801234	0.009189366	11.06345335	0.190814487
13	387.2	Pass		% RSD (STI	0.29796509	0.091875283	3.350530996	3.291198343
14	388	Pass						
15	387.4	Pass						
16	387.9	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	388.8	Pass		Weight (g)	6.583			
18	386.7	Pass		Before		Broken?		
19	386.9	Pass		Cracked?	6.5777			
20	387.7	Pass		After	0.080575277			Pass
Average	387.37							
STD Dev	0.787467627							
% RSD (ST	0.203285651							

Table 29: Formulations of paracetamol (10 % w/w) with MicroceLac® 100

Formula: Paracetamol 10 MicroceLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	375.5	Pass		1	2.75	10.01	277	6.406091252
2	372.3	Pass		2	2.74	10.03	278	6.43981547
3	375.8	Pass		3	2.74	10.01	289	6.708004193
4	375.1	Pass		4	2.75	10.02	292	6.746251988
5	376.5	Pass		5	2.74	10.02	276	6.399866587
6	378.5	Pass		6	2.76	9.99	301	6.949795864
7	366.5	Pass		7	2.81	10.01	207	4.685005133
8	377.1	Pass		8	2.74	10.02	277	6.423054509
9	375.9	Pass		9	2.73	10.02	278	6.469855041
10	374.9	Pass		10	2.8	10.01	278	6.314410472
11	376.5	Pass		Average	2.756	10.014	275.3	6.354215051
12	374	Pass		STD Dev	0.027162065	0.010749677	25.42985996	0.619286013
13	379.3	Pass		% RSD (STI	0.985561141	0.107346485	9.23714492	9.746066316
14	375.6	Pass						
15	380.3	Pass						
16	375.3	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	376.8	Pass		Weight (g)	6.3881			
18	373.1	Pass		Before		Broken?		
19	378.6	Pass		Cracked?	6.3839			
20	376	Pass		After	0.065790504			Pass
Average	375.68							
STD Dev	2.920093726							
% RSD (ST	0.777282189							

Table 30: Formulations of paracetamol (15 % w/w) with MicroceLac® 100

Formula: Paracetamol 15 MicroceLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	390.8	Pass		1	3.72	10.02	265	4.52600819
2	389.4	Pass		2	3.69	10.04	265	4.553715752
3	390.3	Pass		3	3.69	10.03	257	4.420648123
4	389	Pass		4	3.71	10.04	267	4.563349814
5	390.2	Pass		5	3.69	10.03	267	4.592657778
6	388.2	Pass		6	3.71	10.03	254	4.345492422
7	387.9	Pass		7	3.68	10.03	258	4.449908461
8	388.9	Pass		8	3.68	10.01	254	4.389670715
9	377.3	Pass		9	3.68	10.02	239	4.126315998
10	387.6	Pass		10	3.68	10.02	264	4.557939011
11	388.1	Pass		Average	3.693	10.027	259	4.452570626
12	387.4	Pass		STD Dev	0.014944341	0.009486833	8.692269874	0.142014359
13	388.2	Pass		% RSD (STI	0.404666699	0.094612875	3.356088754	3.189491439
14	387.4	Pass						
15	388.1	Pass						
16	390.3	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	389.3	Pass		Weight (g)	6.6013			
18	390.1	Pass		Before		Broken?		
19	389.5	Pass		Cracked?	6.5948			
20	389.9	Pass		After	0.098562504			Pass
Average	388.395							
STD Dev	2.82236836							
% RSD (ST	0.726674741							

Table 31: Formulations of paracetamol (20 % w/w) with MicroceLac® 100

Formula: Paracetamol 20 MicroceLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	390.7	Pass		1	3.84	10.02	161	2.663833358
2	386.4	Pass		2	3.86	10.03	179	2.943370388
3	387.3	Pass		3	3.86	10.03	180	2.959813798
4	390.4	Pass		4	3.85	10.04	176	2.898667148
5	380.4	Pass		5	3.76	10.04	136	2.293493289
6	389.9	Pass		6	3.8	10.03	159	2.655783801
7	391.8	Pass		7	3.81	10.03	168	2.798746065
8	389.5	Pass		8	3.86	10.01	178	2.932774984
9	386.9	Pass		9	3.81	10.03	170	2.832064471
10	388.5	Pass		10	3.84	10.03	178	2.942171389
11	385.3	Pass		Average	3.829	10.029	168.5	2.792071869
12	388.5	Pass		STD Dev	0.033149493	0.00875595	13.68088691	0.208156589
13	391.8	Pass		% RSD (STI	0.865748055	0.087306315	8.119220719	7.455273309
14	385.9	Pass						
15	389	Pass						
16	383.7	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	387.4	Pass		Weight (g)	6.5973			
18	387.7	Pass		Before		Broken?		
19	396.8	Pass		Cracked?	6.5925			
20	386.6	Pass		After	0.072810011			Pass
Average	388.225							
STD Dev	3.405394328							
% RSD (ST	0.877170282							

Table 32: Formulations of paracetamol (25 % w/w) with MicroceLac® 100

Formula: Paracetamol 25 MicroceLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	375.9	Pass		1	3.7	10.02	162	2.781798649
2	363	Pass		2	3.66	10.03	163	2.826738988
3	348	Pass		3	3.63	10.04	145	2.532840182
4	373.5	Pass		4	3.66	10.02	163	2.829560085
5	371.8	Pass		5	3.61	10.02	153	2.692753694
6	358.7	Pass		6	3.68	10.04	165	2.843037157
7	374.2	Pass		7	3.55	10.02	133	2.380321884
8	369.9	Pass		8	3.44	10.02	148	2.733478575
9	349.8	Pass		9	3.66	10.03	149	2.58395159
10	363.2	Pass		10	3.65	10.03	155	2.695367725
11	357.7	Pass		Average	3.624	10.027	153.6	2.689984853
12	361	Pass		STD Dev	0.076768049	0.008232726	10.16748631	0.150478762
13	356.7	Pass		% RSD (STI	2.118323645	0.082105575	6.61945723	5.594037522
14	375.2	Pass						
15	369	Pass						
16	374.8	Pass		**Friability**	(Enough tablets	18 tabs		
17	376.5	Pass		Weight (g)	6.5671			
18	354	Pass		Before		Broken?		
19	340.2	Fail		Cracked?	6.5525			
20	375	Pass		After	0.222815719			Pass
Average	364.405							
STD Dev	10.82975798							
% RSD (ST	2.971901587							

Table 33: Formulations of paracetamol (30 % w/w) with MicroceLac® 100

Formula: Paracetamol 30 MicroceLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	339.8	Pass		1	3.61	10.04	42	0.737714804
2	323.5	Pass		2	3.65	10.05	53	0.919807754
3	319.5	Pass		3	3.65	10.04	62	1.077073238
4	326.6	Pass		4	3.73	10.04	69	1.172969364
5	329.2	Pass		5	3.65	10.04	49	0.851235301
6	301.3	Fail		6	3.65	10.03	54	0.939031336
7	336.5	Pass		7	3.64	10.04	51	0.888413609
8	311.8	Pass		8	3.55	10.04	31	0.553706665
9	320.6	Pass		9	3.56	10.03	41	0.730992715
10	325.9	Pass		10	3.64	10.04	60	1.045192481
11	330.6	Pass		Average	3.633	10.039	51.2	0.891613727
12	314.6	Pass		STD Dev	0.051001089	0.005676462	11.17338107	0.184237715
13	332.9	Pass		% RSD (STI	1.403828497	0.056544099	21.82300989	20.66340045
14	314.7	Pass						
15	331.9	Pass						
16	316.1	Pass		**Friability**	(Enough tablets	20 tabs		
17	318.9	Pass		Weight (g)	6.4968			
18	329.6	Pass		Before		Broken?		
19	340.5	Pass		Cracked?	6.4608			
20	339	Pass		After	0.557206538			Pass
Average	325.175							
STD Dev	10.48542221							
% RSD (ST	3.224547463							

Table 34: Formulations of Paracetamol (14 % w/w) with StarLac®

Formula: Paracetamol 14 StarLac®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	400.2	Pass		1	3.75	10.02	176	2.981904988
2	393.9	Pass		2	3.79	10.02	171	2.866614557
3	400	Pass		3	3.8	10.04	182	3.036925943
4	401.4	Pass		4	3.8	10.07	175	2.911421632
5	400.8	Pass		5	3.7	10.05	184	3.150142211
6	401.1	Pass		6	3.77	10.11	106	1.770490018
7	401.4	Pass		7	3.78	10.03	168	2.820958336
8	393.6	Pass		8	3.76	10.05	171	2.880861148
9	401.2	Pass		9	3.69	10.02	156	2.686028606
10	401.8	Pass		10	3.76	10.03	172	2.903486372
11	399.7	Pass		Average	3.76	10.044	166.1	2.800883381
12	401.2	Pass		STD Dev	0.038297084	0.02836273	22.48678624	0.382859832
13	401.3	Pass		% RSD (STI	1.018539476	0.282384805	13.53810129	13.66925288
14	394.7	Pass						
15	400.8	Pass						
16	402.3	Pass		**Friability**	16 tabs			
17	401.6	Pass		Weight (g)	6.3985			
18	400.8	Pass		Before		Broken?		
19	400.9	Pass		Cracked?	6.3851			
20	401.4	Pass		After	0.209863589			Pass
Average	400.005							
STD Dev	2.634482871							
% RSD (ST	0.658612485							

Table 35: Formulations of Paracetamol (19 % w/w) with StarLac®

Formula: Paracetamol 19 StarLac®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	390.1	Pass		1	3.81	10.03	115	1.915808318
2	390.2	Pass		2	3.81	10.08	97	1.60792708
3	399.6	Pass		3	3.8	10.04	116	1.935623128
4	386.1	Pass		4	3.81	10.04	117	1.947185363
5	389.5	Pass		5	3.8	10.1	80	1.326982329
6	391.5	Pass		6	3.8	10.05	118	1.967036741
7	387.5	Pass		7	3.8	10.05	108	1.800338712
8	392.4	Pass		8	3.81	10.04	115	1.913900143
9	391	Pass		9	3.78	10.04	105	1.761342885
10	390.9	Pass		10	3.8	10.03	111	1.854037748
11	389.9	Pass		Average	3.802	10.05	108.2	1.803018245
12	390.7	Pass		STD Dev	0.009189366	0.022607767	11.8584241	0.199806695
13	391.7	Pass		% RSD (STD	0.241698207	0.224952902	10.95972653	11.08178995
14	391.7	Pass						
15	391.1	Pass						
16	391	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	383.8	Pass		Weight (g)	6.6333			
18	388.9	Pass		Before		Broken?		
19	391	Pass		Cracked?	6.6192			
20	391.8	Pass		After	0.213016679			Pass
Average	390.52							
STD Dev	2.99747262							
% RSD (ST	0.767559311							

Table 36: Formulations of Paracetamol (24 % w/w) with StarLac®

Formula: Paracetamol 24 StarLac®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (m	Diameter (m	Hardness (N)	Tens Str (σt)
1	384.1	Pass		1	4.09	10.09	34	0.524498881
2	384.5	Pass		2	4.09	10.09	33	0.509072443
3	371.4	Pass		3	4.08	10.02	29	0.451596156
4	388	Pass		4	4.1	10.23	24	0.364277103
5	384.7	Pass		5	4.08	10.12	33	0.508807363
6	384.5	Pass		6	4.08	10.18	27	0.413843317
7	385.5	Pass		7	4.08	10.21	32	0.48903979
8	389	Pass		8	4.09	10.25	23	0.349269599
9	384.8	Pass		9	4.07	10.26	20	0.30490767
10	385.9	Pass		10	4.08	10.22	23	0.351153418
11	387.9	Pass		Average	4.084	10.167	27.8	0.426646574
12	388.2	Pass		STD Dev	0.00843274	0.081656462	5.094659513	0.080412503
13	385.8	Pass		% RSD (STD	0.206482381	0.803151981	18.32611336	18.84756802
14	383.7	Pass						
15	384.9	Pass						
16	382	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	388.9	Pass		Weight (g)	6.5302	6.4892	6.5388	
18	379.5	Pass		Cracked?	No	Broken?	No	
19	385.3	Pass		After (g)	6.3744	6.2995	6.3701	
20	384.7	Pass		Diff %	2.444151606	3.011350107	2.648310074	Fail, redo
Average	384.665			Average	2.701270596	Fail		
STD Dev	3.878724017			STD Dev	0.287284088			
% RSD (ST	1.008338169			% RSD (STD	10.63514662			

Appendix J

Tableting Results for Furosemide formulations

This appendix contains raw and calculated results of formulations of furosemide combined with different excipients (in different concentrations). Methods can be seen in Chapter 3. Tablet formulations are indicated with the API, API concentration and lastly the excipient.

Tableting results (Furosemide)

Table 1: Formulations of furosemide (5 % w/w) with Tablettose® 80

Formula: Furosemide 05 Tablettose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (m	Diameter (mr	Hardness (N)	Tens Str (σt)
1	374.3	Pass		1	3.63	10.02	90	1.575245639
2	379.9	Pass		2	3.63	10.06	94	1.63871478
3	375.9	Pass		3	3.66	10.06	107	1.85005583
4	375.7	Pass		4	3.61	10.08	67	1.172160795
5	378.6	Pass		5	3.62	10.08	86	1.500408347
6	380	Pass		6	3.64	10.09	80	1.386684177
7	376.1	Pass		7	3.53	10.07	49	0.877550316
8	374.1	Pass		8	3.6	10.1	86	1.505756337
9	379.2	Pass		9	3.63	10.1	98	1.701681196
10	379.1	Pass		10	3.62	10.09	80	1.394345416
11	380.7	Pass		Average	3.617	10.075	83.7	1.460260283
12	379.5	Pass		STD Dev	0.03465705	0.024152295	16.37783054	0.27714506
13	378.9	Pass		% RSD (STD	0.958171135	0.239725008	19.56730053	18.9791548
14	374.5	Pass						
15	377.5	Pass						
16	376.8	Pass		**Friability**	17 tabs			
17	377.2	Pass		Weight (g)	6.4143			
18	380.6	Pass		Before		Broken?		
19	373.6	Pass		Cracked?	6.3967			
20	373.8	Pass		After	0.27514187			Pass
Average	377.3							
STD Dev	2.424871131							
% RSD (ST	0.642690467							

Table 2: Formulations of furosemide (10 % w/w) with FlowLac® 100

Formula: Furosemide 10 FlowLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (m	Diameter (m	Hardness (N)	Tens Str (σt)
1	384	Pass		1	3.8	10.09	124	2.058861086
2	384.4	Pass		2	3.8	10.05	132	2.200413981
3	371.1	Pass		3	3.8	10.08	136	2.260345892
4	375.3	Pass		4	3.76	10.1	127	2.12899492
5	385.3	Pass		5	3.76	10.08	90	1.511730083
6	374.9	Pass		6	3.75	10.05	139	2.347997303
7	382.4	Pass		7	3.76	10.1	140	2.346923534
8	386.7	Pass		8	3.76	10.07	152	2.555679536
9	377.4	Pass		9	3.75	10.07	139	2.343333952
10	382.2	Pass		10	3.77	10.08	141	2.362094962
11	381.3	Pass		Average	3.771	10.077	132	2.211637525
12	380	Pass		STD Dev	0.020789955	0.017669811	16.70661878	0.282406706
13	379.9	Pass		% RSD (STD	0.551311452	0.175347931	12.65652938	12.76912256
14	384.7	Pass						
15	389	Pass						
16	389.4	Pass		**Friability**	17 tabs			
17	387.7	Pass		Weight (g)	6.503			
18	384.5	Pass		Before		Broken?		
19	383	Pass		Cracked?	6.4898			
20	387	Pass		After	0.203396098			Pass
Average	382.51							
STD Dev	4.908092137							
% RSD (ST	1.283127797							

Table 3: Formulations of furosemide (15 % w/w) with FlowLac® 100

Formula: Furosemide 15 FlowLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	234.7	Pass		1	2.6	9.95	21	0.516776777
2	238.8	Pass		2	2.85	9.99	114	2.549028118
3	215.9	Complete Fail		3	2.9	10	131	2.875765179
4	272.8	Complete Fail		4	2.88	10.04	142	3.126383621
5	189.9	Complete Fail		5	2.6	9.97	19	0.466622007
6	271.5	Complete Fail		6	2.66	10	40	0.957322966
7	270.5	Complete Fail		7	2.7	9.99	44	1.038492937
8	206.4	Complete Fail		8	2.67	10.01	37	0.881325849
9	233.7	Pass		9	2.7	10.01	54	1.271967577
10	244.5	Pass		10	2.81	10.01	95	2.150123129
11	281	Complete Fail		Average	2.737	9.997	69.7	1.583380816
12	266.1	Complete Fail		STD Dev	0.113436228	0.024517567	46.41371924	0.998236867
13	253.7	Pass		% RSD (STD	4.144546138	0.245249249	66.59070192	63.04464832
14	224.1	Fail						
15	262	Fail						
16	242.9	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	253	Pass		Weight (g)	6.4786	6.5124	6.4832	
18	217.2	Complete Fail		Cracked?	Chipped	Broken?	Yes	
19	194.1	Complete Fail		After (g)	5.1979	4.8989	5.2279	
20	263.5	Fail		Diff %	24.63879644	32.93596522	24.0115534	Fail, redo
Average	241.815			Average	27.19543835	Fail		
STD Dev	27.03285087			STD Dev	4.981324622			
% RSD (ST	11.17914558			% RSD (STD	18.31676533			

Table 4: Formulations of furosemide (12 % w/w) with Avicel® PH200

Formula: Furosemide 12 Avicel® PH200

Uniformity of Weight		
Tab No.	Weight (g)	
1	271	Pass
2	269.4	Pass
3	265.6	Pass
4	266	Pass
5	274.1	Pass
6	274.7	Pass
7	268.8	Pass
8	262.3	Pass
9	271	Pass
10	268.9	Pass
11	271.6	Pass
12	273.7	Pass
13	269.9	Pass
14	268.9	Pass
15	264	Pass
16	273.5	Pass
17	268.9	Pass
18	262.2	Pass
19	272.5	Pass
20	269.5	Pass
Average	269.325	
STD Dev	3.725569543	
% RSD (ST	1.383298819	

Tablet Hardness				
	Thickness (m	Diameter (mr	Hardness (N)	Tens Str (σt)
1	2.71	10.01	221	5.186436062
2	2.67	10.04	218	5.17716066
3	2.65	10.01	207	4.967873367
4	2.68	10.02	238	5.642279092
5	2.66	10.06	213	5.067340749
6	2.64	10.02	209	5.029846838
7	2.63	10.03	207	4.995670512
8	2.62	10.03	201	4.869383234
9	2.66	10.03	228	5.440419647
10	2.64	10.02	223	5.366774377
Average	2.656	10.027	216.5	5.174318454
STD Dev	0.026331224	0.014944341	11.2965088	0.241942975
% RSD (STD	0.991386429	0.149041001	5.217786975	4.675842372

Friability	(Enough tablets to be near as possible to 6.5g)			
Weight (g)	6.4324			
Before		Broken?		
Cracked?	6.4273			
After	0.079349027			Pass

Table 5: Formulations of furosemide (6 % w/w) with Emcompress®

Formula: Furosemide 06 Emcompress®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (m	Diameter (m	Hardness (N)	Tens Str (σt)
1	370.4	Pass		1	2.64	10.02	93	2.238161511
2	380.7	Pass		2	2.62	10.03	71	1.720030894
3	363	Pass		3	2.59	10.03	68	1.666434847
4	371.2	Pass		4	2.6	10.05	83	2.02217532
5	368.4	Pass		5	2.6	10.06	87	2.117522564
6	372	Pass		6	2.64	10.03	90	2.163803269
7	370	Pass		7	2.61	10.03	87	2.115718752
8	371.9	Pass		8	2.57	10.05	76	1.873244776
9	371.7	Pass		9	2.59	10.05	83	2.029982947
10	368.9	Pass		10	2.57	10.03	78	1.926374272
11	377.1	Pass		Average	2.603	10.038	81.6	1.987344915
12	368.8	Pass		STD Dev	0.024966644	0.013165612	8.194849331	0.189056151
13	365.1	Pass		% RSD (STD	0.959148844	0.131157718	10.04270751	9.513001496
14	370.8	Pass						
15	372.6	Pass						
16	376.3	Pass		**Friability**	17 tabs			
17	374.9	Pass		Weight (g)	6.3367			
18	355.2	Pass		Before		Broken?		
19	369.3	Pass		Cracked?	6.3174			
20	369.9	Pass		After	0.305505429			Pass
Average	370.41							
STD Dev	5.343456402							
% RSD (ST	1.442578872							

Table 6: Formulations of furosemide (9 % w/w) with Cellactose® 80

Formula: Furosemide 09 Cellactose® 80

Uniformity of Weight		
Tab No.	Weight (g)	
1	357.2	Pass
2	354.7	Pass
3	357.7	Pass
4	353.4	Pass
5	359.3	Pass
6	353.9	Pass
7	354.9	Pass
8	351	Pass
9	354.6	Pass
10	355.1	Pass
11	354.2	Pass
12	352.5	Pass
13	360.7	Pass
14	357.3	Pass
15	354.9	Pass
16	356.7	Pass
17	356.2	Pass
18	356.7	Pass
19	359.1	Pass
20	351	Pass
Average	355.555	
STD Dev	2.607776831	
% RSD (ST	0.73343838	

Tablet Hardness				
	Thickness (m	Diameter (mr	Hardness (N)	Tens Str (σt)
1	3.46	10.04	153	2.803894974
2	3.45	10.05	159	2.919389828
3	3.47	10.03	158	2.89005962
4	3.47	10.03	163	2.981517203
5	3.47	10.06	158	2.881441152
6	3.47	10.05	157	2.866053142
7	3.47	10.03	167	3.05468327
8	3.44	10.04	154	2.838629347
9	3.43	10.05	156	2.881008499
10	3.48	10.04	175	3.188637982
Average	3.461	10.042	160	2.930531502
STD Dev	0.015951315	0.010327956	6.683312552	0.115420455
% RSD (STD	0.460887455	0.102847596	4.177070345	3.93855023

Friability	18 tabs			
Weight (g)	6.6777			
Before		Broken?		
Cracked?	6.6593			
After	0.276305317			Pass

Table 7: Formulations of furosemide (14 % w/w) with MicroceLac® 100

Formula: Furosemide 14 MicroceLac® 100

Uniformity of Weight		
Tab No.	Weight (g)	
1	349.4	Pass
2	351.5	Pass
3	352.7	Pass
4	347	Pass
5	358.5	Pass
6	354.8	Pass
7	354.2	Pass
8	347.7	Pass
9	347.2	Pass
10	346.4	Pass
11	349.6	Pass
12	348	Pass
13	350.8	Pass
14	346.8	Pass
15	343.6	Pass
16	344.3	Pass
17	347.2	Pass
18	349.5	Pass
19	345.1	Pass
20	348.5	Pass
Average	349.14	
STD Dev	3.741432318	
% RSD (ST	1.07161377	

Tablet Hardness				
	Thickness (m	Diameter (mı	Hardness (N)	Tens Str (σt)
1	3.36	10.04	230	4.34045211
2	3.38	10.05	257	4.816488018
3	3.4	10.03	263	4.909712044
4	3.34	10.04	244	4.632226318
5	3.35	10.07	200	3.774294994
6	3.38	10.01	242	4.553493398
7	3.36	10.05	263	4.95827411
8	3.35	10.02	252	4.77934229
9	3.33	10.02	230	4.388296909
10	3.33	10.03	239	4.555466501
Average	3.358	10.036	242	4.570804669
STD Dev	0.022997584	0.017763883	19.06713286	0.348639519
% RSD (STD	0.684859572	0.177001629	7.878980521	7.627530476

Friability	19 tabs		
Weight (g)	6.6116		
Before		Broken?	
Cracked?	6.5923		
After	0.292765803		Pass

Table 8: Formulations of furosemide (19 % w/w) with MicroceLac® 100

Formula: Furosemide 19 MicroceLac® 100

Uniformity of Weight		
Tab No.	Weight (g)	
1	282.8	Pass
2	289.4	Pass
3	288.6	Pass
4	278.7	Pass
5	283.1	Pass
6	287.4	Pass
7	269.4	Fail
8	282.4	Pass
9	279.9	Pass
10	287.1	Pass
11	280.2	Pass
12	285	Pass
13	288.5	Pass
14	291.6	Pass
15	283.6	Pass
16	290.9	Pass
17	279.7	Pass
18	289.5	Pass
19	294.1	Pass
20	288	Pass
Average	284.995	
STD Dev	5.724046691	
% RSD (ST	2.008472672	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	3.18	10	85	1.701656624
2	3.15	10.01	62	1.251777616
3	3.13	10.01	49	0.995629573
4	3.12	10.01	43	0.876516119
5	3.15	10.02	47	0.947981158
6	3.16	10	68	1.369941282
7	3.16	10.01	77	1.549707333
8	3.17	10.01	79	1.584943826
9	3.2	10.01	65	1.291842071
10	3.13	10.01	59	1.198819282
Average	3.155	10.009	63.4	1.276881488
STD Dev	0.024608038	0.005676462	14.26884719	0.281454282
% RSD (STI	0.779969522	0.056713579	22.50606812	22.04231828

Friability	23 tabs			
Weight (g)	6.547			
Before		Broken?		
Cracked?	6.5244			
After	0.346392005			Pass

Table 9: Formulations of furosemide (4 % w/w) with StarLac®

Formula: Furosemide 04 StarLac®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	390.1	Pass		1	3.59	10.01	204	3.613946877
2	388.6	Pass		2	3.61	10	191	3.368265278
3	390.1	Pass		3	3.61	10	190	3.350630381
4	389.3	Pass		4	3.6	10.01	209	3.692239217
5	387.7	Pass		5	3.62	10.06	137	2.39493725
6	390.2	Pass		6	3.64	10.23	201	3.436364019
7	382	Pass		7	3.65	10.02	223	3.881721741
8	395.4	Pass		8	3.59	10.02	198	3.504153668
9	386.9	Pass		9	3.59	10.01	187	3.312784637
10	386.1	Pass		10	3.62	10.01	208	3.654271492
11	389.1	Pass		Average	3.612	10.037	194.8	3.420931456
12	395.6	Pass		STD Dev	0.020976177	0.069928535	22.95793254	0.402337341
13	395.9	Pass		% RSD (STD	0.580735796	0.696707532	11.78538632	11.76104656
14	384.7	Pass						
15	389.2	Pass						
16	378.5	Pass		**Friability**	17 tabs			
17	388.4	Pass		Weight (g)	6.6145			
18	398.3	Pass		Before		Broken?		
19	386.8	Pass		Cracked?	6.5973			
20	392.3	Pass		After	0.260712716			Pass
Average	389.26							
STD Dev	4.755982382							
% RSD (ST	1.221800951							

Table 10: Formulations of furosemide (9 % w/w) with StarLac®

Formula: Furosemide 09 StarLac®

Uniformity of Weight		
Tab No.	Weight (g)	
1	404.6	Pass
2	390.8	Pass
3	382.1	Pass
4	384	Pass
5	388.8	Pass
6	383.5	Pass
7	401.9	Pass
8	399.2	Pass
9	398.4	Pass
10	400.7	Pass
11	406.1	Pass
12	397.1	Pass
13	390.8	Pass
14	396.2	Pass
15	394.1	Pass
16	408.2	Pass
17	397.7	Pass
18	394.3	Pass
19	388.6	Pass
20	394.9	Pass
Average	395.1	
STD Dev	7.425064239	
% RSD (ST	1.879287329	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	3.57	9.99	190	3.391564022
2	3.65	9.99	230	4.01559224
3	3.63	10.01	227	3.977088705
4	3.54	10.03	220	3.944560384
5	3.61	10.01	221	3.893418761
6	3.53	9.99	192	3.466100556
7	3.57	10.08	158	2.795171514
8	3.88	10.01	205	3.360223625
9	3.62	10.01	218	3.829957622
10	3.56	10.02	207	3.69430501
Average	3.616	10.014	206.8	3.636798244
STD Dev	0.100906998	0.02674987	21.94336144	0.385079831
% RSD (STD	2.790569632	0.267124727	10.61090979	10.58842985

Friability	16 tabs			
Weight (g)	6.7353			
Before		Broken?		
Cracked?	6.7204			
After	0.221712993			Pass

Table 11: Formulations of furosemide (14 % w/w) with StarLac®

Formula: Furosemide 14 StarLac®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (m	Diameter (m	Hardness (N)	Tens Str (σt)
1	379	Pass		1	3.62	9.78	161	2.895066698
2	380.8	Pass		2	3.61	9.82	162	2.909219218
3	383.3	Pass		3	3.61	9.79	153	2.756015528
4	381.5	Pass		4	3.62	9.84	161	2.877413852
5	383.8	Pass		5	3.61	9.85	118	2.112606919
6	376	Pass		6	3.59	9.79	158	2.861937001
7	380.2	Pass		7	3.62	9.83	115	2.057386449
8	379.4	Pass		8	3.58	9.82	128	2.317904711
9	380.7	Pass		9	3.6	9.79	174	3.142998536
10	380.6	Pass		10	3.58	9.8	166	3.012167433
11	377.3	Pass		Average	3.604	9.811	149.6	2.694271634
12	381.2	Pass		STD Dev	0.015776213	0.024244129	21.14079784	0.385862438
13	380	Pass		% RSD (STD	0.437741752	0.247111698	14.13154936	14.32158632
14	384.1	Pass						
15	378.2	Pass						
16	379.6	Pass		**Friability**	17 tabs			
17	379.6	Pass		Weight (g)	6.3597			
18	379.5	Pass		Before		Broken?		
19	380.9	Pass		Cracked?	6.3453			
20	383.7	Pass		After	0.226939625			Pass
Average	380.47							
STD Dev	2.126301459							
% RSD (S	0.558861792							

Appendix K

Tableting Results for Pyridoxine formulations

This appendix contains raw and calculated results of formulations of pyridoxine combined with different excipients (in different concentrations). Methods can be seen in Chapter 3. Tablet formulations are indicated with the API, API concentration and lastly the excipient.

Tableting results (Pyridoxine HCl)

Table 1: Formulations of pyridoxine HCl (9 % w/w) with Tablettose® 80

Formula: Pyridoxine HCl 09 Tablettose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	391.9	Pass		1	3.54	10.02	100	1.794771396
2	390.9	Pass		2	3.62	10.01	116	2.037959102
3	387.5	Pass		3	3.6	10.02	107	1.888398637
4	388.3	Pass		4	3.63	10.02	108	1.890294766
5	386.7	Pass		5	3.64	10.03	107	1.865784943
6	393.3	Pass		6	3.65	10.02	110	1.914750635
7	382.3	Pass		7	3.63	10.03	105	1.835954289
8	380.1	Pass		8	3.62	10.02	116	2.03592521
9	386.4	Pass		9	3.63	10.02	111	1.942802954
10	385.7	Pass		10	3.62	10.01	108	1.897410198
11	379.9	Pass		Average	3.618	10.02	108.8	1.910405213
12	385.5	Pass		STD Dev	0.030477679	0.006666667	4.825856286	0.078213695
13	388	Pass		% RSD (STD	0.84239023	0.066533599	4.435529674	4.094089272
14	381.2	Pass						
15	394.3	Pass						
16	395.2	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	392	Pass		Weight (g)	6.5832			
18	390.5	Pass		Before		Broken?		
19	384.8	Pass		Cracked?	6.5462			
20	401.2	Pass		After	0.565213406			Pass
Average	388.285							
STD Dev	5.483110431							
% RSD (ST	1.412135527							

Table 2: Formulations of pyridoxine HCl (14 % w/w) with Tablettose® 80

Formula: Pyridoxine HCl 14 Tablettose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	393.5	Pass		1	3.7	10.02	102	1.751502853
2	389.3	Pass		2	3.71	10.03	106	1.813473216
3	392.8	Pass		3	3.72	10.03	104	1.774473792
4	386.1	Pass		4	3.71	10.04	107	1.828758165
5	393.5	Pass		5	3.68	10.03	105	1.811009258
6	396.6	Pass		6	3.71	10.03	115	1.967447357
7	380	Pass		7	3.63	10.03	98	1.713557336
8	391.9	Pass		8	3.7	10.03	104	1.784065542
9	393.1	Pass		9	3.68	10.03	105	1.811009258
10	393.3	Pass		10	3.71	10.01	111	1.90280864
11	399.2	Pass		Average	3.695	10.028	105.7	1.815810542
12	394.5	Pass		STD Dev	0.026352314	0.007888106	4.667856991	0.073097553
13	399.5	Pass		% RSD (STD	0.713188466	0.078660813	4.416137172	4.025615627
14	385.2	Pass						
15	387.2	Pass						
16	385.8	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	390.7	Pass		Weight (g)	6.6405			
18	392.6	Pass		Before		Broken?		
19	400	Pass		Cracked?	6.623			
20	383.8	Pass		After	0.264230711			Pass
Average	391.43							
STD Dev	5.449104224							
% RSD (ST	1.392101838							

Table 3: Formulations of pyridoxine HCl (19 % w/w) with Tablettose® 80

Formula: Pyridoxine HCl 19 Tablettose® 80

Uniformity of Weight		
Tab No.	Weight (g)	
1	395.1	Pass
2	403.2	Pass
3	396.8	Pass
4	397.1	Pass
5	396.3	Pass
6	397.7	Pass
7	394.8	Pass
8	392.1	Pass
9	384.7	Pass
10	398.7	Pass
11	395	Pass
12	398.5	Pass
13	385.5	Pass
14	397.8	Pass
15	395.6	Pass
16	398	Pass
17	385.4	Pass
18	395	Pass
19	394.8	Pass
20	395.9	Pass
Average	394.9	
STD Dev	4.727411665	
% RSD (ST	1.197116147	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	3.68	10.02	81	1.39845856
2	3.72	10.04	91	1.551118089
3	3.7	10.03	89	1.526748396
4	3.75	10.04	85	1.437255794
5	3.75	10.03	93	1.574094751
6	3.68	10.03	85	1.466055113
7	3.75	10.03	85	1.438688751
8	3.76	10.03	67	1.131009226
9	3.77	10.01	65	1.096523773
10	3.69	10.02	82	1.411886832
Average	3.725	10.028	82.3	1.403183929
STD Dev	0.03503966	0.009189366	9.381423725	0.163623912
% RSD (STI	0.940662015	0.091637075	11.39905677	11.66090268

Friability	(Enough tablets to be near as possible to 6.5g)			
Weight (g)	6.7136	6.3003	6.3219	
Cracked?	No	Broken?	No	
After (g)	6.6499	6.2403	6.2614	
Diff %	0.957909141	0.961492236	0.966237583	Pass
Average	0.961879653	Pass		
STD Dev	0.004177715			
% RSD (STI	0.434328238			

Table 4: Formulations of pyridoxine HCl (24 % w/w) with Tablettose® 80

Formula: Pyridoxine HCl 24 Tablettose® 80

Uniformity of Weight		
Tab No.	Weight (g)	
1	393.9	Pass
2	407.8	Pass
3	401.1	Pass
4	398.1	Pass
5	400.8	Pass
6	392.2	Pass
7	388.1	Pass
8	388.1	Pass
9	399.7	Pass
10	389.6	Pass
11	408.5	Pass
12	407.9	Pass
13	400.4	Pass
14	404	Pass
15	402	Pass
16	392.2	Pass
17	386.9	Pass
18	407.3	Pass
19	389.6	Pass
20	402.6	Pass
Average	398.04	
STD Dev	7.378731884	
% RSD (ST	1.853766426	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	3.83	10.02	71	1.177801156
2	3.77	10.03	87	1.464728367
3	3.77	10.06	73	1.225359867
4	3.73	10.03	79	1.344303872
5	3.71	10.03	63	1.077818987
6	3.79	10.01	91	1.527032316
7	3.73	10.03	81	1.378336881
8	3.84	10.03	67	1.107446534
9	3.79	10.01	89	1.493471166
10	3.86	10.04	85	1.396297728
Average	3.782	10.029	78.6	1.319259687
STD Dev	0.050288059	0.014491377	9.697651491	0.162179099
% RSD (STI	1.329668406	0.144494733	12.337979	12.29318997

Friability	(Enough tablets to be near as possible to 6.5g)			
Weight (g)	6.3602	6.3894	6.3405	
Cracked?	No	Broken?	Yes	
After (g)	6.1622	6.1178	6.1287	
Diff %	3.213138165	4.439504397	3.455871555	Fail, redo
Average	3.702838039	Fail		
STD Dev	0.649413479			
% RSD (STI	17.53826315			

Table 5: Formulations of pyridoxine HCl (29 % w/w) with Tablettose® 80

Formula: Pyridoxine HCl 29 Tablettose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (m	Diameter (m	Hardness (N)	Tens Str (σt)
1	402.9	Pass		1	3.84	9.98	47	0.780757591
2	397.2	Pass		2	3.81	10.01	44	0.734469467
3	393.7	Pass		3	3.79	10.07	36	0.600501288
4	400.8	Pass		4	3.81	10.06	36	0.597942837
5	398.4	Pass		5	3.75	10.03	43	0.727807251
6	395.9	Pass		6	3.84	10	49	0.812353355
7	400.7	Pass		7	3.81	10.06	36	0.597942837
8	398	Pass		8	3.79	10.05	38	0.635123888
9	396.7	Pass		9	3.8	10.06	36	0.59951637
10	410.1	Pass		10	3.81	10.06	40	0.66438093
11	391.6	Pass		Average	3.805	10.038	40.5	0.675079581
12	393.7	Pass		STD Dev	0.025927249	0.031198291	4.949747468	0.082463521
13	408.6	Pass		% RSD (STD	0.681399439	0.310801858	12.22159869	12.21537773
14	401	Pass						
15	409.1	Pass						
16	404	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	401.2	Pass		Weight (g)	6.4145	6.4905	6.3908	
18	411.1	Pass		Cracked?	No	Broken?	Yes	
19	389.5	Pass		After (g)	6.2699	6.2995	6.3059	
20	408.7	Pass		Diff %	2.306256878	3.031986666	1.346358173	Fail, redo
Average	400.645			Average	2.228200572	Fail		
STD Dev	6.405710857			STD Dev	0.845520813			
% RSD (ST	1.598849569			% RSD (STD	37.94635111			

Table 6: Formulations of pyridoxine HCl (34 % w/w) with Tablettose® 80

Formula: Pyridoxine HCl 34 Tablettose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	396.4	Pass		1	3.79	10.02	39	0.653789285
2	398.7	Pass		2	3.82	10.02	38	0.632022639
3	398.6	Pass		3	3.78	10.05	37	0.620046107
4	396.9	Pass		4	3.79	10.03	39	0.653137451
5	401.9	Pass		5	3.84	10.03	41	0.677691163
6	395.1	Pass		6	3.8	10.02	36	0.601909649
7	396.9	Pass		7	3.84	10.01	46	0.76185558
8	399.6	Pass		8	3.84	10.03	46	0.760336426
9	400.7	Pass		9	3.79	10.03	38	0.636390337
10	398.7	Pass		10	3.79	10.02	41	0.68731694
11	395.8	Pass		Average	3.808	10.026	40.1	0.668449558
12	406.3	Pass		STD Dev	0.024404007	0.010749677	3.478505426	0.054958387
13	403.6	Pass		% RSD (STI	0.640861527	0.107218003	8.674577123	8.221770263
14	402.6	Pass						
15	391.8	Pass						
16	397.4	Pass		**Friability**	16 tabs			
17	400.8	Pass		Weight (g)	6.3848			
18	395.3	Pass		Before	Chipping	Broken?		
19	399.6	Pass		Cracked?	6.1892			
20	399.5	Pass		After	3.160343825			Fail
Average	398.81							
STD Dev	3.337648085							
% RSD (ST	0.836901804							

Table 7: Formulations of pyridoxine HCl (34 % w/w) with FlowLac® 100

Formula: Pyridoxine HCl 34 FlowLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	400.4	Pass		1	3.83	10.02	110	1.824762354
2	398.7	Pass		2	3.82	10	108	1.799867419
3	400	Pass		3	3.82	10.05	112	1.857242961
4	399.4	Pass		4	3.85	10.02	108	1.782277922
5	398.8	Pass		5	3.84	10.02	114	1.886192564
6	400.4	Pass		6	3.84	10.03	115	1.900841066
7	399.5	Pass		7	3.8	10.02	114	1.906047223
8	398.9	Pass		8	3.71	10.02	97	1.661155261
9	392	Pass		9	3.81	10.02	124	2.067802761
10	401.6	Pass		10	3.81	10.02	115	1.917720303
11	398.7	Pass		Average	3.813	10.022	111.7	1.860390983
12	399	Pass		STD Dev	0.039454615	0.012292726	6.912950809	0.106161122
13	405.8	Pass		% RSD (STI	1.034739451	0.122657413	6.188854798	5.706387665
14	400.3	Pass						
15	400.6	Pass						
16	400.2	Pass		**Friability**	16 tabs			
17	399.6	Pass		Weight (g)	6.3926			
18	398.7	Pass		Before		Broken?		
19	389.9	Pass		Cracked?	6.3815			
20	398.2	Pass		After	0.173940296			Pass
Average	399.035							
STD Dev	3.221028767							
% RSD (ST	0.807204573							

Table 8: Formulations of pyridoxine HCl (39 % w/w) with FlowLac® 100

Formula: Pyridoxine HCl 39 FlowLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	403.6	Pass		1	3.84	10.02	100	1.654554881
2	403.3	Pass		2	3.84	10.02	109	1.80346482
3	402.2	Pass		3	3.84	10.04	117	1.931972977
4	391.8	Pass		4	3.83	10.05	106	1.753158382
5	402.6	Pass		5	3.83	10.03	109	1.80637084
6	404.5	Pass		6	3.83	10.02	113	1.8745286
7	402.9	Pass		7	3.83	10.03	105	1.740082002
8	402.1	Pass		8	3.81	10.02	118	1.967747789
9	405.3	Pass		9	3.85	10.02	116	1.914298509
10	400.4	Pass		10	3.83	10.01	121	2.009243823
11	401.3	Pass		Average	3.833	10.026	111.4	1.845542262
12	404.4	Pass		STD Dev	0.010593499	0.011737878	6.686636756	0.112648928
13	400.2	Pass		% RSD (STD	0.276376182	0.117074386	6.002366927	6.103838973
14	402.1	Pass						
15	404	Pass						
16	394.5	Pass		**Friability**	16 tabs			
17	404.5	Pass		Weight (g)	6.4326			
18	403.3	Pass		Before		Broken?		
19	403.7	Pass		Cracked?	6.4178			
20	404.7	Pass		After	0.23060862			Pass
Average	402.07							
STD Dev	3.379364624							
% RSD (ST	0.840491612							

Table 9: Formulations of pyridoxine HCl (44 % w/w) with FlowLac® 100

Formula: Pyridoxine HCl 44 FlowLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (m	Diameter (m	Hardness (N)	Tens Str (σt)
1	395.3	Pass		1	3.71	10.03	67	1.146251938
2	394	Pass		2	3.71	10.08	60	1.021402536
3	395.3	Pass		3	3.72	10.09	51	0.86500017
4	391.7	Pass		4	3.77	10.09	54	0.90373555
5	394.8	Pass		5	3.71	10.1	59	1.00239029
6	393.4	Pass		6	3.71	10.05	61	1.04152569
7	393.2	Pass		7	3.72	10.11	54	0.914070698
8	394.6	Pass		8	3.7	10.1	59	1.005099453
9	394	Pass		9	3.8	10.09	51	0.84678964
10	394.3	Pass		10	3.72	10.09	57	0.966764896
11	394.1	Pass		Average	3.727	10.083	57.3	0.971303086
12	394.6	Pass		STD Dev	0.031989582	0.024517567	4.967673276	0.091178884
13	392.2	Pass		% RSD (STD	0.858319872	0.243157467	8.669586869	9.387274192
14	406.1	Pass						
15	396.4	Pass						
16	393.1	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	392.7	Pass		Weight (g)	6.3144	6.4103	6.4321	
18	394	Pass		Cracked?	Yes	Broken?	Capping	
19	394.9	Pass		After (g)	5.3441	5.4089	5.2075	
20	392.3	Pass		Diff %	18.15647162	18.51393074	23.51608257	Fail, redo
Average	394.5105263			Average	20.06216165	Fail		
STD Dev	3.037706506			STD Dev	2.996518243			
% RSD (ST	0.769993778			% RSD (STD	14.93616837			

Table 10: Formulations of pyridoxine HCl (31 % w/w) with Avicel® PH200

Pyridoxine HCl 31 Avicel® PH200

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	387	Pass		1	3.73	9.98	162	2.770484753
2	390	Pass		2	3.73	9.99	158	2.69937294
3	390.2	Pass		3	3.71	9.99	166	2.85133873
4	392.5	Pass		4	3.73	9.99	169	2.887303967
5	389.1	Pass		5	3.65	9.99	168	2.933128245
6	388.2	Pass		6	3.72	9.99	166	2.843673841
7	388.3	Pass		7	3.75	9.99	157	2.667982763
8	393	Pass		8	3.71	9.99	168	2.885692209
9	392.4	Pass		9	3.7	9.98	164	2.827428984
10	392.7	Pass		10	3.7	9.97	176	3.037357476
11	392.5	Pass		Average	3.713	9.986	165.4	2.840376391
12	395.4	Pass		STD Dev	0.027100635	0.006992059	5.561774297	0.108753153
13	390.5	Pass		% RSD (STI	0.729885147	0.070018616	3.362620494	3.828828916
14	392.4	Pass						
15	377.9	Pass						
16	389.8	Pass		**Friability**	17 tabs			
17	391.5	Pass		Weight (g)	6.6307			
18	387	Pass		Before		Broken?		
19	391.1	Pass		Cracked?	6.6172			
20	388.6	Pass		After	0.204013782			Pass
Average	390.005							
STD Dev	3.602407821							
% RSD (ST	0.923682471							

Table 11: Formulations of pyridoxine HCl (36 % w/w) with Avicel® PH200

Formula: Pyridoxine HCl 36 Avicel® PH200

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	384	Pass		1	3.73	9.98	135	2.308737294
2	381.9	Pass		2	3.72	9.99	134	2.295495751
3	384.7	Pass		3	3.7	9.99	122	2.101225881
4	380	Pass		4	3.69	9.99	114	1.968761554
5	382.8	Pass		5	3.72	9.99	135	2.312626316
6	386.5	Pass		6	3.72	9.99	137	2.346887447
7	378	Pass		7	3.72	9.99	135	2.312626316
8	380.2	Pass		8	3.71	9.99	136	2.33603655
9	380.1	Pass		9	3.72	9.99	136	2.329756882
10	382.7	Pass		10	3.7	9.99	136	2.342350162
11	372.9	Pass		Average	3.713	9.989	132	2.265450415
12	377	Pass		STD Dev	0.012516656	0.003162278	7.659416862	0.126440531
13	376.5	Pass		% RSD (STI	0.33710357	0.0316576	5.802588532	5.581253511
14	379.7	Pass						
15	382.5	Pass						
16	381.2	Pass		**Friability**	17 tabs			
17	372.6	Pass		Weight (g)	6.4767			
18	381.9	Pass		Before		Broken?		
19	384.1	Pass		Cracked?	6.4672			
20	380.9	Pass		After	0.146895101			Pass
Average	380.51							
STD Dev	3.651661482							
% RSD (ST	0.959675562							

Table 12: Formulations of pyridoxine HCl (41 % w/w) with Avicel® PH200

Formula: Pyridoxine HCl 41 Avicel® PH200

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	383.5	Pass		1	3.73	9.98	131	2.240330263
2	382	Pass		2	3.64	9.99	125	2.188382656
3	380.4	Pass		3	3.69	9.97	139	2.405322971
4	380.4	Pass		4	3.64	9.99	129	2.258410901
5	379.3	Pass		5	3.66	9.98	134	2.335464631
6	385.3	Pass		6	3.72	9.97	137	2.351595346
7	384.7	Pass		7	3.64	9.97	134	2.350652218
8	379.4	Pass		8	3.7	9.97	139	2.398822098
9	380.3	Pass		9	3.65	9.98	131	2.289433392
10	386.7	Pass		10	3.7	9.99	129	2.221788021
11	386.9	Pass		Average	3.677	9.979	132.8	2.30402025
12	374.6	Pass		STD Dev	0.034976182	0.00875595	4.638007235	0.075395186
13	376.4	Pass		% RSD (STI	0.951215186	0.087743765	3.492475327	3.272331751
14	386.4	Pass						
15	371.2	Pass						
16	383.3	Pass		**Friability**	17 tabs			
17	382.4	Pass		Weight (g)	6.4957			
18	379.3	Pass		Before		Broken?		
19	386.4	Pass		Cracked?	6.4828			
20	387.1	Pass		After	0.198988092			Pass
Average	381.8							
STD Dev	4.379497688							
% RSD (ST	1.147065921							

Table 13: Formulations of pyridoxine HCl (46 % w/w) with Avicel® PH200

Formula: Pyridoxine HCl 46 Avicel® PH200

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (m	Diameter (m	Hardness (N)	Tens Str (σt)
1	400.5	Pass		1	3.8	10.01	75	1.255231162
2	400.6	Pass		2	3.82	10.02	73	1.214148754
3	397.8	Pass		3	3.79	10.06	76	1.268985105
4	402.2	Pass		4	3.94	10.04	58	0.933422321
5	399.2	Pass		5	3.76	10.05	63	1.061369897
6	402.6	Pass		6	3.8	10.06	70	1.165726276
7	400.5	Pass		7	3.91	10.06	76	1.230039271
8	395.3	Pass		8	3.77	10.07	72	1.207373942
9	398.5	Pass		9	3.84	10.07	67	1.103047541
10	400.1	Pass		10	3.85	10.07	66	1.083761848
11	402.6	Pass		Average	3.828	10.051	69.6	1.152310612
12	391.5	Pass		STD Dev	0.058651513	0.021317703	6.022181222	0.105720443
13	392.7	Pass		% RSD (STD	1.532171191	0.21209534	8.652559227	9.174648036
14	400.3	Pass						
15	401.1	Pass						
16	399.4	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	400.2	Pass		Weight (g)	6.3825	6.3754	6.3894	
18	396.9	Pass		Cracked?	No	Broken?	No	
19	402.6	Pass		After (g)	6.2746	6.2542	6.2786	
20	401.1	Pass		Diff %	1.71963153	1.937897733	1.76472462	Fail, redo
Average	399.285			Average	1.807417961	Fail		
STD Dev	3.10894719			STD Dev	0.11522619			
% RSD (ST	0.778628596			% RSD (STD	6.375182288			

Table 14: Formulations of pyridoxine HCl (35 % w/w) with Emcompress®

Formula: Pyridoxine HCl 35 Emcompress®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	397.6	Pass		1	3.04	10.02	99	2.069064419
2	403.5	Pass		2	3.06	10.02	101	2.097067206
3	405.2	Pass		3	3.03	10.02	100	2.096861631
4	401.6	Pass		4	3.05	10.02	103	2.14560507
5	403.2	Pass		5	3.03	10.01	96	2.014998142
6	400.3	Pass		6	3.04	10.06	91	1.894305198
7	404.4	Pass		7	3.05	10.02	98	2.041449484
8	402.8	Pass		8	3.04	10.02	100	2.08996406
9	386.6	Pass		9	3.02	10.02	99	2.082766833
10	395.9	Pass		10	3.04	10.03	107	2.234031971
11	403.9	Pass		Average	3.04	10.024	99.4	2.076611401
12	404.9	Pass		STD Dev	0.011547005	0.013498971	4.195235393	0.087503092
13	404.9	Pass		% RSD (STD	0.379835703	0.134666512	4.220558745	4.213744166
14	391	Pass						
15	403.9	Pass						
16	404.5	Pass		**Friability**	16 tabs			
17	403.4	Pass		Weight (g)	6.413			
18	406.1	Pass		Before		Broken?		
19	406	Pass		Cracked?	6.3943			
20	401.2	Pass		After	0.292447961			Pass
Average	401.545							
STD Dev	5.128196051							
% RSD (ST	1.277116152							

Table 15: Formulations of pyridoxine HCl (40 % w/w) with Emcompress®

Formula: Pyridoxine HCl 40 Emcompress®

Uniformity of Weight		
Tab No.	Weight (g)	
1	397.4	Pass
2	393.6	Pass
3	395.8	Pass
4	393.5	Pass
5	391.8	Pass
6	393.5	Pass
7	388.1	Pass
8	370.9	Fail
9	393.9	Pass
10	392.8	Pass
11	397.8	Pass
12	395.4	Pass
13	392.8	Pass
14	393.2	Pass
15	391.5	Pass
16	387	Pass
17	395.1	Pass
18	394.2	Pass
19	394.8	Pass
20	397.9	Pass
Average	392.55	
STD Dev	5.799047109	
% RSD (ST	1.477276043	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	2.96	10	84	1.806623678
2	3.04	10	94	1.968495349
3	3.03	10	94	1.974992033
4	2.98	10.04	77	1.638403516
5	3.04	10	87	1.82190527
6	3.01	10	83	1.75546316
7	3.07	10	98	2.032206439
8	3.03	10	97	2.038023694
9	3.03	10	94	1.974992033
10	2.97	10	79	1.693365724
Average	3.016	10.004	88.7	1.87044709
STD Dev	0.035339622	0.012649111	7.660142151	0.145515874
% RSD (STI	1.171738133	0.12644053	8.636011445	7.77973754

Friability	17 tabs			
Weight (g)	6.6651			
Before		Broken?		
Cracked?	6.6444			
After	0.311540545			Pass

Table 16: Formulations of pyridoxine HCl (45 % w/w) with Emcompress®

Formula: Pyridoxine HCl 45 Emcompress®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	387.3	Pass		1	3.03	10	81	1.701854837
2	370.1	Pass		2	3.03	10	82	1.722865391
3	386	Pass		3	3.04	10.01	85	1.778244146
4	389.6	Pass		4	3.03	10	81	1.701854837
5	387.9	Pass		5	2.96	10	74	1.591549431
6	375.4	Pass		6	3.03	10	81	1.701854837
7	385	Pass		7	3.03	10	81	1.701854837
8	386.9	Pass		8	3.05	10	82	1.711567913
9	385.4	Pass		9	3.04	9.99	83	1.739879389
10	387.4	Pass		10	3.01	10	86	1.818913635
11	387.7	Pass		Average	3.025	10	81.6	1.717043925
12	379.3	Pass		STD Dev	0.025055494	0.004714045	3.204163958	0.059047948
13	379.7	Pass		% RSD (STI	0.828280792	0.047140452	3.926671517	3.438930525
14	390	Pass						
15	386.5	Pass						
16	388.1	Pass		**Friability**	17 tabs			
17	386.5	Pass		Weight (g)	6.5286			
18	389.1	Pass		Before		Broken?		
19	388.2	Pass		Cracked?	6.5001			
20	376.6	Pass		After	0.438454793			Pass
Average	384.635							
STD Dev	5.436163024							
% RSD (ST	1.413330306							

Table 17: Formulations of pyridoxine HCl (50 % w/w) with Emcompress®

Formula: Pyridoxine HCl 50 Emcompress®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	370.6	Fail		1	3.16	9.99	61	1.230148063
2	392.6	Pass		2	3.03	10.01	44	0.923540815
3	394.6	Pass		3	3.17	10	66	1.325454416
4	396.3	Pass		4	3.14	10.01	56	1.134238604
5	388.3	Pass		5	3.18	10	65	1.30126683
6	396	Pass		6	3.08	10.02	56	1.155180135
7	392.7	Pass		7	3.17	10.02	59	1.182510895
8	395.3	Pass		8	3.11	10	49	1.003034368
9	390.1	Pass		9	3.07	9.98	52	1.08047457
10	393.5	Pass		10	3.17	10.02	66	1.322808798
11	395.2	Pass		Average	3.128	10.005	57.4	1.165865749
12	395	Pass		STD Dev	0.052451035	0.013540064	7.486283754	0.136008144
13	392.2	Pass		% RSD (STD	1.676823381	0.135332974	13.04230619	11.66584953
14	386	Pass						
15	393.3	Pass						
16	392.5	Pass		**Friability**	17 tabs			
17	391.8	Pass		Weight (g)	6.6598			
18	391.6	Pass		Before		Broken?		
19	392.6	Pass		Cracked?	6.6343			
20	378.8	Pass		After	0.384366097			Pass
Average	390.95							
STD Dev	6.242764233							
% RSD (ST	1.59681909							

Table 18: Formulations of pyridoxine HCl (55 % w/w) with Emcompress®

Formula: Pyridoxine HCl 55 Emcompress®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	391	Pass		1	3.19	10	55	1.097620297
2	391.5	Pass		2	3.21	10.01	61	1.208567324
3	393	Pass		3	3.19	10.02	54	1.075512539
4	390.4	Pass		4	3.21	10.01	56	1.109504429
5	390.8	Pass		5	3.19	10.01	56	1.116460569
6	387.8	Pass		6	3.22	10.02	57	1.124686249
7	387.7	Pass		7	3.2	10.01	59	1.17259511
8	389.5	Pass		8	3.19	10.03	56	1.114234327
9	387.6	Pass		9	3.2	10.02	60	1.191279514
10	390.5	Pass		10	3.17	10.01	59	1.183692225
11	393.2	Pass		Average	3.197	10.014	57.3	1.139415258
12	390.1	Pass		STD Dev	0.014181365	0.00843274	2.311805451	0.045504867
13	389.2	Pass		% RSD (STI	0.443583513	0.084209511	4.034564487	3.993703498
14	387.1	Pass						
15	389.2	Pass						
16	394.4	Pass		**Friability**	17 tabs			
17	387.6	Pass		Weight (g)	6.637			
18	392.3	Pass		Before		Broken?		
19	394	Pass		Cracked?	6.6084			
20	389.7	Pass		After	0.432782519			Pass
Average	390.33							
STD Dev	2.220739564							
% RSD (ST	0.568938991							

Table 19: Formulations of pyridoxine HCl (60 % w/w) with Emcompress®

Formula: Pyridoxine HCl 60 Emcompress®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	383	Pass		1	3.18	10.01	48	0.95997553
2	379.2	Pass		2	3.19	10.01	48	0.956966202
3	383.1	Pass		3	3.19	10.01	49	0.976902998
4	379.4	Pass		4	3.21	10.01	46	0.911378638
5	378.3	Pass		5	3.19	10.01	44	0.877219019
6	382.5	Pass		6	3.2	10.01	53	1.05334815
7	381.3	Pass		7	3.19	10.01	45	0.897155815
8	385.7	Pass		8	3.2	10.01	43	0.854603216
9	387.3	Pass		9	3.2	10.01	49	0.973850176
10	379.6	Pass		10	3.17	10.01	49	0.983066424
11	369.3	Pass		Average	3.192	10.01	47.4	0.944446617
12	383.4	Pass		STD Dev	0.011352924	1.87244E-15	2.951459149	0.059243569
13	377.5	Pass		% RSD (STI	0.355668053	1.87057E-14	6.226707066	6.272834073
14	380.9	Pass						
15	377.8	Pass						
16	379.4	Pass		**Friability**	17 tabs			
17	379.1	Pass		Weight (g)	6.4861			
18	384.7	Pass		Before		Broken?		
19	383	Pass		Cracked?	6.4412			
20	380.9	Pass		After	0.697075079			Pass
Average	380.77							
STD Dev	3.808176798							
% RSD (ST	1.000125219							

Table 20: Formulations of pyridoxine HCl (65 % w/w) with Emcompress®

Formula: Pyridoxine HCl 65 Emcompress®

Uniformity of Weight		
Tab No.	Weight (g)	
1	363.4	Pass
2	348.9	Fail
3	389.9	Pass
4	390.8	Pass
5	352.6	Fail
6	375.8	Pass
7	392.7	Pass
8	381.9	Pass
9	349.6	Fail
10	390	Pass
11	370	Pass
12	391.1	Pass
13	389.5	Pass
14	387.7	Pass
15	387	Pass
16	392.2	Pass
17	387.1	Pass
18	395.3	Pass
19	383.9	Pass
20	359.9	Fail
Average	378.965	
STD Dev	15.6739232	
% RSD (ST	4.135981739	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	3.3	10.01	52	1.002156273
2	3.28	10.01	50	0.969487483
3	3.09	10.02	42	0.863581266
4	3.28	10.02	51	0.987890329
5	3.23	10.02	48	0.944171999
6	3.32	10.01	52	0.996119187
7	3.25	10.01	48	0.939299134
8	3.32	10.02	53	1.014262076
9	3.27	10.02	52	1.010341035
10	3.2	10.01	46	0.914226696
Average	3.254	10.015	49.4	0.964153548
STD Dev	0.068992753	0.005270463	3.438345856	0.048678677
% RSD (STI	2.120244414	0.052625689	6.960214282	5.048851067

Friability	(Enough tablets to be near as possible to 6.5g)			
Weight (g)	6.5581	6.5423	6.6109	
Cracked?	No	Broken?	No	
After (g)	6.4432	6.4219	6.5021	
Diff %	1.783275391	1.874834551	1.673305547	Fail, redo
Average	1.777138496	Fail		
STD Dev	0.100904563			
% RSD (STI	5.677923439			

Table 21: Formulations of pyridoxine HCl (23 % w/w) with Cellactose® 80

Formula: Pyridoxine HCl 23 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	405.6	Pass		1	3.71	10.01	154	2.639932707
2	402.9	Pass		2	3.81	10.01	184	3.071417772
3	401.2	Pass		3	3.8	9.99	180	3.018585929
4	402.9	Pass		4	3.73	10.01	161	2.745131098
5	404.7	Pass		5	3.83	10.01	202	3.354274812
6	402.8	Pass		6	3.8	9.99	185	3.102435538
7	402.3	Pass		7	3.72	10.01	164	2.803799498
8	398.8	Pass		8	3.81	9.99	184	3.077566756
9	403.8	Pass		9	3.78	10.01	184	3.095794103
10	408.6	Pass		10	3.79	10.01	186	3.121186931
11	401.8	Pass		Average	3.778	10.004	178.4	3.003012514
12	400	Pass		STD Dev	0.042373996	0.009660918	14.37745148	0.211958984
13	401.3	Pass		% RSD (STD	1.121598629	0.09657055	8.059109575	7.058211807
14	393.8	Pass						
15	407.6	Pass						
16	390.9	Pass		**Friability**	16 tabs			
17	400.3	Pass		Weight (g)	6.403			
18	387.1	Pass		Before		Broken?		
19	399.3	Pass		Cracked?	6.3904			
20	399.9	Pass		After	0.197170756			Pass
Average	400.78							
STD Dev	5.198441062							
% RSD (ST	1.297080958							

Table 22: Formulations of pyridoxine HCl (28 % w/w) with Cellactose® 80

Formula: Pyridoxine HCl 28 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (m	Diameter (m	Hardness (N)	Tens Str (σt)
1	395.3	Pass		1	3.82	10.03	159	2.641879174
2	383.2	Pass		2	3.78	10.07	139	2.324736063
3	383.6	Pass		3	3.79	10.09	129	2.147531076
4	397.3	Pass		4	3.78	10.07	135	2.257837184
5	398.4	Pass		5	3.73	10.09	133	2.249737077
6	395.5	Pass		6	3.81	10.09	146	2.417780312
7	397.9	Pass		7	3.8	10.08	153	2.542889128
8	395.4	Pass		8	3.7	10.08	123	2.09953432
9	396.1	Pass		9	3.82	10.09	149	2.461001408
10	393.1	Pass		10	3.82	10.1	146	2.409063469
11	393.2	Pass		Average	3.785	10.079	141.2	2.355198921
12	394	Pass		STD Dev	0.040620192	0.019692074	11.32156251	0.171737844
13	400.1	Pass		% RSD (STD	1.073188693	0.195377259	8.018103764	7.29186153
14	397.2	Pass						
15	401.5	Pass						
16	395.4	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	406.3	Pass		Weight (g)	6.3213			
18	397.1	Pass		Before		Broken?		
19	395	Pass		Cracked?	6.3134			
20	384.1	Pass		After	0.125130674			Pass
Average	394.985							
STD Dev	5.749990847							
% RSD (ST	1.455749167							

Table 23: Formulations of pyridoxine HCl (33 % w/w) with Cellactose® 80

Formula: Pyridoxine HCl 33 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	383.4	Pass		1	3.52	10	141	2.550096247
2	379.2	Pass		2	3.54	10.01	148	2.658915274
3	376.7	Pass		3	3.59	10.01	164	2.905329842
4	383.8	Pass		4	3.61	10.01	162	2.853999273
5	375.2	Pass		5	3.56	10.01	146	2.608248122
6	378.4	Pass		6	3.52	10.01	139	2.511413256
7	377.3	Pass		7	3.56	10.01	155	2.76903054
8	375.4	Pass		8	3.53	9.99	144	2.599575417
9	379.3	Pass		9	3.51	9.99	138	2.505454987
10	376.3	Pass		10	3.56	10.01	156	2.786895253
11	377.1	Pass		Average	3.55	10.005	149.3	2.674895821
12	377.5	Pass		STD Dev	0.032317866	0.008498366	9.416887903	0.144516527
13	374.5	Pass		% RSD (STI	0.910362415	0.084941188	6.307359614	5.402697388
14	379.3	Pass						
15	380.3	Pass						
16	380.5	Pass		**Friability**	17 tabs			
17	376.7	Pass		Weight (g)	6.4035			
18	368.2	Pass		Before		Broken?		
19	375.1	Pass		Cracked?	6.3878			
20	381.1	Pass		After	0.24578102			Pass
Average	377.765							
STD Dev	3.456081596							
% RSD (ST	0.914876073							

Table 24: Formulations of pyridoxine HCl (38 % w/w) with Cellactose® 80

Formula: Pyridoxine HCl 38 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	392.2	Pass		1	3.69	10	152	2.62239039
2	389.6	Pass		2	3.68	10	154	2.664115352
3	392.2	Pass		3	3.62	9.99	143	2.517341304
4	387.4	Pass		4	3.69	10.01	152	2.61977062
5	383.3	Pass		5	3.69	10.01	147	2.533593955
6	392.8	Pass		6	3.68	9.99	155	2.684098901
7	392.7	Pass		7	3.68	10.01	155	2.678736066
8	391.4	Pass		8	3.69	10.01	155	2.671476619
9	391	Pass		9	3.67	10.01	151	2.61671804
10	392.5	Pass		10	3.64	10.01	147	2.568396069
11	389.5	Pass		Average	3.673	10.004	151.1	2.617663732
12	386.4	Pass		STD Dev	0.02406011	0.00843274	4.148627618	0.060354817
13	386.9	Pass		% RSD (STI	0.65505336	0.084293687	2.745617219	2.305674961
14	382.6	Pass						
15	392.3	Pass						
16	392.7	Pass		**Friability**	16 tabs			
17	396.8	Pass		Weight (g)	6.6476			
18	397.8	Pass		Before		Broken?		
19	394.5	Pass		Cracked?	6.6303			
20	391	Pass		After	0.260923337			Pass
Average	390.78							
STD Dev	3.921277987							
% RSD (ST	1.003448996							

Table 25: Formulations of pyridoxine HCl (43 % w/w) with Cellactose® 80

Formula: Pyridoxine HCl 43 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	382.6	Pass		1	3.66	10	115	2.000308028
2	381.3	Pass		2	3.74	9.99	127	2.163947667
3	384.5	Pass		3	3.7	10	127	2.185154354
4	383.7	Pass		4	3.67	10	115	1.994857597
5	377.8	Pass		5	3.67	10.03	117	2.023480332
6	377	Pass		6	3.65	10	111	1.936021774
7	394.5	Pass		7	3.65	10	110	1.918580136
8	383.4	Pass		8	3.67	10	120	2.081590536
9	379.6	Pass		9	3.66	10	112	1.948126079
10	383.9	Pass		10	3.75	10	134	2.274854653
11	378.3	Pass		Average	3.682	10.002	118.8	2.052692116
12	382.4	Pass		STD Dev	0.036147845	0.010327956	8.052604824	0.11999521
13	380.2	Pass		% RSD (STI	0.981744828	0.103258904	6.778286889	5.845748093
14	381	Pass						
15	384.5	Pass						
16	379.6	Pass		**Friability**	17 tabs			
17	383.5	Pass		Weight (g)	6.4937			
18	385.2	Pass		Before		Broken?		
19	379.2	Pass		Cracked?	6.4708			
20	385	Pass		After	0.353897509			Pass
Average	382.36							
STD Dev	3.818569586							
% RSD (ST	0.998684378							

Table 26: Formulations of pyridoxine HCl (48 % w/w) with Cellactose® 80

Formula:Pyridoxine HCl 48 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	385.5	Pass		1	3.72	10	111	1.899591256
2	391.2	Pass		2	3.75	10	121	2.054159799
3	393.3	Pass		3	3.74	9.99	117	1.993558087
4	397.4	Pass		4	3.74	10	117	1.991564529
5	398.4	Pass		5	3.71	10	104	1.78459451
6	385.1	Pass		6	3.71	10	105	1.801754073
7	391.5	Pass		7	3.74	9.99	119	2.027636003
8	397.4	Pass		8	3.72	10	116	1.98515843
9	393.5	Pass		9	3.72	9.99	112	1.918623314
10	392.3	Pass		10	3.72	10	114	1.95093156
11	391.1	Pass		Average	3.727	9.997	113.6	1.940757156
12	390.4	Pass		STD Dev	0.014181365	0.004830459	5.660781257	0.090520458
13	400.6	Pass		% RSD (STI	0.380503486	0.048319085	4.983082093	4.664182619
14	391	Pass						
15	390.7	Pass						
16	387	Pass		**Friability**	17 tabs			
17	390.6	Pass		Weight (g)	6.6639			
18	394.4	Pass		Before		Broken?		
19	391	Pass		Cracked?	6.6471			
20	391.3	Pass		After	0.252741797			Pass
Average	392.185							
STD Dev	4.023650477							
% RSD (ST	1.025957259							

Table 27: Formulations of pyridoxine HCl (53 % w/w) with Cellactose® 80

Formula: Pyridoxine HCl 53 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	398.6	Pass		1	3.84	9.99	121	2.008023452
2	403.4	Pass		2	3.79	10	118	1.982087946
3	411.8	Pass		3	3.76	9.99	108	1.830419127
4	401.9	Pass		4	3.85	10	117	1.934662685
5	404	Pass		5	3.82	10	112	1.866529176
6	401.9	Pass		6	3.79	10	108	1.814114391
7	392.1	Pass		7	3.8	10	116	1.943365621
8	408.5	Pass		8	3.78	9.99	111	1.871310324
9	403	Pass		9	3.8	10	116	1.943365621
10	402.9	Pass		10	3.78	10	116	1.953647979
11	397.1	Pass		Average	3.801	9.997	114.3	1.914752632
12	401.8	Pass		STD Dev	0.028067379	0.004830459	4.347413024	0.065177609
13	378.7	Fail		% RSD (STI	0.738420922	0.048319085	3.803510957	3.403970193
14	402.3	Pass						
15	403.7	Pass						
16	401.2	Pass		**Friability**	16 tabs			
17	411.5	Pass		Weight (g)	6.4366			
18	402.4	Pass		Before		Broken?		
19	410.3	Pass		Cracked?	6.4011			
20	401.8	Pass		After	0.554592179			Pass
Average	401.945							
STD Dev	7.201935047							
% RSD (ST	1.791771274							

Table 28: Formulations of pyridoxine HCl (58 % w/w) with Cellactose® 80

Formula: Pyridoxine HCl 58 Cellactose® 80

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	394	Pass		1	3.74	10	86	1.463885038
2	402.1	Pass		2	3.74	9.99	85	1.44831143
3	394.9	Pass		3	3.77	10.02	85	1.43248465
4	394	Pass		4	3.73	10.02	82	1.396745954
5	392.9	Pass		5	3.8	10.01	89	1.489540979
6	396.3	Pass		6	3.7	10.02	79	1.356556131
7	397.6	Pass		7	3.76	10	85	1.439167039
8	393.5	Pass		8	3.8	10	84	1.40726476
9	395.3	Pass		9	3.76	10	82	1.388372908
10	394.1	Pass		10	3.78	10.03	89	1.494436261
11	393.3	Pass		Average	3.758	10.009	84.6	1.431676515
12	395.3	Pass		STD Dev	0.031552426	0.012866839	3.098386677	0.044711799
13	398.4	Pass		% RSD (STI	0.839606852	0.128552696	3.662395599	3.123037803
14	394.9	Pass						
15	394.8	Pass						
16	396.4	Pass		**Friability**	17 tabs			
17	396.1	Pass		Weight (g)	6.7046			
18	402.6	Pass		Before		Broken?		
19	375.2	Pass		Cracked?	6.6895			
20	395.3	Pass		After	0.225726885			Pass
Average	394.85							
STD Dev	5.309524709							
% RSD (ST	1.344694114							

Table 29: Formulations of pyridoxine HCl (63 % w/w) with Cellactose® 80

Formula: Pyridoxine HCl 63 Cellactose® 80

Uniformity of Weight		
Tab No.	Weight (g)	
1	394.8	Pass
2	391.9	Pass
3	396.4	Pass
4	398	Pass
5	393.5	Pass
6	396.6	Pass
7	396.6	Pass
8	393.4	Pass
9	394.2	Pass
10	397.2	Pass
11	391.4	Pass
12	392.6	Pass
13	392	Pass
14	393.1	Pass
15	392.7	Pass
16	393.5	Pass
17	393.4	Pass
18	393.1	Pass
19	393.2	Pass
20	392.7	Pass
Average	394.015	
STD Dev	1.921971302	
% RSD (ST	0.487791404	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	3.74	10.01	80	1.360393131
2	3.81	9.98	79	1.322670591
3	3.73	10.02	82	1.396745954
4	3.79	10.02	79	1.324342397
5	3.73	9.98	78	1.333937103
6	3.75	10	82	1.392075236
7	3.75	10.02	79	1.338468716
8	3.7	10.02	76	1.305041342
9	3.75	10.02	79	1.338468716
10	3.75	10.01	77	1.305886713
Average	3.75	10.008	79.1	1.34180299
STD Dev	0.030912062	0.016193277	1.91195072	0.032124838
% RSD (STI	0.824321644	0.161803328	2.417131125	2.394154606

Friability	(Enough tablets to be near as possible to 6.5g)			
Weight (g)	6.6964	6.59897	6.7014	
Cracked?	No	Broken?	No	
After (g)	6.231	6.3147	6.2986	
Diff %	7.469106082	4.501718213	6.395071921	Fail, redo
Average	6.121965405	Fail		
STD Dev	1.502427392			
% RSD (STI	24.54158579			

Table 30: Formulations of pyridoxine HCl (68 % w/w) with Cellactose® 80

Formula: Pyridoxine HCl 68 Cellactose® 80

Uniformity of Weight		
Tab No.	Weight (g)	
1	391.5	Pass
2	395.6	Pass
3	389	Pass
4	376.5	Pass
5	371.8	Fail
6	397.5	Pass
7	396	Pass
8	396.9	Pass
9	384.7	Pass
10	397.3	Pass
11	395.7	Pass
12	395.6	Pass
13	399.1	Pass
14	394.6	Pass
15	396.8	Pass
16	396.2	Pass
17	394.2	Pass
18	396.2	Pass
19	395.1	Pass
20	395.2	Pass
Average	392.775	
STD Dev	7.170691444	
% RSD (ST	1.82564864	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	3.81	10.02	65	1.083928867
2	3.8	10.02	71	1.187099586
3	3.73	10	69	1.177661241
4	3.78	10.02	72	1.210188713
5	3.75	10.02	69	1.169042297
6	3.66	9.99	67	1.166563414
7	3.81	10.02	67	1.117280524
8	3.78	10.02	68	1.142956007
9	3.74	10.02	70	1.189156021
10	3.72	10	70	1.197940432
Average	3.758	10.013	68.8	1.16418171
STD Dev	0.047562824	0.011595018	2.097617696	0.039025643
% RSD (STI	1.265641936	0.115799641	3.048862931	3.352195129

Friability	(Enough tablets to be near as possible to 6.5g)			
Weight (g)	6.6778	6.7019	6.6049	
Cracked?	No	Broken?	No	
After (g)	6.2355	6.2471	6.10889	
Diff %	7.093256355	7.280178003	8.119478334	Fail, redo
Average	7.497637564	Fail		
STD Dev	0.546579714			
% RSD (STI	7.29002581			

Table 31: Formulations of pyridoxine HCl (32 % w/w) with MicroceLac® 100

Formula: Pyridoxine HCl 32 MicroceLac® 100

Uniformity of Weight		
Tab No.	Weight (g)	
1	388.7	Pass
2	402.9	Pass
3	391.4	Pass
4	391.8	Pass
5	399.6	Pass
6	396.6	Pass
7	393	Pass
8	401.5	Pass
9	396.6	Pass
10	401	Pass
11	392.6	Pass
12	398.2	Pass
13	394.2	Pass
14	401.3	Pass
15	393.6	Pass
16	390.2	Pass
17	400.1	Pass
18	396.8	Pass
19	394.5	Pass
20	401.4	Pass
Average	396.3	
STD Dev	4.303120043	
% RSD (ST	1.085823882	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	4.02	10.01	129	2.040843501
2	3.99	10	115	1.834869018
3	3.99	10.02	112	1.783435998
4	3.98	10.02	118	1.88369826
5	3.98	10.02	114	1.819844082
6	3.97	10.01	100	1.601974279
7	4.03	10.01	124	1.956873196
8	3.98	10.02	120	1.915625349
9	4	10.02	130	2.064884491
10	4.01	10.01	132	2.093512721
Average	3.995	10.014	119.4	1.899556089
STD Dev	0.0195789	0.006992059	9.81155781	0.149550052
% RSD (STD	0.490085112	0.069822838	8.217385101	7.872894749

Friability	16 tabs			
Weight (g)	6.3321			
Before		Broken?		
Cracked?	6.3251			
After	0.110670187			Pass

Table 32: Formulations of pyridoxine HCl (37 % w/w) with MicroceLac® 100

Formula: Pyridoxine HCl 37 MicroceLac® 100

Uniformity of Weight		
Tab No.	Weight (g)	
1	394.4	Pass
2	390.7	Pass
3	393.1	Pass
4	389.3	Pass
5	392	Pass
6	398.3	Pass
7	396.2	Pass
8	396.2	Pass
9	380	Pass
10	394.3	Pass
11	395.1	Pass
12	396.1	Pass
13	383.6	Pass
14	392.4	Pass
15	391.7	Pass
16	393	Pass
17	390.6	Pass
18	393.3	Pass
19	394.4	Pass
20	394.9	Pass
Average	392.48	
STD Dev	4.302092514	
% RSD (ST	1.09613038	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	3.98	10.01	95	1.518051757
2	3.99	10.02	95	1.512735891
3	4.01	10.02	98	1.552723423
4	3.98	10.02	94	1.50057319
5	4.01	10.02	104	1.647788123
6	3.99	10.02	101	1.608277105
7	3.98	10.02	97	1.548463824
8	3.99	10.02	102	1.624200641
9	3.98	10.02	88	1.404791923
10	4	10.02	104	1.651907593
Average	3.991	10.019	97.8	1.556951347
STD Dev	0.01197219	0.003162278	5.072803301	0.077684472
% RSD (STI	0.299979704	0.031562807	5.186915441	4.989524684

Friability	16 tabs			
Weight (g)	6.3321			
Before		Broken?		
Cracked?	6.3251			
After	0.110670187			Pass

Table 33: Formulations of pyridoxine HCl (42 % w/w) with MicroceLac® 100

Formula: Pyridoxine HCl 42 MicroceLac® 100

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	400	Pass		1	4.17	10	61	0.931266334
2	399.4	Pass		2	4.17	10.01	63	0.960838817
3	398.7	Pass		3	4.15	10.02	59	0.903267359
4	394.7	Pass		4	4.18	10.02	63	0.957583533
5	395.1	Pass		5	4.15	10.02	55	0.842028894
6	399.6	Pass		6	4.16	10.03	59	0.900197642
7	397.4	Pass		7	4.14	10.02	51	0.782676396
8	401.5	Pass		8	4.14	10.02	56	0.859409376
9	401.5	Pass		9	4.14	10.02	62	0.951488952
10	399	Pass		10	4.14	10.02	66	1.012875336
11	408.1	Pass		Average	4.154	10.018	59.5	0.910163264
12	401.9	Pass		STD Dev	0.015055453	0.007888106	4.478342948	0.067608048
13	398.8	Pass		% RSD (STD	0.362432669	0.078739333	7.526626803	7.42812316
14	399.6	Pass						
15	399.8	Pass						
16	399.9	Pass		**Friability**	16 tabs			
17	397.7	Pass		Weight (g)	6.3963			
18	398.8	Pass		Before		Broken?		
19	396.9	Pass		Cracked?	6.3854			
20	398.5	Pass		After	0.170701914			Pass
Average	399.345							
STD Dev	2.785767399							
% RSD (ST	0.697584144							

Table 34: Formulations of pyridoxine HCl (47 % w/w) with MicroceLac® 100

Formula: Pyridoxine HCl 47 MicroceLac® 100

Uniformity of Weight		
Tab No.	Weight (g)	
1	402	Pass
2	396.8	Pass
3	399.7	Pass
4	403.2	Pass
5	396.4	Pass
6	400.3	Pass
7	399.7	Pass
8	389.6	Pass
9	399.7	Pass
10	400.7	Pass
11	385.1	Pass
12	369.9	Fail
13	396	Pass
14	397.2	Pass
15	391.8	Pass
16	400.7	Pass
17	398.6	Pass
18	398.6	Pass
19	395.1	Pass
20	395.8	Pass
Average	395.845	
STD Dev	7.491502203	
% RSD (ST	1.89253425	

Tablet Hardness				
	Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	4.15	10	53	0.81303248
2	4.16	10.01	49	0.74911552
3	4.14	10.01	51	0.78345829
4	4.17	10.01	51	0.7778219
5	4.15	10.02	56	0.85733851
6	4.15	10.01	56	0.858194992
7	4.15	10.01	51	0.781570439
8	4.15	10.01	57	0.873519902
9	4.09	10.01	27	0.419842599
10	4.13	10.01	49	0.754557037
Average	4.144	10.01	50	0.766845167
STD Dev	0.021705094	0.004714045	8.589399151	0.129758768
% RSD (STI	0.523771576	0.047093359	17.1787983	16.92111706

Friability	(Enough tablets to be near as possible to 6.5g)			
Weight (g)	6.3509	6.4087	6.3704	
Cracked?	No	Broken?	No	
After (g)	5.9271	6.0129	5.9445	
Diff %	7.150208365	6.582514261	7.164605938	Fail, redo
Average	6.965776188	Fail		
STD Dev	0.331992622			
% RSD (STI	4.766053532			

Table 35: Formulations of pyridoxine HCl (13 % w/w) with StarLac®

Formula: Pyridoxine HCl 13 StarLac®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	397.6	Pass		1	3.86	10.01	99	1.631150131
2	398.2	Pass		2	3.87	10	99	1.628562208
3	395.7	Pass		3	3.85	10.02	101	1.666759909
4	398.9	Pass		4	3.86	10.02	105	1.72828116
5	398.8	Pass		5	3.88	10.02	105	1.719372495
6	398.2	Pass		6	3.86	10.02	103	1.695361519
7	397.2	Pass		7	3.84	10.03	94	1.553730958
8	398.5	Pass		8	3.86	10.02	96	1.580142775
9	399.3	Pass		9	3.87	10.02	97	1.592477008
10	398	Pass		10	3.85	10.02	104	1.716267629
11	397.3	Pass		Average	3.86	10.018	100.3	1.651210579
12	398.7	Pass		STD Dev	0.011547005	0.007888106	3.917198545	0.063181696
13	398	Pass		% RSD (STI	0.299145217	0.078739333	3.905482099	3.82638632
14	392.4	Pass						
15	397.9	Pass						
16	398.4	Pass		**Friability**	16 tabs			
17	401.9	Pass		Weight (g)	6.3743			
18	397.5	Pass		Before		Broken?		
19	399.9	Pass		Cracked?	6.3539			
20	406.7	Pass		After	0.321062654			Pass
Average	398.455							
STD Dev	2.642661139							
% RSD (ST	0.663226999							

Table 36: Formulations of pyridoxine HCl (18 % w/w) with StarLac®

Formula: Pyridoxine HCl 18 StarLac®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	399.7	Pass		1	3.87	10.01	96	1.577634204
2	400.1	Pass		2	3.88	10.02	96	1.571997709
3	402.5	Pass		3	3.86	10.02	92	1.514303493
4	403.8	Pass		4	3.87	10.02	96	1.576059719
5	399.9	Pass		5	3.8	10.05	66	1.100206991
6	400.1	Pass		6	3.91	10.02	98	1.59243502
7	401.6	Pass		7	3.88	10.02	92	1.506497805
8	404.5	Pass		8	3.85	10.03	93	1.533209173
9	397.9	Pass		9	3.86	10.02	100	1.645982058
10	399.7	Pass		10	3.85	10.02	92	1.518236749
11	398.4	Pass		Average	3.863	10.023	92.1	1.513656292
12	403.5	Pass		STD Dev	0.028303906	0.010593499	9.573690801	0.151475176
13	400.2	Pass		% RSD (STD	0.732692371	0.105691899	10.39488686	10.00723725
14	396.2	Pass						
15	398.8	Pass						
16	401.8	Pass		**Friability**	16 tabs			
17	404.1	Pass		Weight (g)	6.4058			
18	401.7	Pass		Before		Broken?		
19	398.5	Pass		Cracked?	6.3881			
20	403.1	Pass		After	0.277077691			Pass
Average	400.805							
STD Dev	2.30205286							
% RSD (ST	0.574357321							

Table 37: Formulations of pyridoxine HCl (23 % w/w) with StarLac®

Formula: Pyridoxine HCl 23 StarLac®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	403.7	Pass		1	3.85	10.02	82	1.353211015
2	404.5	Pass		2	3.87	10.03	93	1.525285612
3	402.3	Pass		3	3.85	10.04	88	1.449333574
4	400.3	Pass		4	3.84	10.02	83	1.373280551
5	402.4	Pass		5	3.86	10.02	92	1.514303493
6	403.1	Pass		6	3.88	10.02	88	1.4409979
7	403.8	Pass		7	3.86	10.03	75	1.233255749
8	402.8	Pass		8	3.87	10.03	93	1.525285612
9	401.1	Pass		9	3.85	10.02	87	1.435723882
10	404.5	Pass		10	3.88	10.02	91	1.490122829
11	402.7	Pass		Average	3.861	10.025	87.2	1.434080022
12	399.8	Pass		STD Dev	0.013703203	0.007071068	5.769652406	0.092534385
13	405.5	Pass		% RSD (STI	0.354913318	0.070534342	6.61657386	6.452525899
14	398.7	Pass						
15	398.1	Pass						
16	405.6	Pass		**Friability**	16 tabs			
17	405.7	Pass		Weight (g)	6.4405			
18	403.6	Pass		Before		Broken?		
19	400.6	Pass		Cracked?	6.4148			
20	400.8	Pass		After	0.400636029			Pass
Average	402.48							
STD Dev	2.249116786							
% RSD (ST	0.558814546							

Table 38: Formulations of pyridoxine HCl (28 % w/w) with StarLac®

Formula: Pyridoxine HCl 28 StarLac®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (mm)	Diameter (mm)	Hardness (N)	Tens Str (σt)
1	391.6	Pass		1	3.69	10	103	1.777014541
2	389.9	Pass		2	3.67	9.99	103	1.788487031
3	391.9	Pass		3	3.69	10.02	109	1.876776398
4	389.2	Pass		4	3.69	10.01	111	1.913121966
5	389.5	Pass		5	3.66	10.01	102	1.772413837
6	389.7	Pass		6	3.66	10.03	102	1.768879612
7	389.5	Pass		7	3.7	10.01	98	1.684497602
8	391.1	Pass		8	3.65	10.01	95	1.655300272
9	388.6	Pass		9	3.69	10.01	106	1.826945301
10	388.8	Pass		10	3.65	10.01	102	1.777269765
11	394.5	Pass		Average	3.675	10.01	103.1	1.784070632
12	393.2	Pass		STD Dev	0.019002924	0.010540926	4.724639904	0.077506724
13	390.5	Pass		% RSD (STI	0.517086361	0.105303951	4.582579926	4.344375279
14	390.4	Pass						
15	390	Pass						
16	389.5	Pass		**Friability**	17 tabs			
17	389.5	Pass		Weight (g)	6.6368			
18	389.9	Pass		Before		Broken?		
19	391.9	Pass		Cracked?	6.6104			
20	395	Pass		After	0.399370689			Pass
Average	390.71							
STD Dev	1.805809339							
% RSD (ST	0.462186619							

Table 39: Formulations of pyridoxine HCl (33 % w/w) with StarLac®

Formula: Pyridoxine HCl 33 StarLac®

Uniformity of Weight				Tablet Hardness				
Tab No.	Weight (g)				Thickness (m	Diameter (m	Hardness (N)	Tens Str (σt)
1	390.7	Pass		1	3.45	10.04	21	0.385963832
2	389.6	Pass		2	3.45	10.08	20	0.366125933
3	385.5	Pass		3	3.45	10.07	22	0.403138465
4	379.7	Pass		4	3.47	10.1	22	0.399624361
5	390.3	Pass		5	3.46	10.11	22	0.400382926
6	390.1	Pass		6	3.44	10.09	21	0.385167654
7	390	Pass		7	3.43	10.09	18	0.331106222
8	388.5	Pass		8	3.43	10.1	22	0.404284704
9	390.4	Pass		9	3.42	10.1	21	0.387036513
10	390.2	Pass		10	3.42	10.09	21	0.387420097
11	385.3	Pass		Average	3.442	10.087	21	0.385025071
12	388.9	Pass		STD Dev	0.016865481	0.020027759	1.247219129	0.022168884
13	392.1	Pass		% RSD (STD	0.489990728	0.198550198	5.939138709	5.75777681
14	386.3	Pass						
15	393.6	Pass						
16	390.2	Pass		**Friability**	(Enough tablets to be near as possible to 6.5g)			
17	385.4	Pass		Weight (g)	6.6068	6.64089	6.5867	
18	384.4	Pass		Cracked?	No	Broken?	No	
19	385.6	Pass		After (g)	6.3001	6.3407	6.3042	
20	391.8	Pass		Diff %	4.868176696	4.734335326	4.481139558	Fail, redo
Average	388.43			Average	4.694550526	Fail		
STD Dev	3.322665385			STD Dev	0.196561846			
% RSD (ST	0.855409053			% RSD (STD	4.187021626			

Appendix L

Current Drug Targets:

Instructions for Authors

This appendix contains the instructions to authors for the publications of manuscripts and articles within the Bentham Science Publishers' journal entitled Current Drug Targets.

Instructions for Authors

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 manuscript@benthamscience.org

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

MANUSCRIPTS PUBLISHED:

The Journal publishes peer-reviewed mini- and full-length review articles, letters and drug clinical trial studies written in English. Single topic/thematic issues may also be considered for publication.

As a service to authors publishing in Current Drug Targets, all articles will be published as open access via the journal's website for a period of six months only.

Single Topic Issues:

These peer reviewed issues may contain invited 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-thematic issue) to 6-10 (for full-length thematic issue) from leading scientists. Authors interested in editing a single topic issue on current topics of drug targets may submit their proposal to the Editor-in-Chief at cdt@benthamscience.org for consideration.

Conference Proceedings:

For proposals to publish conference proceedings in this journal, please contact us at email: proceedings@benthamscience.org.

MANUSCRIPT LENGTH:

Mini-Reviews:

Mini-reviews should be 3000-6000 words excluding figures, structures, photographs, schemes, tables etc.

Full-Length Reviews:

Full-length reviews should be 8000-40000 words excluding figures, structures, photographs, schemes, tables etc.

Randomized Drug Clinical Trial Studies:

Trial studies should be 1500 to 40000 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).

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.

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. Download the Template.

Our contracted service provider Eureka Science can, if needed, provide professional assistance to authors for the improvement of English language and figures in manuscripts.

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)

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

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.

Title Page:

Title page should include paper title, author(s) full name and affiliation, corresponding author(s) names complete affiliation/address, along with phone, fax and email.

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

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".

Keywords:

6 to 8 keywords must be provided.

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 List of Abbreviations, Conflict of Interest, Acknowledgement and Reference sections. For Review, the manuscript 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. The review article should mention any previous important 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. in vivo, in vitro, 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_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.

Randomized Drug Clinical Trial Studies:

Randomized drug clinical trial studies are biomedical or health-related interventional and/or observational research studies conducted in phases in human beings who are randomly allocated to receive or not receive a preventive, therapeutic, or diagnostic intervention that follows a pre-defined protocol. The study is intended to determine the safety and efficacy of approaches to disease prevention, diagnosis and treatment.

Authors of randomized controlled trials are encouraged to submit trial protocols along with their manuscripts. All clinical trials must be registered (before recruitment of the first participant) at an appropriate online public trial registry that must be independent of for-profit interest (e.g., www.clinicaltrials.gov). If you wish the editor(s) to consider an unregistered trial, please explain briefly why the trial has not been registered.

- All randomized clinical trials should include a flow diagram and authors should provide a completed randomized trial checklist (see CONSORT Flow Diagram and Checklist; www.consort-statement.org) and a trial protocol.
- Studies of diagnostic accuracy must be reported according to STARD guidelines; (www.stard-statement.org)
- Observational studies (cohort, case-control, or cross-sectional designs) must be reported according to the STROBE statement, and should be submitted with their protocols; (www.strobe-statement.org).
- Genetic association studies must be reported according to STREGA guidelines; (www.medicine.uottawa.ca)
- Systematic reviews and meta-analyses must be reported according to PRISMA guidelines; (www.prisma-statement.org)
- To find the reporting guidelines see (www.equator-network.org)

Important points to remember while submitting clinical trials:

- Each manuscript should clearly state an objective or hypothesis; the design and methods (including the study setting and dates, patients or participants with inclusion and exclusion criteria, or data sources, and how these were selected for the study); the essential features of any interventions; the main outcome measures; the main results of the study; a comment section placing the results in context with the published literature and addressing study limitations; and the conclusions. Data included in research reports must be original.
- Trial registry name, registration identification number, and the URL for the registry should be included at the end of the abstract and also in the space provided on the online manuscript submission form. If the research article reports the results of a controlled health care intervention, list the trial registry, along with the unique identifying number (Please note that there should be no space between the letters and numbers of your trial registration number). Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., phase 1 trials), are exempted.
- All reports of randomized trials should include a section entitled "Randomization and Masking", within the Methods section.
- The manuscript must include a statement identifying the institutional and/or licensing committee that has approved the experiments, including any relevant details.
- The SI system of units and the recommended international non-proprietary name (rINN) for drug names must be used. Kindly ensure that the dose, route, and frequency of administration of any drug you mention are correct.
- Please ensure that the clinical trials sponsored by pharmaceutical companies follow the guidelines on good publication practice: (www.gpp-guidelines.org)

The editors reserve the right to reject manuscripts that do not comply with the above-mentioned requirements. The author will be held responsible for false statements or failure to fulfill the above-mentioned requirements.

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 identity 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.

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 names, 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).

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.

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.

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.

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.

References:

References must be listed in the Vancouver 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 Vancouver Style:

Journal Reference:

- [1] Bossert JM, Ghitza UE, Lu L, Epstein DH, Shaham Y. Neurobiology of relapse to heroin and cocaine seeking: an update and clinical implications. Eur J Pharmacol 2005; 526: 36-50.
- [2] Phekoo KJ, Schey SA, Richards MA, *et al*. A population study to define the incidence and survival of multiple myeloma in a National Health Service Region in UK. Br J Haematol 2004; 127: 299-30.

Book Reference:

- [3] Crabtree RH. The Organometallic Chemistry of the Transition Metals, 3rd ed. New York: Wiley & Sons 2001.

Book Chapter Reference:

- [4] Wheeler DMS, Wheeler MM. In: Studies in Natural Products Chemistry; Atta-ur-Rahman, Ed. Amsterdam: Elsevier Science BV 1994; Vol. 14: pp 3-46.

Conference Proceedings:

- [5] Jakeman DL. Withers SGE. In: Carbohydrate Bioengineering: Interdisciplinary Approaches, Proceedings of the 4th Carbohydrate Bioengineering Meeting, Stockholm, Sweden, June 10-13, 2001; Teeri TT, Svensson B, Gilbert HJ, Feizi T, Eds. Cambridge, UK: Royal Society of Chemistry 2002; pp 3-8.

URL(WebPage):

- [6] Multimodality Treatment for Patients With Resectable Non-Small Cell Lung Cancer (NSCLC) – BEACON Study: Bevacizumab and Chemotherapy for Operable NSCLC. Available at: clinicaltrials.gov/ct2/show/NCT00130780 [accessed June 30, 2009].

Patent:

- [7] Hoch JA, Huang S. Screening Methods For The Identification Of Novel Antibiotics. U.S. Patent 6043045, March 28, 2000.

Thesis:

- [8] Mackel H. Capturing the Spectra of Silicon Solar Cells. PhD Thesis. Canberra: The Australian National University December 2004.

E-citations:

- [9] 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.
- List all authors if the total number of authors is six or less and for more than six authors use et al. after three (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 EndNote (version 5 and above) or Reference Manager (version 10) when formatting their reference list, as this allows references to be automatically extracted.

Appendices:

In case there is a need to present lengthy, but essential methodological details, appendices must be used, 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.

Figures/Illustrations:

All authors must strictly follow the guidelines below for preparing illustrations for publication in ***Current Drug Targets***. 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 each individual page of color figures 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%

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.

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.

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.

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.

PERMISSION FOR REPRODUCTION:

Bentham Science has collaborated with the Copyright Clearance Center to meet our customer’s licensing, besides rights & permission needs.

The Copyright Clearance Center's RightsLink® service makes it faster and easier to secure permission from Bentham Science's journal titles. Simply visit Journals by Title and locate the desired content. Then go to the article's abstract and click on "Rights and Permissions" to open the RightsLink's page. If you are unable to locate the content you wish to use or you are unable to secure the rights you are seeking, please e-mail us at permissions@benthamscience.org

Published/reproduced material should not be included unless written permission has been obtained from the copyright holder, which should be forwarded to the Editorial Office in case of acceptance of the article for publication.

AUTHORS AND INSTITUTIONAL AFFILIATIONS:

The author will be required to provide their full names, the institutional affiliations and the location, with an asterisk in front of the name of the principal/corresponding 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.

PAGE CHARGES:

No page charges will be levied to authors for the publication of their review articles.

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.

PROOF CORRECTIONS:

Authors will receive page proofs of their accepted paper before publications. To avoid delays in publication, proofs should be checked immediately for typographical errors and returned within **48 hours**. Major changes are not acceptable at the proof stage. If unable to send corrections within **48 hours** due to some reason, the author(s) must at least send an acknowledgement on receiving the galley proofs or the article will be published exactly as received and the publishers will not be responsible for any error occurring in the published manuscript in this regard.

The corresponding author will be solely responsible for ensuring that the revised version of the manuscript incorporating all the submitted corrections receives the approval of all the co-authors of the manuscript.

언어 및 편집:

영문 오타가 많은 원고는 출판되지 않을 것입니다. 영문 오타를 없애겠다는 조건으로 받은 원고는 영어 편집 전문회사인 유럽 공동 기술개발 기구로부터 가격 견적서가

보내 질 것입니다. 영어 작문에 어려움이 있는 비영어권 국가의 저자들은 원고를 학술지에 제출하기 전에 영어 편집회사와 접촉할 것을 권합니다. 영어 편집 견적서를 받기 위해서 교정될 원고의 단어수를 적은 메일을 유럽 공동 기술개발 기구 메일인 info@eureka-science.com 로 보내시기 바랍니다.

语言和编辑:

含有很多英文印刷错误的提交稿将不予发表。接受发表的稿件其英文写作应是正确的；专业的语言编辑公司（尤里卡科学），可对稿件的英文润色提供报价。建议非英语国家、且英文写作欠佳的作者在投稿前先与语言编辑公司联系。请与尤里卡科学联系 info@eureka-science.com.

EDITION ET LANGUE:

Les manuscrits soumis avec plusieurs erreurs typographiques en Anglais ne seront pas publiés en l'état. Les manuscrits sont acceptés pour publication à la condition que l'anglais utilisé soit corrigé après la soumission et seront envoyés pour examen à Eureka Science, une société d'édition de langue professionnelle. Les auteurs en provenance de pays où la langue est différente de l'anglais et qui ont de médiocres compétences en anglais écrit, sont priés de contacter la société d'édition de langue avant de soumettre leur manuscrit à la revue. Merci de contacter Eureka Science à info@eureka-science.com pour un devis en indiquant le nombre total de mot de l'article à éditer.

REPRINTS:

Printed reprints and e-prints may be ordered from the Publisher prior to publication of the article. First named authors may also order a personal print and online subscription of the journal at 50% off the normal subscription rate by contacting the subscription department at e-mail: subscriptions@benthamscience.org.

OPEN ACCESS PLUS:

Bentham Science also offers authors the choice of "Open Access Plus" publication of articles at a fee of **US$ 2,900** per article. This paid service allows for articles to be disseminated to a much wider audience, on the terms of the Creative Commons CC BY-NC-ND (Attribution-NonCommercial-NoDerivs) Licence (http://creativecommons.org/licenses/by-nc-nd/4.0/). Authors are asked to indicate whether or not they wish to pay to have their article made more widely available on this "Open Access Plus" basis. Where an author does not opt-in to this paid service, then the author's article will be published only on Bentham Science's standard subscription-based access, at no additional cost to the author.

Authors who select the "Quick Track" publication option (see below) and also wish to have their article made available on an "Open Access Plus" basis will be entitled to a **50% discount** on the "Open Access Plus" publication fee.

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.

For more information please contact us at e-mail: openaccess@benthamscience.org

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**.

REVIEWING AND PROMPTNESS OF PUBLICATION:

All papers submitted for publication are immediately subjected to editorial scrutiny, usually in consultation with members of the journal Editorial Advisory Board and outside independent reviewers. Every effort will be made to peer review submitted papers quickly. Papers which are delayed by authors in revision for more than 30 days will have to be re-submitted as a new submission. Papers accepted for publication are typeset and proofs are dispatched to authors for any corrections prior to final publication.

QUICK TRACK Publication:

For this journal an optional fast publication fee-based service called QUICK TRACK is available to authors for their submitted manuscripts.

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 cdt@benthamscience.org.

COPYRIGHT:

Authors who publish in Bentham Science print & online journals will transfer copyright to their work to ***Bentham Science Publishers***. Submission of a manuscript to the respective journals implies that all authors have read and agreed to the content of the Copyright Letter or the Terms and Conditions. It is a condition of publication that manuscripts submitted to this journal have not been published and will not be simultaneously submitted or published elsewhere. Plagiarism is strictly forbidden, and by submitting the article for publication the authors agree that the publishers have the legal right to take appropriate action against the authors, if plagiarism or fabricated information is discovered. By submitting a manuscript the authors agree that the copyright of their article is transferred to the publishers if and when the article is accepted for publication. Once submitted to the journal, the author will not withdraw their manuscript at any stage prior to publication.

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:

1. 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.
2. 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.
3. 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.
4. 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]
5. 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.

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.

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**

Disclaimer:

Articles appearing in E-Pub Ahead-of-Schedule sections have been peer-reviewed and accepted for publication in this journal and posted online before scheduled publication. Articles appearing here may contain statements, opinions, and information that have errors in facts, figures, or interpretation. Accordingly, ***Bentham Science Publishers***, the editors and authors and their respective employees are not responsible or liable for the use of any such inaccurate or misleading data, opinion or information contained of articles in the E-Pub Ahead-of-Schedule.

Member of Cope

Appendix M

Powder Technology:

Instructions for Authors

This appendix contains the instructions to authors for the publications of manuscripts and articles within the Elsevier Publishers' journal entitled Powder Technology.

Introduction

It is now possible to submit your paper online and benefit from the considerably shorter time required to reach an editorial decision about publication. For all further information, please go to the journal's homepage on http://www.elsevier.com/locate/powtec.

Types of Paper

•**Normal length research papers** - these should be complete & authoritative accounts of work which has a special significance and must be presented clearly and concisely.
•**Review articles** - these will normally be commissioned by one of the Editors. Prospective authors of a review article should consult with one of the Editors to check the suitability of their topic & material before submitting their review.
•**Short communications** - will be accepted for the early communication of important and original advances. Such accounts may be of a preliminary nature but should always be complete and should not exceed the equivalent of 3000 words, including figures and tables.
•The journal also publishes **Letters to the editors** (commenting on work published in the journal) and **Book reviews**.

Contact Details for Submission

Professor L.S. Fan
Ohio State University
Department of Chemical Engineering
140 West 19th Avenue
Columbus, OH 43210-1180
USA
Tel: +1 (614) 292 6591
Fax: +1 (614) 292 3769
fan@che.eng.ohio-state.edu

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:
• E-mail address
• Full postal address

All necessary files have been uploaded:
Manuscript:
• Include keywords
• All figures (include relevant captions)

• All tables (including titles, description, footnotes)
• Ensure all figure and table citations in the text match the files provided
• Indicate clearly if color should be used for any figures in print
Graphical Abstracts / Highlights files (where applicable)
Supplemental files (where applicable)

Further considerations
• Manuscript has been 'spell checked' and 'grammar checked'
• All references mentioned in the Reference List are cited in the text, and vice versa
• Permission has been obtained for use of copyrighted material from other sources (including the Internet)
• Relevant declarations of interest have been made
• Journal policies detailed in this guide have been reviewed
• Referee suggestions and contact details provided, based on journal requirements

For further information, visit our Support Center.

Before You Begin

Ethics in publishing

Please see our information pages on Ethics in publishing and Ethical guidelines for journal publication.

Declaration of interest

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. More information.

Submission declaration and verification

Submission of an article implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis or as an electronic preprint, see 'Multiple, redundant or concurrent publication' section of our ethics policy for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. To verify originality, your article may be checked by the originality detection service CrossCheck.

Changes to authorship

Authors are expected to consider carefully the list and order of authors **before** submitting their manuscript and provide the definitive list of authors at the time of the original submission. Any addition, deletion or rearrangement of author names in the authorship list should be made only **before** the manuscript has been accepted and only if approved by the

journal Editor. To request such a change, the Editor must receive the following from the **corresponding author**: (a) the reason for the change in author list and (b) written confirmation (e-mail, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed.
Only in exceptional circumstances will the Editor consider the addition, deletion or rearrangement of authors **after** the manuscript has been accepted. While the Editor considers the request, publication of the manuscript will be suspended. If the manuscript has already been published in an online issue, any requests approved by the Editor will result in a corrigendum.

Copyright

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (see more information on this). An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement.

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution and for all other derivative works, including compilations and translations. If excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has preprinted forms for use by authors in these cases.

For open access articles: Upon acceptance of an article, authors will be asked to complete an 'Exclusive License Agreement' (more information). Permitted third party reuse of open access articles is determined by the author's choice of user license.

Author rights
As an author you (or your employer or institution) have certain rights to reuse your work. More information.

Elsevier supports responsible sharing
Find out how you can share your research published in Elsevier journals.

Role of the funding source

You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement then this should be stated.

Funding body agreements and policies
Elsevier has established a number of agreements with funding bodies which allow authors to comply with their funder's open access policies. Some funding bodies will reimburse the author for the Open Access Publication Fee. Details of existing agreements are available online.

Open access

This journal offers authors a choice in publishing their research:

Open access
• Articles are freely available to both subscribers and the wider public with permitted reuse.
• An open access publication fee is payable by authors or on their behalf, e.g. by their research funder or institution.
Subscription
• Articles are made available to subscribers as well as developing countries and patient groups through our universal access programs.
• No open access publication fee payable by authors.

Regardless of how you choose to publish your article, the journal will apply the same peer review criteria and acceptance standards.

For open access articles, permitted third party (re)use is defined by the following Creative Commons user licenses:

Creative Commons Attribution (CC BY)
Lets others distribute and copy the article, create extracts, abstracts, and other revised versions, adaptations or derivative works of or from an article (such as a translation), include in a collective work (such as an anthology), text or data mine the article, even for commercial purposes, as long as they credit the author(s), do not represent the author as endorsing their adaptation of the article, and do not modify the article in such a way as to damage the author's honor or reputation.

Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)
For non-commercial purposes, lets others distribute and copy the article, and to include in a collective work (such as an anthology), as long as they credit the author(s) and provided they do not alter or modify the article.

The open access publication fee for this journal is **USD 2850**, excluding taxes. Learn more about Elsevier's pricing policy: https://www.elsevier.com/openaccesspricing.

Green open access
Authors can share their research in a variety of different ways and Elsevier has a number of green open access options available. We recommend authors see our green open access page for further information. Authors can also self-archive their manuscripts immediately and enable public access from their institution's repository after an embargo period. This is the version that has been accepted for publication and which typically includes author-incorporated changes suggested during submission, peer review and in editor-author communications. Embargo period: For subscription articles, an appropriate amount of time is needed for journals to deliver value to subscribing customers before an article becomes freely available to the public. This is the embargo period and it begins from the date the article is formally published online in its final and fully citable form. Find out more.

This journal has an embargo period of 24 months.

Elsevier Publishing Campus
The Elsevier Publishing Campus (www.publishingcampus.com) is an online platform offering free lectures, interactive training and professional advice to support you in publishing your research. The College of Skills training offers modules on how to prepare, write and structure your article and explains how editors will look at your paper when it is submitted for publication. Use these resources, and more, to ensure that your submission will be the best that you can make it.

Language (usage and editing services)
Please write your text in good English (American or British usage is accepted, but not a mixture of these). Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service available from Elsevier's WebShop.

Submission

Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

Referees

Powder Technology authors are required to provide the names, affiliations and e-mails of, at least, 5 referees who are excited with this research topic to be willing to volunteer their time in assessing the novelty and quality of the submitted manuscript.

Authors must adhere to the following:

* Each suggested referee cannot be a current or former colleague or employee, or a collaborator within the past 10 years.

* At least two of the referees must have published unique articles in Powder Technology during the past 10 years, preferably on a topic similar to that of the submitted manuscript. Exceptions can be made for manuscripts in non-traditional areas where two additional referees (total 7) should be given.

* Justify the selection of each referee by explicitly stating the referee's expertise in connection to the paper. Example: "Dr. XYZ is an expert on solving population balance equations and pharmaceutical process design while he has published in Powder Technology in 2015 and 2013".

Note that following the standard in the scientific community, editors retain the sole right to decide whether or not the suggested referees are used.

Perspectives Section

This section is a forum to address various important aspects of the particle technology field. These brief articles will reflect on the state of the art in particle technology, offer in-depth analysis of historical approaches, and consider the potential of various techniques, theories, and emerging areas of significance. This compact presentation of information should allow the reader to gain a good idea of the subject matter in a short time.
Length and style of contributions:
• Brief articles, limited to 3000 words
• References and figures should be easy to read, informative and interesting to experts and non-specialists.
Ideally, manuscripts will be proofread for clarity as well as grammatical correctness prior to initial submission. Submission of contributions: Perspectives manuscripts will be coordinated and handled by L.-S. Fan, and suggestions for Perspectives authors should be directed to him.

Preparation

Use of word processing software

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.
To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

LaTeX

You are recommended to use the Elsevier article class elsarticle.cls to prepare your manuscript and BibTeX to generate your bibliography.
Our LaTeX site has detailed submission instructions, templates and other information.

Article structure

Subdivision - numbered sections

Divide your article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Use this numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods
Provide sufficient detail to allow the work to be reproduced. Methods already published should be indicated by a reference: only relevant modifications should be described.

Theory/calculation
A Theory section should extend, not repeat, the background to the article already dealt with in the Introduction and lay the foundation for further work. In contrast, a Calculation section represents a practical development from a theoretical basis.

Results
Results should be clear and concise.

Discussion
This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions
The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices
If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Vitae
Include in the manuscript a short (maximum 100 words) biography of each author, along with a passport-type photograph accompanying the other figures.

Essential title page information

• ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
• ***Author names and affiliations.*** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
• ***Corresponding author.*** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. **Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.**
• ***Present/permanent address.*** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

Graphical abstract

A Graphical abstract is mandatory for this journal. It should summarize the contents of the paper in a concise, pictorial form designed to capture the attention of a wide readership online. Authors must provide images that clearly represent the work described in the paper. Graphical abstracts should be submitted as a separate file in the online submission system. Maximum image size: 400 × 600 pixels (h × w, recommended size 200 × 500 pixels). Preferred file types: TIFF, EPS or MS Office files. See http://www.elsevier.com/graphicalabstracts for examples.

Highlights

Highlights are mandatory for this journal. They consist of a short collection of bullet points that convey the core findings of the article and should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point). You can view example Highlights on our information site.

Keywords

Immediately after the abstract, provide a maximum of 6 keywords, using British spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Abbreviations

Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Formatting of funding sources

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, please include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Math formulae

Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Footnotes

Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors can build footnotes into the text, and this feature may be used. Otherwise, please indicate the position of footnotes in the text and list the footnotes themselves separately at the end of the article. Do not include footnotes in the Reference list.

Artwork

Electronic artwork

General points

• Make sure you use uniform lettering and sizing of your original artwork.
• Embed the used fonts if the application provides that option.
• Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, Symbol, or use fonts that look similar.
• Number the illustrations according to their sequence in the text.
• Use a logical naming convention for your artwork files.
• Provide captions to illustrations separately.
• Size the illustrations close to the desired dimensions of the published version.
• Submit each illustration as a separate file.

A detailed guide on electronic artwork is available.

You are urged to visit this site; some excerpts from the detailed information are given here.

Formats

If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format.

Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings, embed all used fonts.
TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.
TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi.
TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.
Please do not:
• Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
• Supply files that are too low in resolution;
• Submit graphics that are disproportionately large for the content.

Color artwork
Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. **For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article**. Please indicate your preference for color: in print or online only. Further information on the preparation of electronic artwork.

Figure captions
Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables

Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules.

References

Citation in text
Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Web references
As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source

publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

References in a special issue
Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

Reference management software
Most Elsevier journals have their reference template available in many of the most popular reference management software products. These include all products that support Citation Style Language styles, such as Mendeley and Zotero, as well as EndNote. Using the word processor plug-ins from these products, authors only need to select the appropriate journal template when preparing their article, after which citations and bibliographies will be automatically formatted in the journal's style. If no template is yet available for this journal, please follow the format of the sample references and citations as shown in this Guide.

Users of Mendeley Desktop can easily install the reference style for this journal by clicking the following link:
http://open.mendeley.com/use-citation-style/powder-technology
When preparing your manuscript, you will then be able to select this style using the Mendeley plug-ins for Microsoft Word or LibreOffice.

Reference style
Text: Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given.
Example: '..... as demonstrated [3,6]. Barnaby and Jones [8] obtained a different result ....'
List: Number the references (numbers in square brackets) in the list in the order in which they appear in the text.
Examples:
Reference to a journal publication:
[1] J. van der Geer, J.A.J. Hanraads, R.A. Lupton, The art of writing a scientific article, J. Sci. Commun. 163 (2010) 51–59.
Reference to a book:
[2] W. Strunk Jr., E.B. White, The Elements of Style, fourth ed., Longman, New York, 2000.
Reference to a chapter in an edited book:
[3] G.R. Mettam, L.B. Adams, How to prepare an electronic version of your article, in: B.S. Jones, R.Z. Smith (Eds.), Introduction to the Electronic Age, E-Publishing Inc., New York, 2009, pp. 281–304.
Reference to a website:
[4] Cancer Research UK, Cancer statistics reports for the UK. http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/, 2003 (accessed 13.03.03).

Journal abbreviations source
Journal names should be abbreviated according to the List of Title Word Abbreviations.

Video

Elsevier accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with

their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be properly labeled so that they directly relate to the video file's content. In order to ensure that your video or animation material is directly usable, please provide the files in one of our recommended file formats with a preferred maximum size of 150 MB. Video and animation files supplied will be published online in the electronic version of your article in Elsevier Web products, including ScienceDirect. Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our video instruction pages. Note: since video and animation cannot be embedded in the print version of the journal, please provide text for both the electronic and the print version for the portions of the article that refer to this content.

Supplementary material

Supplementary material can support and enhance your scientific research. Supplementary files offer the author additional possibilities to publish supporting applications, high-resolution images, background datasets, sound clips and more. Please note that such items are published online exactly as they are submitted; there is no typesetting involved (supplementary data supplied as an Excel file or as a PowerPoint slide will appear as such online). Please submit the material together with the article and supply a concise and descriptive caption for each file. If you wish to make any changes to supplementary data during any stage of the process, then please make sure to provide an updated file, and do not annotate any corrections on a previous version. Please also make sure to switch off the 'Track Changes' option in any Microsoft Office files as these will appear in the published supplementary file(s). For more detailed instructions please visit our artwork instruction pages.

ARTICLE ENRICHMENTS

AudioSlides

The journal encourages authors to create an AudioSlides presentation with their published article. AudioSlides are brief, webinar-style presentations that are shown next to the online article on ScienceDirect. This gives authors the opportunity to summarize their research in their own words and to help readers understand what the paper is about. More information and examples are available. Authors of this journal will automatically receive an invitation e-mail to create an AudioSlides presentation after acceptance of their paper.

Interactive MATLAB Figure Viewer

This journal features the Interactive MATLAB Figure Viewer, allowing you to display figures created in MATLAB in the .FIG format in an interactive viewer next to the article. More information and submission instructions.

Interactive plots

This journal enables you to show an Interactive Plot with your article by simply submitting a data file. Full instructions.

After Acceptance

Online proof correction

Corresponding authors will receive an e-mail with a link to our online proofing system, allowing annotation and correction of proofs online. The environment is similar to MS Word: in addition to editing text, you can also comment on figures/tables and answer questions from the Copy Editor. Web-based proofing provides a faster and less error-prone process by allowing you to directly type your corrections, eliminating the potential introduction of errors.
If preferred, you can still choose to annotate and upload your edits on the PDF version. All instructions for proofing will be given in the e-mail we send to authors, including alternative methods to the online version and PDF.
We will do everything possible to get your article published quickly and accurately. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. It is important to ensure that all corrections are sent back to us in one communication. Please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility.

Offprints

The corresponding author will, at no cost, receive a customized Share Link providing 50 days free access to the final published version of the article on ScienceDirect. The Share Link can be used for sharing the article via any communication channel, including email and social media. For an extra charge, paper offprints can be ordered via the offprint order form which is sent once the article is accepted for publication. Both corresponding and co-authors may order offprints at any time via Elsevier's Webshop. Corresponding authors who have published their article open access do not receive a Share Link as their final published version of the article is available open access on ScienceDirect and can be shared through the article DOI link.

Author Inquiries

Visit the Elsevier Support Center to find the answers you need. Here you will find everything from Frequently Asked Questions to ways to get in touch.
You can also check the status of your submitted article or find out when your accepted article will be published.