The effect of filler, active ingredient and Kollidon® VA64 solubility on the release profile of the active ingredient from wet granulation tablet formulations

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2012

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Acknowledgements

I never thought that doing a Masters degree was in my reach, but now that I am finished I know that everything is within my reach through Christ that gives me strength.

I thank Lord Jesus for the opportunity He gave to me to excel in my studies. Without Him, this would not have been possible and to Him comes all the glory! Thank you God Almighty.

My wife, Esti, thank you for all your support. This path that I wandered would have been a heavy load if it wasn't for you who kept me motivated and kept me looking forward. I can't thank you enough. You are my rock, my everything. I love you!

My parents, Kobie and Christa. You have made it possible for me to attend the university and undertake a 4-year B.Pharm degree followed by a post-graduate study. Thank you for your support and love. I love you both very much

My parents-in-law, Freddie and Linette.Thank you for all your support and caring towards my post-graduate study. You have kept me positive throughout and your prayers have been a blessing. I do appreciate all your love and kindness.

My brother and sister, Christoph and Jackie. Thank you for your friendship and love.

Dr. Jan Steenekamp, my study leader, thank you so much for your patience and for your guidance. Your support and help throughout this study was immensely appreciated. You are truly a great man.

Prof. A.F. Marais, thank you for giving me the opportunity to do a post-graduate study. I admire your wisdom and determination.

Dr. Joe Viljoen, thank you for all the help with the dissolutions and for guiding me in the right direction.

Prof. Faan Steyn, thank you for guiding me in the right direction with regard to the data needed for my study to work.

Me. Breytenbach, thank you for your help with the statistical analysis of the raw results, shaping it into usable data for my thesis.

The effect of filler, active ingredient and Kollidon® VA64 solubility on the release profile of the active ingredient from wet granulation tablet formulations

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(B.Pharm)

Dissertation submitted for the partial fulfilment of the degree

MAGISTER SCIENTIAE in PHARMACEUTICS

in the

School of Pharmacy

at the

NORTH-WEST UNIVERSITY – POTCHEFSTROOM CAMPUS

Supervisor: Dr. J.H. Steenekamp

Potchefstroom

2012

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INTRODUCTION, AIM AND OBJECTIVES

Active pharmaceutical ingredients (API's) are administered as dosage forms. Tablets account for 80% of all dosage forms. This can be attributed to the ease of manufacturing, stability and convenience of dosing (Jivraj, 2000:58). There are two common manufacturing methods employed in the pharmaceutical industry namely, direct compression and granulation. Granulation can be subdivided into wet granulation and dry granulation (slugging). Wet granulation is one of the oldest techniques still used today in the pharmaceutical industry due to its advantages. Advantages of wet granulation include: improved flow properties, improved compaction characteristics and the prevention of segregation of powder constituents (Summers & Aulton, 2002:365-366).

An integral part of the pharmaceutical formulation process is the selection of appropriate excipients such as fillers. This, in part, determines the outcome of how successful or unsuccessful a formulation can be. The properties of formulations generally depend on the physicochemical properties of the filler since it often comprises over 50% of the tablet on a weight basis. Fillers for example lactose and microcrystalline cellulose are commonly used in the pharmaceutical industry and both of these have their own advantages and disadvantages when used in preparing tablet formulations. Excipients play a major role when it comes to the disintegration of the tablet and the dissolution of the drug; therefore, it is of utmost importance to choose the correct filler and excipients for formulation.

Wet granulation is a size amplification process converting small-diameter solids (typically powders) into larger diameter agglomerates to generate a specific size, improve flow properties and to produce a granulated powder formulation with specific characteristics such as granule strength, apparent bulk density, dissolution rates and to ensure composition uniformity (Rajniak*et al*., 2007:92). Some fillers are not compressible (e.g. lactose) without a binder solution and therefore a binder should be incorporated into the formulation to produce a compressible powder by means of granulation. The type of binder and the properties thereof will influence the characteristics of the prepared granules and these properties will affect tablet properties. A suitable binder for example polyvinylpyrrolidone (PVP) plays a major role in producing granules during wet granulation.

Aim and objectives

The aim of this study was to evaluate the effect of a water soluble- and insoluble filler, and Kollidon® VA64 as binder on the release profile of a water soluble- and poorly soluble active ingredient from tablets prepared by wet granulation.

The following objectives were set to accomplish the aim:

1. Conduct a literature study on tablets as a dosage form and tablet manufacturing.

2. Preparation of compressible powders (granulates) using a water soluble- and insoluble filler, Kollidon® VA64 and a water soluble- and insoluble active ingredient.

3. Manufacturing of tablets from different powder mixtures at two different compression settings.

4. Evaluation of the physical properties of the tablets prepared from different formulations with regard to weight variation, mechanical strength (crushing strength and friability) and disintegration.

5. Evaluation of dissolution profiles of the active ingredients.

In chapter 1, a literature overview of wet granulation as a manufacturing process is discussed. In chapter 2 the experimental methods used in this study are described. Chapter 3 deals with a discussion of the different tablet properties prepared from different powder formulations. Dissolution data and the discussion thereof are presented in chapter 4 followed by a summary and the future prospects in chapter 5.

ABSTRACT

There are mainly two manufacturing processes used in the pharmaceutical industry, namely direct compression and granulation of which granulation can be subdivided into wet granulation and dry granulation. Wet granulation is a process still widely used in the pharmaceutical industry and provides better control of drug content uniformity and compactibility at low drug concentrations. Lactose monohydrate and microcrystalline cellulose (MCC) were used as fillers in this study. Both these fillers possess unacceptable powder flow properties and the use of wet granulation may improve this property. One of the advantages of lactose monohydrate over MCC is that it is partially water soluble.

A fractional factorial design was used in this study. Twelve tablet formulations were formulated containing different combinations of active ingredients (furosemide or pyridoxine hydrochloride), fillers (lactose monohydrate or MCC) and a binder (Kollidon® VA64) in three different concentrations (0.75, 1.5 or 3.0% w/w). The binder was used to produce granules by means of wet granulation, using ethanol as granulating fluid. The granules were dried in an oven and screened through different sized sieves to produce the final granulated powder formulations ready for tableting. A disintegrant (Ac-di-sol®) and lubricant (magnesium stearate) were incorporated into the granulated powder formulations extra-granular (0.5% w/w) and were kept as a constant in this study throughout all the formulations. A Turbula® mixer was used to mix the granulated powder formulations for a constant 5 minutes.

During the first phase of the study, tablets were compressed using 2 compression settings (22 and 24). These compression settings were used to determine what effect different external pressures would have on the different tablet properties. Tablet weight for all the formulations was kept constant at 250 mg, although the volume of the matrix differed for each tablet formulation. The physical properties of the tablets were evaluated with regard to weight variation, mechanical strength (crushing strength and friability) and disintegration. Tablet formulation 12 yielded unsatisfactory tablets, due to poor powder flow into the die. Tablet formulations that contained the highest binder concentration (3.0% w/w) and were compressed at the highest compression setting (24) (formulations 4 and 9), exhibited the highest mechanical strength. The disintegration results revealed that the tablet formulations

containing MCC as filler disintegrated faster compared to those containing lactose monohydrate. The increase in binder concentration caused an increase in mechanical strength, possibly decreasing tablet porosity, therefore prolonging disintegration time due to impeded water penetration into the tablet matrix.

During the final phase of the study, dissolution studies were conducted on the different tablet formulations in 0.1 M HCl for 120 minutes. In terms of dissolution results, the initial dissolution rate (DR_i) and extent of dissolution (AUC) were compared. It was found that the tablet formulations containing pyridoxine hydrochloride as active pharmaceutical ingredient (API) exhibited faster drug dissolution (higher DR_i and AUC-values) compared to those tablet formulations containing furosemide. The faster dissolution exhibited by the pyridoxine hydrochloride containing formulations can possibly be attributed to the fact that pyridoxine hydrochloride is good water soluble whereas furosemide is practically insoluble in water. The effect of the filler depended on the aqueous solubility of the filler and the concentration of the binder (Kollidon® VA64) employed. An increase in binder concentration led to a decrease in the initial rate of dissolution as well as the extent of drug dissolution. In the case of the pyridoxine hydrochloride containing formulations, formulation 9 exhibited the slowest DR_i and lowest extent of drug dissolution (1.40 ± 0.03 $\mu g.cm^{-3}.min^{-1}$ and 2396.52 ± 26.43 $\mu g.cm^{-3}.min$ respectively). In the case of the furosemide containing formulations, formulation 4 exhibited the slowest DR_i and lowest extent of drug dissolution (0.22 ± 0.07 $\mu g.cm^{-3}.min^{-1}$ and 1018.62 ± 59.74 $\mu g.cm^{-3}.min$ respectively). In both cases, the formulations contained Kollidon® VA64 in a concentration of 3% w/w and were compressed at compression setting 24. The disintegration process of tablets goes hand in hand with the dissolution process and results have shown that by establishing rapid contact between drug particles and the surrounding medium proves to be a necessity for rapid drug dissolution. Disintegration does not assure drug dissolution, but when prolonged, slower dissolution rates can be obtained, implying a slow rate and low extent of drug dissolution. The disintegrant in this study was incorporated extra-granular ensuring rapid tablet disintegration. However, due to a binder concentration of 3% w/w, granule disintegration was probably negatively affected resulting in a lower drug surface area exposed to the surrounding dissolution medium, leading to a slower initial rate and extent of drug dissolution.

From the results obtained during this study it was evident that formulation variables such as the type of filler, the concentration of the binder and compression setting employed during tablet manufacturing can have a pronounced effect on the pharmaceutical availability of the active ingredient. However, the extent of the effect was dependent on the aqueous solubility of the active ingredient.

Keywords: Granulation; Furosemide; Pyridoxine hydrochloride; Fillers; Water solubility; Dissolution

UITTREKSEL

Daar is hoofsaaklik twee vervaardigingsprosesse wat in die farmaseutiese nywerheid tydens tabletvervaardiging gebruik word, naamlik direkte samepersing en granulering, waarvan granulering in nat- en droë granulering onderverdeel kan word. Natgranulering is ‘n proses wat steeds wye toepassing in die farmaseutiese nywerheid geniet aangesien dit beter beheer oor geneesmiddelinhoudsuniformiteit en saampersbaarheid by lae geneesmiddelkonsentrasies verskaf. Laktose monohidraat en mikrokristallyne sellulose (MCC) is as vulstowwe in hierdie studie gebruik. Beide die vulstowwe beskik oor swak poeiervloei-eienskappe en die gebruik van natgranulering kan hierdie eienskap verbeter. Een van die voordele van laktose monohidraat in vergelyking met MCC is dat dit wateroplosbaar is.

‘n Gedeeltelike faktoriaalontwerp is in die studie gebruik. Twaalf tabletformulerings wat verskillende kombinasies van aktiewe bestanddele (furosemied of piridoksien hidrochloried), vulstowwe (laktose monohidraat of MCC) en ‘n bindmiddel (Kollidon® VA64) in drie verskillende konsentrasies (0.75, 1.5 of 3.0% m/m) bevat het, is geformuleer. Die bindmiddel is gebruik om granules met behulp van natgranulering te vervaardig. Tydens die granuleringsproses is etanol as granuleringsvloeistof gebruik. Die granules is in ‘n oond gedroog. Daar is van twee verskillende sifgroottes tydens verskillende fases van die granuleringsproses gebruik gemaak om die finale gegranuleerde poeierformules, gereed vir tablettering, te lewer. Die disintegreermiddel (Ac-di-sol®) en smeermiddel (magnesiumstearaat) is ekstra-granulêr in die gegranuleerde poeierformules ingesluit (0.5% m/m) en is as ‘n konstante in al die formulerings gehou. Die gegranuleerde poeierformules is met behulp van ‘n Turbula®-menger gemeng vir ‘n konstante 5 minute.

Gedurende die eerste fase van die studie, is tablette saamgepers deur gebruik te maak van 2 persdrukstellings (22 en 24). Hierdie persdrukke is gebruik om die invloed van eksterne drukke op die verskillende tableteienskappe te bepaal. Tabletmassa vir al die formules was 250 mg, alhoewel die volume van die matriks verskillend was vir elke tabletformulering. Die fisiese eienskappe van die tablette is geëvalueer met betrekking tot massavariasie, meganiese sterkte (breeksterkte en afsplyting) en disintegrasie. Tabletformulering 12 het nie aanvaarbare tablette opgelewer nie, as gevolg van swak poeiervloei. Tabletformulerings wat die hoogste

bindmiddelkonsentrasie (3.0% m/m) bevat het en by die hoogste persdrukstelling (24) saamgepers was, het die hoogste meganiese sterkte getoon. Die disintegrasieresultate het getoon dat die tabletformulerings wat MCC as vulstof bevat het, aansienlik vinniger gedisintegreer het in vergelyking met die wat laktose monohidraat bevat het. ‘n Verhoging in bindmiddelkonsentrasie het ‘n verhoging in meganiese sterkte veroorsaak, wat moontlik gelei het tot ‘n verlaging in tabletporositeit, wat disintegrasietyd vertraag het as gevolg van verlaagde waterpenetrasie in die tabletmatriks.

Tydens die finale fase van die studie, is dissolusiestudies op die verskillende tabletformulerings in 0.1 M HCl oor ‘n tydperk van 120 minute uitgevoer. Die dissolusieresultate is vergelyk deur middel van die aanvanklike dissolusietempo (DR_i) en omvang van dissolusie (AUC) te bepaal. Daar is bevind dat die tabletformulerings wat piridoksienhidrochloried as aktiewe bestanddeel bevat het beter geneesmiddeldissolusie getoon het in vergelyking met die tabletformulerings wat furosemied as aktiewe bestanddeel bevat het. Hierdie verskynsel kan waarskynlik daaraan toegeskryf word dat piridoksienhidrochloried ‘n goed wateroplosbare geneesmiddel is, in teenstelling met furosemied wat prakties onoplosbaar in water is. Die invloed van die vulstof was afhanklik van die wateroplosbaarheid van die vulstof asook die konsentrasie van die bindmiddel (Kollidon® VA64) wat gebruik is. ‘n Verhoging in bindmiddelkonsentrasie het tot ‘n afname in die omvang van geneesmiddeldissolusie gelei. In die geval van die tabletformulerings wat piridoksienhidrochloried bevat het, het formule 9 die stadigste DR_i en laagste omvang van geneesmiddeldissolusie (AUC) (1.40 ± 0.03 µg.cm^{-3}.min^{-1}en 2396.52 ± 26.43 µg.cm^{-3}.min onderskeidelik) getoon. In die geval van die tabletformulerings wat furosemied bevat het, het formule 4 die stadigste DR_i en laagste omvang van geneesmiddeldissolusie (AUC) (0.22 ± 0.07 µg.cm^{-3}.min^{-1}en 1018.62 ± 59.74 µg.cm^{-3}.minonderskeidelik) getoon. In beide hierdie gevalle het die formulerings Kollidon® VA64 in ‘n konsentrasie van 3% m/m bevat en is beide formules by ‘n persdrukstelling van 24 getabletteer. Die disintegrasie van tablette loop hand-aan-hand met die dissolusieproses en resultate het getoon dat vinnige kontak tussen deeltjies en die omringde dissolusiemedium noodsaaklik vir vinnige geneesmiddel dissolusie is. Disintegrasie verseker nie dissolusie nie, maar wanneer dit vertraag word, kan stadiger dissolusietempos verkry word wat ‘n stadige

aanvangstempo en lae omvang van geneesmiddeldissolusie impliseer. Tydens hierdie studie was die disintegreermiddel ekstra-granulêr ingesluit wat verseker het dat tabletdisintegrasie vinnig plaasgevind het, maar, as gevolg van ‘n bindmiddelkonsentrasie van 3% m/m (formule 4 en 9) is die disintegrasie van die granules waarskynlik belemmer met ‘n gevolglike kleiner geneesmiddeloppervlakte wat aan die dissolusiemedium blootgestel is, en gevolglik was die aanvanklike dissolusietempo stadiger en die omvang van geneesmiddeldissolusie kleiner.

Na aanleiding van die resultate van hierdie studie, is dit duidelik dat formuleringsveranderlikes soos die tipe vulstof, bindmiddelkonsentrasie en persdrukstelling tydens vervaardiging ‘n betekenisvolle invloed kan uitoefen op die farmaseutiese beskikbaarheid van die aktiewe bestanddeel. Die mate waartoe hierdie veranderlikes ‘n invloed uitoefen is afhanklik van die wateroplosbaarheid van die geneesmiddel.

Sleutelwoorde: Granulering; Furosemied; Piridoksienhidrochloried; Vulstowwe; Wateroplosbaarheid; Dissolusie

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Chapter 1

TABLETS AS DOSAGE FORM AND MANUFACTURING OF TABLETS

1.1. Introduction

Active pharmaceutical ingredients (API's) are administered to man as dosage forms. Tablets account for 80% of all dosage forms. Reasons for this is the fact that they are easily manufactured, more stable compared to liquids and semi-solid preparations and convenient in dosing (Jivraj, 2000:58).

The European Pharmacopoeia (5th edition, 2005) define tablets as solid preparations each containing a single dose of one or more active ingredient(s) and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration and can be swallowed whole, chewed, dissolved in water before being administered or retained in the mouth giving time for the active ingredient to release (Alderborn, 2007:442).

Besides the advantages already named, tablets as a dosage form also offers other advantages, including:

- easy transport,
- uniform physical properties for example weight and appearance,
- mass production is usually quick and very cost-effective,
- an accurate amount of active ingredient can be administered, and
- bioavailability can be pharmaceutically altered to meet specific needs (Rubenstein, 1988:309).

1.2. Tablets as dosage form

The term 'tablet' (from Latin *tabuletta*) can be associated with the appearance of the dosage form, i.e. small disc-like or cylindrical specimens. According to the *European Pharmacopoeia*, the Latin name for the tablet dosage form is *compressi* which underlines the fact that the dominating process of tablet manufacturing is powder compression in a confined space. The idea of the formation of a solid dosage form

(tablet) by powder compression existed since 1843 when the first patent for a hand operated device used to form tablets was granted (Alderborn, 2007:442).

Tablets are popular for the following reasons:

- tablets have general advantages in terms of the physical and chemical stability of the dosage form when compared to liquid dosage forms,
- tablets are convenient to handle,
- accurate dosing of the drug can be enabled by the preparation procedure,
- the oral route represents a safe and convenient way of drug administration, and
- tablets can be economically mass produced, with robust and quality-controlled production procedures rendering an elegant preparation of consistent quality.

However, the bioavailability of poorly water-soluble/absorbable drugs is the main disadvantage of tablets as a dosage form (Alderborn, 2007:442).

1.3. Tablet formulation

The process whereby the formulator insures that the correct amount of *drug* in the right *form* is delivered at or over the proper *time* at the proper *rate* and in the desired *location*, while having its chemical *integrity* protected to that point, can be described as tablet formulation and design. Selecting the correct balance of excipients for each active ingredient or ingredient combination in a tablet formulation to achieve the desired response (safe, effective and reliable product) proves to be a difficult task to achieve. Therefore, it is important to spend time on the formulation and design of tablets (Peck *et al*., 1989:76).

1.3.1. Excipients used

In addition to the active ingredient(s), a series of excipients are normally included in a tablet. The term ‘excipients’ comes from the Latin word *excipiens* present participle of the verb *exipere* which means to receive, to gather, to take out. This refers to one of the properties of an excipient, which is to ensure that the medicinal

product has the weight, consistency and volume necessary for the correct administration of the active principle to the patient. Excipients can briefly be defined as the components of a formulation other than the active ingredient (Pefferi & Restani, 2003:541).

Excipients are subcategorised into different groups, depending on the intended main function. Some of these excipients can be multifunctional because they have a series of ways to affect powder and tablet properties (Alderborn, 2007:449). In the following sections, different groups of excipients will be discussed.

1.3.1.1. Fillers (or diluents)

It is impossible to compress tablets which only contain an API, the reason being the fact that the API constitutes a small percentage of the overall tablet weight and API's are mostly not compressible. To reach tablettable weights and to overcome the problem of only having to compress an API into a tablet, fillers are incorporated into the formulation. The primary function of a filler in a tablet is to act as a carrier for the API (Khan *et al*., 1973:2). Other functions include:

- improved powder flow, minimising weight variation,
- improved disintegration,
- provision of certain characteristics such as: controlled, delayed and slow release of the API out of the tablet matrix and for site specific delivery,
- provision of certain binding properties, and
- to enable direct compression (Khan *et al*., 1973:2).

Directly compressible fillers are mostly used today and they include: Ludipress® (filler 93.4%, binder 3.2% and disintegrant 3.4%), Tablettose® and Avicel®. These fillers are also co-processed and can be multifunctional regarding their uses i.e., they can be used as dry binders and disintegrants. Lactose is still extensively used as filler in wet granulation.

The ideal filler should fulfil a series of requirements, including:

- it should be chemically and physiologically inert,
- it should be biocompatible,
- it should be cheap,
- it should have acceptable organoleptic properties,
- it should be non-hygroscopic,
- it should not affect API bioavailability,
- it should have good technical properties (compressibility and flow properties),
- it should have a good pressure-hardness profile, and
- it should have good biopharmaceutical properties (water soluble and hydrophilic) (Khan *et al*., 1973:3).

1.3.1.2. Binders

A binder is a material that is added to a formulation in order to improve the mechanical strength of a tablet (Nyström *et al*., 1993:2145). The addition of binders to a formulation can be done in three different ways:

1. As a solution which is used as an agglomeration liquid during wet granulation. Also referred to as a *solution binder*.
2. As a dry powder mixed with all the other ingredients before compaction. Also referred to as a *dry binder*.
3. As a dry powder mixed with all the other ingredients before wet agglomeration with the possibility of dissolving partly or completely in the agglomeration liquid (Alderborn, 2007:452).

Solution binders and dry binders are both included in the formulation at relatively low concentrations (between 2-10% w/w) (Peck *et al*., 1989:105). The primary criterion when deciding upon a binder is its compatibility with the other tablet components. Secondarily, it must impart sufficient cohesion to the powders to allow for normal processing (sizing, lubrication, compression and packaging), yet allow tablet disintegration and drug dissolution upon ingestion, releasing the API for absorption (Healey *et al*., 1974:41). Traditional solution binders include starch, sucrose and

gelatine. The most frequently used binders used today are solutions of polymers such as cellulose derivatives (hydroxypropyl methylcellulose) and polyvinylpyrrolidone. These polymers exhibit improved adhesive properties compared to the more traditional binders. Solutions of binders are considered to be the most effective and for this reason it remains the most common way to incorporate a binder into granules. Examples of dry binders include microcrystalline cellulose and crosslinked polyvinylpyrrolidone (Alderborn, 2007:452).

1.3.1.2.1. Applications of povidone in the pharmaceutical industry

Povidone is widely used in the pharmaceutical industry, mostly for its binding properties in tablet formulations. Table 1.1 lists the applications for povidone in general.

Table 1.1: Applications of povidone (Bühler, 2003:79).

Function	***Pharmaceutical form***
Binder	Tablets, capsules, granules
Bioavailability enhancer	Tablets, capsules, granules, pellets, suppositories
Film former	Ophthalmic solutions, tablet cores, medical plastics
Solubiliser	Oral, parenteral and topical solutions
Taste masking agent	Oral solutions, chewing tablets
Suspension stabiliser	Injectables, oral lyophilisates
Lyophilisation agent	Suspensions, instant granules, dry syrups
Hydrophiliser	Medical plastics, sustained release forms, suspensions
Adhesive	Adhesive gels, transdermal systems
Stabiliser	Enzymes in diagnostics, different forms
Intermediate	Povidone-Iodine as active ingredient
Toxicity reduction	Injectables, oral preparations

1.3.1.2.2. Vinylpyrrolidone-vinyl acetate copolymer (Kollidon® VA64)

Vinylpyrrolidone-vinyl acetate copolymer is a water soluble copolymer which is manufactured by free-radical polymerization and contains two monomers in a ratio of 6:4, namely: vinylpyrrolidone and vinyl acetate. The number in the trade name, 64, is not a K-value but the mass ratio of the two monomers. It is a white or yellowish-white spray dried powder with a relatively fine particle size and also has good flow properties. A typical slight odour and a faint taste in aqueous solutions can be expected (Bühler, 2003:199-200).

Kollidon® VA64 is almost universally soluble because of the two monomers vinylpirrolidone and vinyl acetate. It dissolves in extremely hydrophilic liquids for example water as well as in more hydrophobic solvents for example butanol (Bühler, 2003:201). The importance of the hygroscopicity of Kollidon® VA64 depends on the application. A certain degree of hygroscopicity is useful when Kollidon® VA64 is used as a binder and granulating aid in tablets, but in film-coatings, a problem may occur. In the end, Kollidon® VA64 absorbs approximately three times less water than povidone (Kollidon® 30) at a given humidity (Bühler, 2003:207).

The applications of Kollidon® VA64 rely mainly on its affinity for hydrophilic and hydrophobic surfaces, good binding and film-forming properties and its relatively low hygroscopicity. These properties make it possible for Kollidon® VA64 to be used in:

- the production of granules,
- the production of tablets,
- direct compression,
- film coatings on tablets,
- a protective layer and sub coat for tablet cores,
- a film-forming agent in sprays, and
- a matrix (Bühler, 2003:224).

1.3.1.2.3. Particle size

The particle size distribution of excipients such as Kollidon® can play a major role during the manufacturing of solid dosage forms. This particularly applies to direct compression, because in wet granulation Kollidon® is dissolved in the appropriate solvent. There are some important effects the particle size has on the manufacturing of pharmaceuticals. These include:

- a high proportion of fines disrupts the flow properties,
- fine particles produce dust,
- a high proportion of coarse particles may lead to demixing,
- the coarse particle fraction can be unevenly distributed in tablets,
- with high-molecular polymers, a large coarse particle fraction delays dissolution drastically, and
- coarse particles of a binder demonstrate a weaker binding effect during direct compression (Bühler, 2003:30).

1.3.1.2.4. Particle structure

All soluble grades of Kollidon®, with the exception of roller dried Kollidon® 90F, are spray-dried powders and because of this, possess typical particle structures of this technology. In Fig. 1.1 the particle structure of spray-dried Kollidon® 30 are displayed which consists mainly of hollow and spherical particles. Fig. 1.2 shows an example of roller dried Kollidon® 90F particles (Bühler, 2003:31-32). Fig. 1.3 displays the hollow spherical particles of Kollidon® VA64, like Kollidon® 30, which are almost all broken (Bühler, 2003:206).

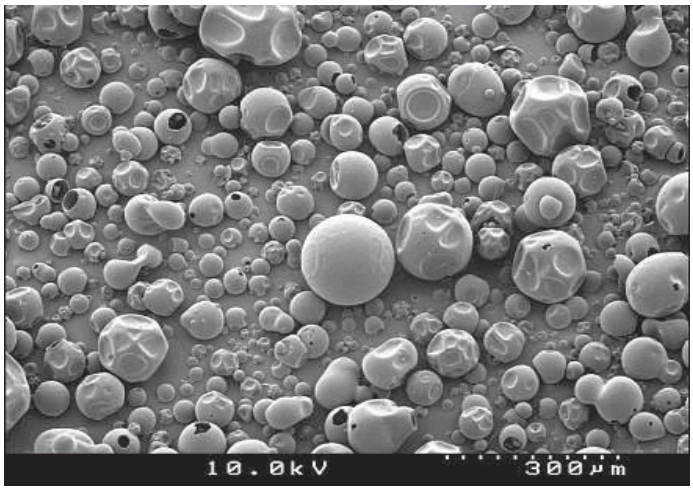


Fig. 1.1: Particle structure of Kollidon® 30 (Bühler, 2003:31).

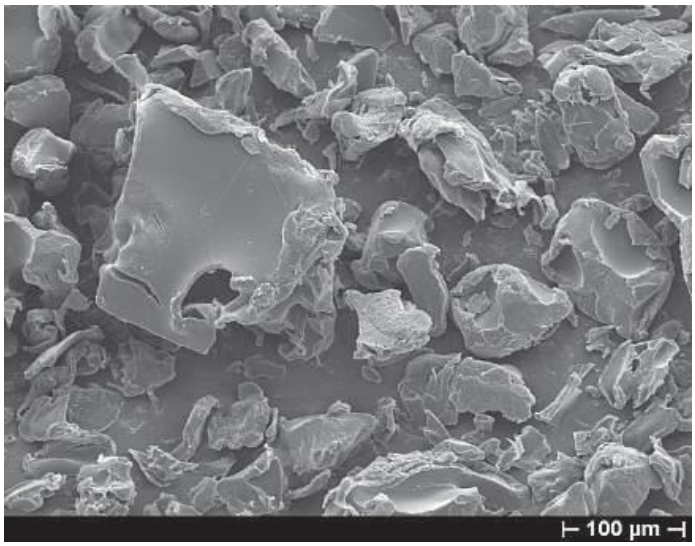


Fig. 1.2: Particle structure of Kollidon® 90F (Bühler, 2003:32).

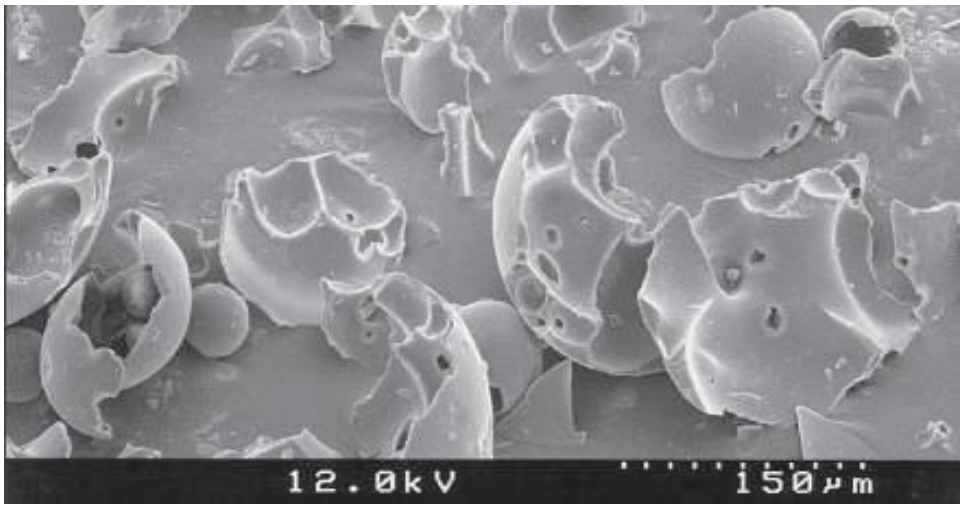


Fig. 1.3: Particle structure of Kollidon® VA64 (Bühler, 2003:206).

1.3.1.3. Disintegrants

For a drug to be bioavailable after oral administration, it must be in solution in the gastrointestinal fluids to be absorbed. Dissolution can be defined as the transfer of molecules or ions from a solid state into solution (Aulton, 2007:17). In order for dissolution to take place the drug must be released from the intact tablet. The process where the tablet breaks up after coming into contact with water is called disintegration. Without disintegration, dissolution is negatively affected and it is thus the rate limiting step during this process. Conventional dosage forms are divided into disintegrating and non-disintegrating tablets. By breaking down the physical integrity of the tablet with disintegrating or gas-releasing agents, the active ingredient is released. The contents of non-disintegrating dosage forms are combined in such a way that it will assist in the quick dissolution of the API's in the gastrointestinal fluids. Most conventional tablet formulations are designed and manufactured in such a way that rapid drug release from the tablet matrix is ensured. This is then followed by the dissolution of the active ingredient (Bhatia *et al*., 1978:38; Kanig & Rudnic, 1984:50; Gordon & Chowhan, 1987:907; Abdou, 1989:554; Bühler, 1993:157).

Fig. 1.4 displays a mechanistic representation of the drug release process from a tablet by disintegration and dissolution (Wells & Rubenstein, 1976:629).

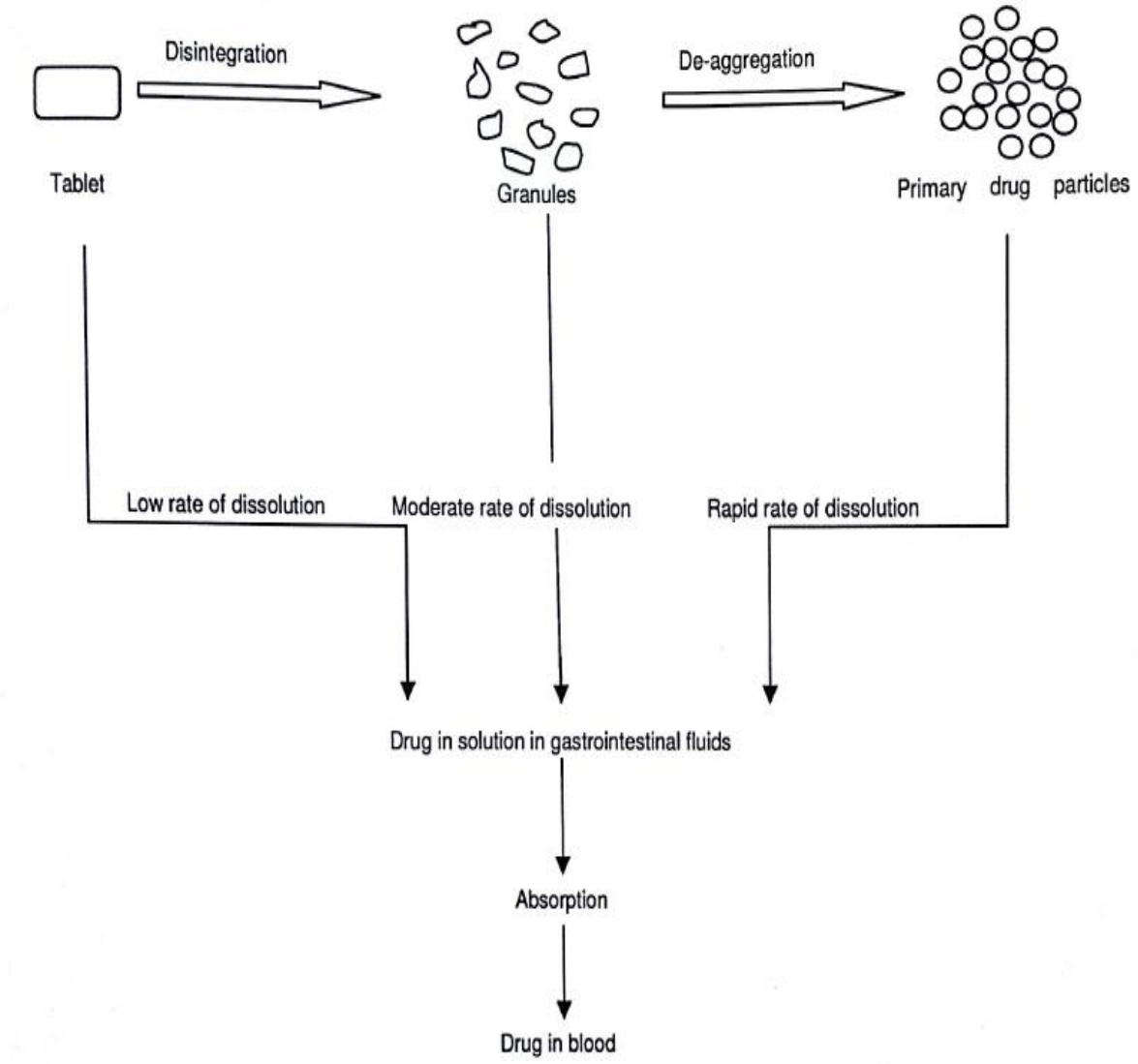


Fig. 1.4: Schematic presentation of tablet disintegration and subsequent drug dissolution (Wells & Rubenstein, 1976:629).

Disintegrants can be defined as any solid, pharmaceutical acceptable material included in the formulation that acts to cause the tablet matrix to break up when the tablet comes into contact with aqueous media (Moreton, 2008:217). The reason for including a disintegrant into the tablet formulation is to ensure the disintegration of the tablet when it comes into contact with a liquid. In an ideal situation the tablet should break up into smaller fragments enlarging the surface area, thereby speeding up the dissolution process.

There are mainly two working mechanisms of disintegrants:

1. Disintegrants that function by swelling. The transport of liquid into the pores of the tablet is facilitated by these disintegrants, consequently fracturing the tablet into smaller pieces as the particles swell. This process ensures enlargement of the surface that is in contact with the surrounding liquid (Alderborn, 2002:406).

2. Disintegrants that will rupture the tablet by gas formation (Alderborn, 2002:406).

Tablet disintegrants can be divided into "superdisintegrants" and "traditional" disintegrants. Examples of superdisintegrants include sodium starch glycolate (Explotab®, Primojel®), croscarmellose sodium (Ac-di-sol®) and crosspovidone (Kollidon® CL). Traditional disintegrants include materials such as native starch of different origins, ion exchange resins and alginic acid. In comparison to traditional disintegrants, lower concentrations of the superdisintegrants can be used to give effective tablet disintegration (Moreton, 2008:218).

1.3.1.4. Lubricants

The term "lubricant" is derived from the Latin verb *lubricare* meaning "to make slippery". The function of the lubricant is to overcome (reduce) friction, particularly die wall friction, which occurs between the wall of the die and the side of the tablet. Particle rearrangement occurs as a particulate mass is compressed in the die, particles then move to fill pores and renders a less porous aggregate. As a result, the contact between the particles and the wall of the die is increased, creating friction. An ideal lubricant would exhibit the following properties:

- regulatory approval for use in medicines,
- should significantly reduce friction,
- be effective at low concentrations to not increase the bulk of the tablet,
- should be chemically inert,
- should be cosmetically inert (white, tasteless, odourless),

- no adverse effect on the formulation or properties of the tablet,
- batch-to-batch consistency,
- be cheap and readily available, and
- be unaffected by changes in processing variables (Armstrong, 2008:251-253).

The most commonly used lubricant, still today, is magnesium stearate added mainly extra-granular at low concentrations (<1% w/w) (Alderborn, 2007:452).

1.3.1.5. Glidants

Glidants are used to improve powder flowability. It is mainly used during the process of direct compression, but can be added to a granulate before tableting to ensure sufficient flowability for high production speeds. A more traditional glidant used in tablet formulations is talc (1-2% w/w). The most commonly used glidant today is colloidal silica which is added in very low proportions (0.2% w/w). The silica particles are very small and adhere to particle surfaces of other ingredients, improving flow by reducing interparticulate friction (Alderborn, 2007:452).

1.3.1.6. Other ingredients

There are other ingredients that can be added into a formulation to help with the organoleptic and aesthetic properties of the tablet. These include colourants, flavours and sweeteners. Colourants are incorporated into tablets generally for three purposes. Firstly, it may be used for the identification of similar products within the same product line. Secondly, colours can help minimise manufacturer's mix-ups and finally colours are incorporated to improve the tablet's aesthetic or marketing value (Peck *et al*, 1989:116).

Flavourants and sweeteners are most commonly used to improve the taste of chewable tablets. Flavourants are incorporated as solids (spray-dried beadlets) or aqueous (water soluble) solutions into the tablet formulation. Examples of sweeteners include saccharin, which is 400 times sweeter than sucrose and aspartame, which is 180 times sweeter than sucrose. The sweeteners are primarily

incorporated into chewable tablets when the frequently used carriers such as lactose, sucrose, dextrose and mannitol do not sufficiently mask the taste of the components (Peck *et al*., 1989:117-118).

1.4. Manufacturing process

There are mainly two manufacturing processes used in the pharmaceutical industry, direct compression and granulation of which granulation can be sub divided into wet granulation and dry granulation. These processes will be discussed further.

1.4.1. Direct compression

Direct compression is the best suited technique to use when manufacturing a tablet containing thermolabile and moisture-sensitive drugs. It holds many advantages but it is still less popular than wet granulation because the technique has only recently become more established thanks to the introduction of excipients specifically designed for direct compression (Jivraj, 2000:58-59).

These excipients are directly compressible but contain the possibility to be mixed with large quantities of active pharmaceutical ingredients with no significant influence on tablet quality. There are a few must-have attributes these excipients should possess for example a similar particle size distribution to most drug substances to ensure no segregation and a high bulk density. Batch-to-batch quality must be reproducible. The advantages and disadvantages for direct compression are as follow:

Advantages:

- low energy consumption and shorter processing time,
- there are fewer stability issues for active ingredients that are sensitive to moisture or heat,
- faster dissolution rates obtained for certain actives, and
- uses less excipients in formula

Disadvantages:

- segregation of components,
- drug content is limited to about 30% per tablet,
- materials possessing a low bulk density may not be usable because after compression, the tablets may be too thin,
- not suited for poorly flowing actives, and
- as a result of static charges forming on the drug or excipient particles, agglomeration may occur which in turn produces poor mixing (Jivraj, 2000:59)

1.4.1.1. Fillers used in the direct compression process

Examples of fillers used in the direct compression process include, microcrystalline cellulose and a co-processed filler Ludipress®.

- Microcrystalline cellulose (MCC)

Microcrystalline cellulose has been widely used and was rated the most useful filler for direct compression. Reasons for this are the fact that it has relatively low chemical reactivity together with excellent compactibility at low pressures (Shangraw & Demarest, 1993). MCC is a purified, partially depolymerised cellulose, which is prepared by treating α-cellulose with mineral acids, producing bundles of needle-like crystals. This excipient is a white, crystalline powder composed of agglomerated porous particles (Wade & Weller, 1994:84).

- Ludipress®

This is a co-processed filler that contains three components namely a filler (93.4% α-lactose monohydrate), binder (3.2% polyvinylpyrrolidone) and disintegrant (3.4% crosspovidone). Ludipress® has excellent flowability because the material consists of spherical particles made up of a large number of small crystals with smooth surfaces (Schmidt & Rubensdörfer, 1994b:2901).

1.4.2. Wet granulation

Wet granulation is a process still widely used in the pharmaceutical industry. It has not been replaced by direct compression for the simple reason of development cost considerations and because it is still an attractive technique in some cases. At low drug concentrations, it provides better control of drug content uniformity as well as control of product bulk density and ultimately compactibility (even in high drug content formulations). Processing takes place in one of two closed granulating systems: fluid bed granulators or high-shear mixers. These two techniques differ technically on the mode of solid agitation, and fundamentally on the mode of granule growth (Faure *et al*., 2001:269)

Direct compression is a less expensive and simpler process than wet granulation, therefore it is important to understand the advantages of the wet granulation process in order to value its necessity. The advantages of wet granulation are as follow:

- Adding a binder which coats the individual powder particles, causing them to adhere to one another to form agglomerates, improves the cohesiveness and compressibility of powders – these powders are then called granules. This means that lower pressures are required to compress tablets – resulting in improvements in the tooling life and machine wear.

- Drugs having poor flow or compressibility properties for example high-dosage drugs must be prepared by wet granulation to obtain suitable flow and cohesive properties for compression.

- Good distribution and uniform content are ensured when soluble low dosage drugs and colour additives are in the binder solution.

- In the processing, transferring and handling of a homogeneous powder mix, segregation of the components are decreased by wet granulation.

- An improvement of the dissolution rate by means of wet granulation of a hydrophobic drug can be seen with the proper choice of solvent and binder. (Sheth *et al*., 1980: 114-115)

There are a few limitations related to the wet granulation process. These are as follow:

- Cost is most probably the greatest disadvantage of wet granulation. The whole process is expensive because of the labour, time, equipment, energy and space requirements.
- Loss of material during the different steps of processing.
- Stability is a concern for moisture sensitive and thermolabile drugs.
- Validation and control are difficult to achieve because of multiple processing steps which adds complexity.
- Any incompatibility between formulation components are aggravated.

1.4.2.1. Fillers suited for wet granulation

- Lactose

Lactose is a widely used filler in tablet formulations and there are a number of different grades commercially available with differing physical properties such as particle size distribution and flow characteristics. Lactose has a sweet taste and is white in colour. It occurs naturally in the milk of mammals and can be chemically produced by combining galactose and glucose. Lactose monohydrate is soluble in water. There are a few general properties that contribute to the popularity of lactose being used as an excipient, these include:

- cost effectiveness,
- availability,
- insipid taste,
- hygroscopicity,
- outstanding physical and chemical stability, and
- water solubility (Gohel & Jogani, 2005:80).

Lactose can be divided into two groups namely crystalline and amorphous. Crystalline can be divided into two further categories namely hydrous (α-lactose monohydrate, α-crystals) and anhydrous (unstable α-lactose, stable α-lactose and β-

lactose). One can expect physicochemical properties to differ from one another (Bolhuis & Lerk, 1973; Lerk, 1993; Van Kamp *et al*., 1986).

- α-Lactose monohydrate

α-Lactose monohydrate is commercially available in the hydrous state and is produced by means of crystallisation from an over saturated solution, below temperatures of 93 °C. Compared to other fillers, α-lactose monohydrate exhibits poor binding properties, but coarse sieve fractions exhibit exceptional flow when used in direct compression, thus emphasising the use of α-lactose monohydrate as filler in direct compression systems (Gohel & Jogani, 2005:81). The binding of the particles can be improved by spray-drying (Gohel & Jogani, 2005:82).

- Anhydrous α-lactose

During thermal dehydration, α-lactose monohydrate changes from single crystals into aggregates of anhydrous α-lactose particles which are softer, weaker and less elastic. The major disadvantage of tablets containing anhydrous lactose is the relatively slow disintegration of the tablets (Wong *et al*., 1988:2106-2126; Van Kamp *et al*., 1986:229-233).

- Anhydrous β-lactose

Anhydrous β-lactose is commercially available as agglomerates of extremely fine crystals. This form of lactose can be produced by means of roller drying of an α-lactose monohydrate solution followed by subsequent comminution and sieving. Anhydrous β-lactose is an ideal excipient for moisture sensitive API's because of its low moisture content (Gohel & Jogani, 2005:81).

1.4.3. Dry granulation

Roll compaction/dry granulation is an agglomeration process, which has been known since the end of the 19th century (Miller, 1994:58). In the dry granulation process the powder formulation is compressed without the use of heat and solvent which in turn is the greatest advantage it has over wet granulation. The above mentioned are mostly suited for drugs which are moisture or heat sensitive. Two methods are used for dry granulation. The most commonly used method is called slugging, where the

powder is pre-compressed on a heavy-duty tablet press, and the resulting tablets or slugs are milled to yield the granulated product. The other known method is to pre-compress the powder with pressure rolls using a machine such as the Chilsonator or Hutt compactor (Sheth *et* al. 1980:173). This process is also environmentally friendly. The aim of dry granulation is to improve the handling of the powders with the use of a larger particle size and better flowability. Die filling during the tableting process are improved, which is also attainable by having an increase in bulk density because less air will escape during the tableting process (Kleinebudde, 2004:318).

The main advantages of dry granulation or slugging are the fact that it uses less equipment and space. There is also no need for a binder solution, heavy mixing equipment and the expensive process of drying as in wet granulation. The disadvantages, however, include the following:

- a specialised heavy-duty tablet press are required to form the slug,
- uniform colour distribution is not possible using this method,
- a pressure roll press such as the Chilsonator cannot be used with insoluble drugs – it slows down the dissolution rate, and
- more dust creation, increasing potential cross-contamination (Sheth *et al.* 1980:173).

Examples of fillers used in the dry granulation process are:

- lactose,
- MCC,
- dextrose,
- sucrose, and
- calcium sulfate dehydrate.

1.5. Mixing

Mixing is an important step in the production process. It can be defined as a unit operation that aims to treat two or more components, initially in an unmixed or partially mixed state, so that each unit of the components lies as nearly as possible in contact with a unit of each of the other components. If any formulation contains

more than one excipient, a mixing procedure is necessary for ensuring that the patient is taking the correct amount of active ingredient. Mixing makes it possible for the tablet to have an even appearance and contributes to the homogeneity of the tablet. Homogeneity is very important when any pharmaceutical formulation is manufactured, thus making sure that every formulation of the same sort is equal (Twitchell, 2007:153).

1.6. Factors influencing bioavailability

Disintegration and dissolution are very important to bioavailability, as discussed in section 1.3.1.3. There are some factors that influence the dissolution rates of solid dosage forms namely:

- tablet disintegration rates,
- the mixing process,
- flow properties of granulate through hopper into die,
- particle size of the drug,
- compression force in the production of the tablet,
- type, quantity and method of incorporation of disintegrants and lubricants,
- nature of fillers, and
- age of the finished tablet (McGinty *et al*., 1981:336).

1.7. Active ingredients

1.7.1. Furosemide

Furosemide is a white, slightly yellow crystalline powder which is odourless and tasteless. Furosemide is practically insoluble in water, which contributes to the reason for using furosemide in this study. Furosemide is more stable in basic media than acidic aqueous solutions where hydrogen ion-catalysed hydrolysis, following first-order kinetics, takes place (Doherty & York, 1988;47:141-155;Cruz, Maness & Yakatan, 1979;2:275-281).

1.7.2. Pyridoxine hydrochloride (Vitamin B6)

Pyridoxine hydrochloride is a vitamin of the B-group. It is a white crystalline powder which is freely soluble in water and slightly soluble in alcohol. The solubility in water is the reason for using pyridoxine hydrochloride in this study as the second active ingredient. It is fairly stable under ordinary conditions (British Pharmacopoeia, 2012).

1.8. Summary

About 80% of pharmaceutical preparations are in the form of tablets which make it a very popular choice as dosage form. One of the oldest techniques for the granulation process is wet granulation. It is still widely used today even though the main drawbacks of this process are the cost, energy and labour intensity. Despite this drawback, it is a very popular choice of granulation still used in the pharmaceutical industry today, especially for high-dose active ingredients. Direct compression on the other hand is ineffective when using large concentrations of active ingredient, because of poor binding properties.

Direct compression is best suited for thermolabile and moisture sensitive drugs, but in these formulations, properties such as compressibility, anti-adherent qualities and flow properties are required. Similar to tablets manufactured by granulation, disintegration as well as low friability should be favourable for direct compression. This opened up the next door to develop excipients specifically for direct compression. Although the direct compression process may look more appropriate, wet granulation is still more popular and there are binders that can be used as dry- or wet binders. Using a solution binder requires it to be dissolved in a solvent for example ethanol to produce a binder solution that is added to a filler such as microcrystalline cellulose. The wet granules that were produced by wet massing should be dried, followed by dry massing, then mixing with the rest of the excipients for example the disintegrating agent, lubricant, glidant etc. Wet granulation is a long and time consuming process but it is very effective to increase the flow properties of powder mixtures.

Chapter 2

EXPERIMENTAL METHODS

2.1. Introduction

The formulation of solid dosage forms is a very delicate and precise process. The reason for this is to have a homogenous tablet ensuring that the correct amount of API is evenly spread throughout the tablet. A wide range of excipients are available to use in formulations and care should be taken when combining all of these into one acceptable formulation to ensure uniformity. The aim of this chapter was to specify the ingredients used in this study and the experimental methods used during formulation, manufacturing and characterisation of the tablets.

2.2. Materials

2.2.1. Active ingredients

In this study two active ingredients were used, furosemide (Lot no. 90111045) and pyridoxine hydrochloride (Lot no. 081206). Furosemide is practically insoluble in water and has a pK_a value of 3.9 (20°C). Dissolution is often the rate-limiting step during the absorption process for this drug, therefore; the disintegration of a tablet affects the rate and extent of dissolution (Marais, 2000:60). The cohesive properties of the powder particles may cause agglomeration which in turn may lead to poor dissolution overall (De Villiers, 1988:39; De Villiers *et al.* 1993:160).

Pyridoxine hydrochloride is freely soluble in water and has pK_a values of 5.0 and 9.0 (25°C) (Aboul-Enein *et al*., 1984:449).

The choice of using a practically insoluble (furosemide) and good water soluble (pyridoxine hydrochloride) API was decided upon to see whether the effect of formulation variables on API dissolution will be influenced by API solubility.

2.2.2. Fillers

Two fillers were used in this study namely lactose monohydrate (Lactochem®, Lot no. 19233, DOMO®) and microcrystalline cellulose (Avicel® PH-101, Lot no. 60839C, FMC BioPolymer®). The reason for using these two fillers was that they are water soluble (lactose monohydrate) and water insoluble (microcrystalline cellulose) as the aim of this study was to investigate the effect of filler, active ingredient and Kollidon® VA64 on the dissolution properties of the active ingredient from wet granulated tablet formulations. Both are readily available and cost-effective and they are still widely used today, whether it is in direct compression (co-processed fillers i.e. Ludipress®, Avicel®) or wet granulation.

2.2.3. Binder

The binder used in this study was Kollidon® VA64 (BASF, SA.,Lot no. 93520356P0). In this study Kollidon® VA64 was employed in different formulations at different concentration levels (0.75, 1.5 and 3% w/w) to determine at which concentration level this binder proved to be the most effective.

2.2.4. Lubricant

Magnesium stearate (Lot no. 21203) is the most widely used lubricant in the industry and was employed in this study as the lubricant of choice. The reasons for its popularity are the fact that it eases the flow of powder into the die, preventing the tablets from sticking to the punches and ensures the tablet to be ejected from the die without any complications. Furthermore, magnesium stearate is very effective at low concentrations. Care should be taken when using magnesium stearate in formulations, because it causes the tablet to be hydrophobic, thereby affecting tablet hardness, its disintegration and drug dissolution. The type and extent of mixing of formulations containing magnesium stearate plays an important role and may influence tablet properties (Sheth*et al.*, 1980:129-131).

2.2.5. Disintegrant

Ac-di-sol® (Lot no. T017C, FMC BioPolymer®) was used as disintegrant. Ac-di-sol® is a superdisintegrant and causes the tablet to break up as soon as it comes in contact with an aqueous solution. In an ideal situation, a disintegrant should cause the tablet not only to break up into granules from which it was compressed, but to break up into the primary powder particles from which it was granulated (Sheth *et al*., 1980:135).

2.3. The granulation process

The process of wet granulation was employed in this study to ensure a uniform granulated powder ready for tableting. Twelve tablet formulations, each with its unique composition of excipients, were formulated (see section 3.1 table 3.1). An amount of lactose monohydrate or Avicel® was weighed and mixed with 8% (w/w) of the active ingredient furosemide or pyridoxine hydrochloride, respectively, in a Turbula® mixer (Turbula, Type T2C, Serial no. 840640) for five minutes at a mixing speed of 69 rpm. A binder solution of Kollidon® VA64 was prepared for each formula using a concentration of 0.75, 1.5 or 3% (w/w) dissolved in ethanol depending on the formula. The binder solutions were added to the powder mixtures and mixed with a mortar and pestle until a uniform wet mass was obtained. The wet mass was screened through a 10 mesh sieve to render coarse granules. The coarse granules were dried in an oven at 60 ± 1°C for 45 minutes. The dried coarse granules were screened through a 20 mesh sieve to render finer granules suitable for tableting. The finer granules were mixed with 0.5% (w/w) magnesium stearate (lubricant) and 0.5% (w/w) Ac-di-sol® (disintegrant) in a Turbula® mixer (Turbula, Type T2C, Serial no. 840640) for five minutes at 69 rpm.

2.4. Compression of tablets

Tablets were compressed on a Cadmach® (Cadmach Machinery Co., India, Type: SSF3) single-punch tablet press (Fig. 2.1 gives the schematic drawing of a single-punch tablet press). Flat faced punches with a diameter of 9 mm were used. Tablets

with a weight of 250 mg were compressed. The weight was kept constant for all formulas.

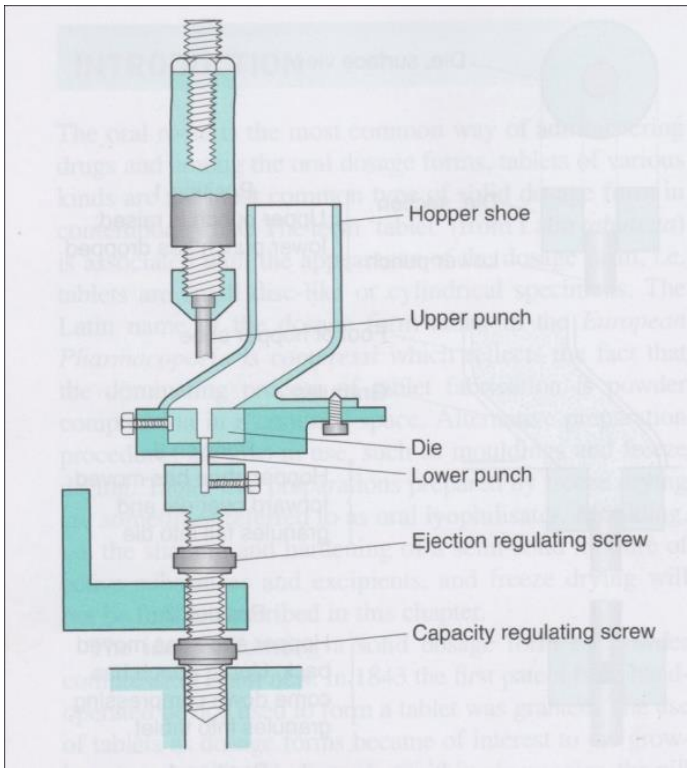


Fig. 2.1: Schematic drawing of a single-punch tablet press (Alderborn, 2007:444).

Two different compression settings (stroke length settings 22 and 24) were used to determine the compressibility of the filler (hardness and friability) and to conclude whether this would have an effect on the different tablet formulations containing different amounts of binder concentrations. The compression pressure was applied by the upper punch and controlled by the upper punch displacement (Alderborn, 2007:444). Crushing strength values, disintegration times, tablet diameter and thickness were the four parameters that would be influenced by the different compression pressures. By shifting the lower punch up or down, the volume (amount of powder flowing into die) of the die opening can be controlled to ensure that the correct amount of powder will fill the die to reach the constant tablet mass of 250 mg before every tablet formulation was compressed. The first ten tablets of each powder batch were disposed of. After tableting, the tablets were placed in glass containers, sealed airtight with Parafilm® and locked tight with screw caps, stored away in a dark storage area until testing.

2.5. Determining tablet properties

2.5.1. Weight variation

The weight variation test was done according to the British Pharmacopoeia (BP) (2012). A total number of twenty tablets were randomly selected from each batch and individually weighed on an analytical balance, (Zeiss®, West Germany, Type 1601 A MP8-1). The average weight, standard deviation (SD) and the percentage relative standard deviation (%RSD) were calculated. The %RSD was calculated using equation 2.1.

$$\%RSD = \frac{SD}{Average} \times 100 \qquad \textbf{2.1}$$

Where *SD* represents standard deviation and *Average* represents the average weight of twenty randomly selected tablets.

2.5.2. Crushing strength, thickness and diameter

The crushing strength, thickness and diameter of ten randomly selected tablets from each formulation were measured with a Pharma Test (see Fig. 2.2) crushing strength test unit (Pharma Test, Switzerland, Type PTB 311).

Fig. 2.2: Pharma Test crushing strength test unit.

2.5.3. Friability

A total number of ten tablets from each formulation was selected at random and were dusted with a brush to remove the excess dust from the tablets. Thereafter it was weighed on an analytical balance (Zeiss®, West Germany, Type 1601 A MP8-1). The ten tablets were placed in the drum of a Roche® Friabilator (see Fig. 2.3). The

lid on the Roche® was closed, tightened and rotation commenced for four minutes at 25 rpm. After rotation stopped, the ten tablets were removed from the drum, dusted off and weighed. The percentage friability (weight loss) was calculated using equation 2.2.

$$\% \, Friability = \frac{m_1 - m_2}{m_1} \times 100 \qquad \textbf{2.2}$$

Where m_1 represents the initial mass and m_2 represents the mass after rotation.

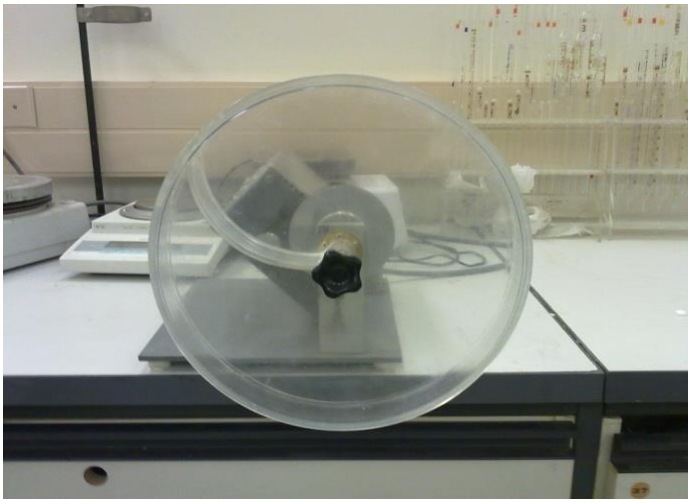
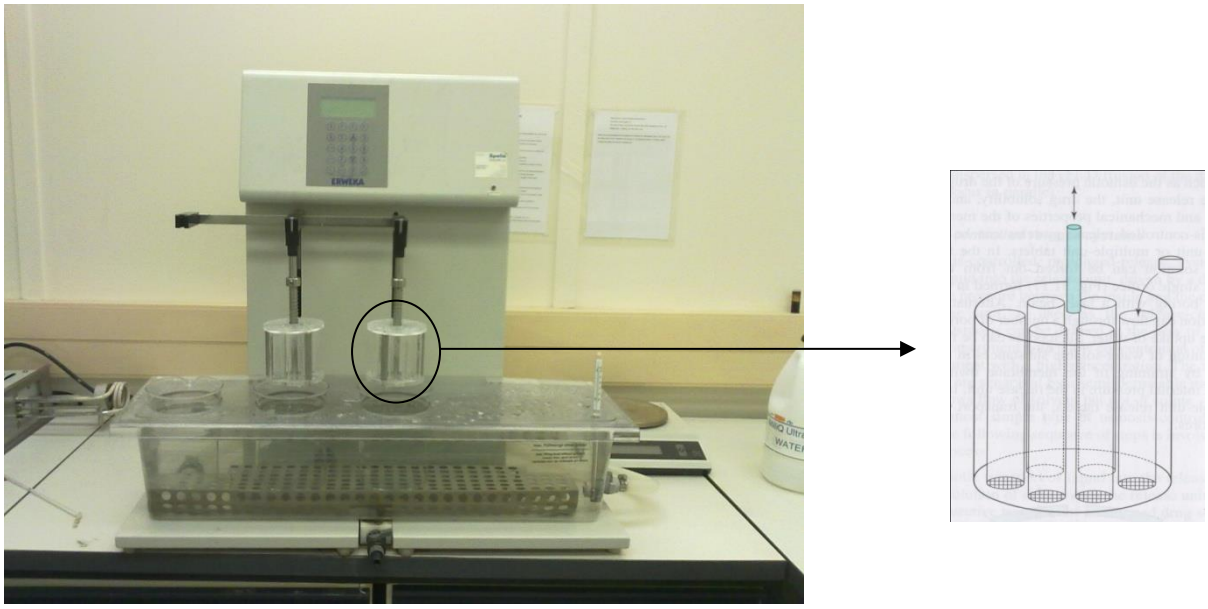


Fig. 2.3: Roche® Friabilator.

2.5.4. Disintegration

The standard Erweka® (Erweka®, Heusenstamm, Germany, Type ZT503) test unit was used in this study to conduct the disintegration tests. The unit was filled with distilled water and heated to 37 ± 1 °C. This test unit was fitted with a thermostat to regulate the temperature (see Fig. 2.4a). An illustration of glass tubes and small sieves used for containing the six randomly selected tablets can be seen in fig. 2.4b. Once locked into place the test unit was switched on to move up and down into the water medium at a steady rate. The disintegration times were determined by carefully noting the time it took for each tablet to disintegrate fully (no tablet fragments left on sieves). Disintegration tests were conducted according to BP (2012) standards.



(a) (b)

Fig. 2.4: Erweka® disintegration test unit (a) and an illustration of the unit with glass tubes and sieves containing the tablets (b) (Alderborn, 2007:462).

2.6. Dissolution studies

2.6.1. Apparatus

Dissolution studies were conducted using an Erweka® (Erweka®, Heustenstramm, Germany,Type DT6R) six-station dissolution apparatus with the standard USP specified paddles. The apparatus was fitted with a variable speed synchronous motor and a thermostat and was operated at a temperature of 37 ± 0.5 °C. Fig. 2.5 illustrates the paddles used in the study.

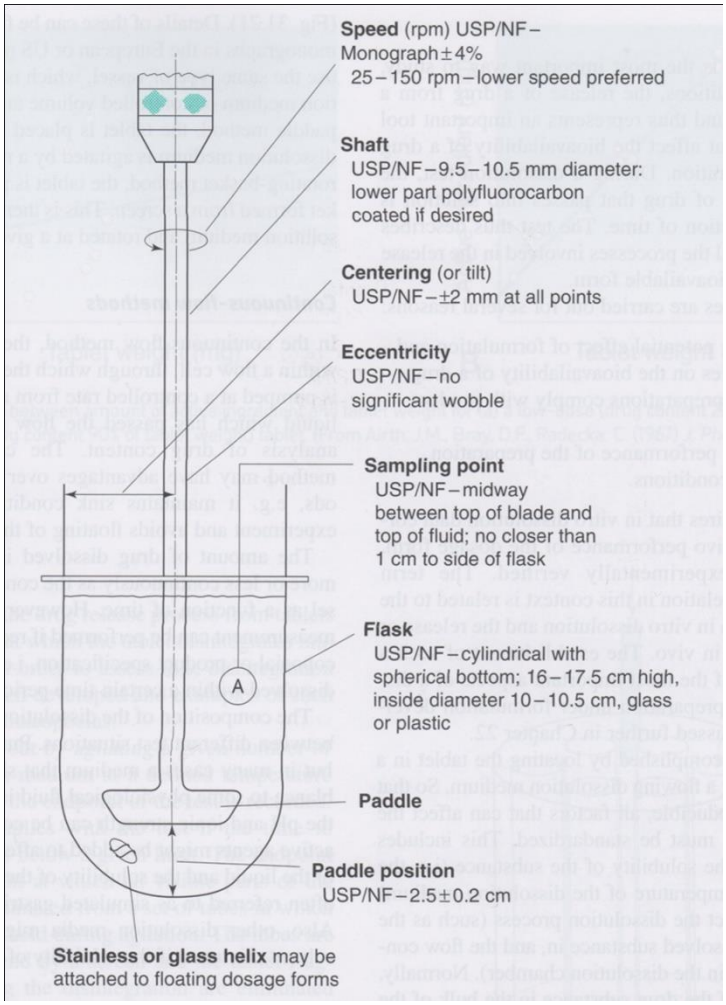


Fig. 2.5: Diagram of a dissolution instrument based on the rotating paddle method (Alderborn, 2007:464).

2.6.2. Settings and conditions

Furosemide and pyridoxine hydrochloride are weak acidic drugs (pKa 3.6 and 5.0). The pH of a dissolution medium are said to play an important role in detecting the differences between good and poor formulations (Rubenstein & Price, 1977:5P).

Dissolution tests were done in 900 cm^3 0.1 M HCl as it simulates the pH conditions one would have inside the human stomach at a temperature of 37 ± 0.5 °C, which was regulated by the thermostat, and at a rotational speed of 50 rpm, which was kept constant by the synchronous motor.

2.6.3. Method

Prior to every dissolution run, the rods were pushed down into the medium to a constant depth in the dissolution beaker. The synchronous motor was started and allowed to reach the required speed of 50 rpm. As soon as the required speed was reached by the motor, the tablets were introduced and dropped directly into the medium at time zero (t = 0). At times t = 2, 5, 7.5, 10, 20, 30, 45, 60, 90 and 120 minutes, a 10 cm^3 sample was withdrawn through a filter unit containing a Millipore® pre-filter. The samples were transferred to 20 cm^3 glass poly tops. Immediately after sampling, the volume lost was replaced with an equal volume of fresh, preheated dissolution medium, using an Eppendorf® pipette. During dissolution calculations, a correction was made for the amount of drug lost through sampling (see section 2.6.5).

The UV-absorbencies of the samples were measured in duplicate at 277 nm and 293 nm for furosemide and pyridoxine hydrochloride, respectively, against 0.1 M HCl as blank, using a double beam UV spectrophotometer (Shimadzu UV1701, Japan) fitted with a super sipper and 1 cm^3 flow-through quartz cell.

The furosemide and pyridoxine hydrochloride concentrations in the withdrawn samples were determined from standard curves by means of linear regression.

2.6.4. Standard curve

Standard curves were constructed each day prior to dissolution testing. Standard solutions with concentrations ranging from 2 to 30 $\mu g.cm^3$ were prepared from stock solutions containing 50 mg furosemide and pyridoxine hydrochloride, respectively, which were accurately and precisely weighed. The stock solutions were prepared by dissolving the APIs in ± 70 ml of 90% (v/v) ethanol and it was made up to 250 $cm^3$with 0.1 M HCl. The UV-absorbencies of the standard solutions were determined spectrophotometrically at 277 nm for furosemide and 293 nm for pyridoxine hydrochloride against 0.1 M HCl as blank. The absorbencies were plotted against API concentration and the best straight line through the data points was fitted using linear regression. All standard curves obeyed Beer's Law in the concentration range employed, with correlation coefficients (r^2) ≥ 0.999.

2.6.5. Dissolution data

The amount of furosemide and pyridoxine hydrochloride dissolved (μg.cm^3) at each sampling time was calculated using equation 2.3, while equation 2.4 was used to compensate for drug lost through sampling.

$$x = \frac{y^* - c}{1000m} \qquad \textbf{2.3}$$

Where y^* is the corrected absorbency (from equation 2.4); x is the drug concentration (μg.cm^3) and *m* and *c* are the slope and y-axis intercept-values, respectively, obtained from the standard curve.

$$y_n^* = y_n + \frac{V_s}{V_m} \cdot \sum^{n-1} y^* \qquad \textbf{2.4}$$

Where y_n^* is the corrected absorbency of the n^{th} sample; y_n is the measured absorbency of the n^{th} sample; V_s is the sampling volume; V_m is the dissolution medium volume and $\sum^{n-1} y^*$ is the sum of all the corrected absorbencies prior to the n^{th} sample.

Dissolution profiles in this study are presented as furosemide or pyridoxine hydrochloride dissolved (in μg.cm^{-3}) as function of time (minutes) and are the means of at least four runs for each formulation.

2.6.6. Calculations

All calculations were done using Microsoft® Excel 2007 for Windows (Microsoft Corporation, Seatle, Washington, USA).

2.6.7. Dissolution parameters, DR_i and AUC

The initial slope of the dissolution curve between t_0 and t_{10} was suggested to be a fair estimate for the initial dissolution rate of the APIs (DR_i) from the various tablet formulations, whereas the area under the dissolution profile up to 120 minutes (AUC) would be an indication of the extent of drug dissolution.

The DR_i (mg.cm^{-3}.min^{-1}) of the furosemide and pyridoxine hydrochloride from each tablet formulation was determined from the slope of the dissolution curve between t_0

and t_{10}, while the AUC (mg.min.cm^{-3}) of the dissolution profile between t_0 and t_{120} was determined using the trapezoidal rule, which is given by equation 2.5.

$$AUC = 0.5 \times \sum_{t=n}^{t=0}(t_n - t_{n-1})(c_n + c_{n-1}) \quad \textbf{2.5}$$

Where t_n - t_{n-1} is the time difference between two consecutive sampling times and c_n and c_{n-1} are the drug concentration (mg.cm^{-3}) in the samples at sampling times corresponding to t_n and t_{n-1}.

The use of the area under the dissolution profile as a method to compare the effects of formulation or processing variables on drug release profiles from tablets were based on the following assumption: If two formulations do not differ much in the rate and extent to which they make the drug available *in vitro*, they will not differ much in their area under the concentration/time curves obtained from dissolution tests (Banakar, 1991:437; Rescigno, 1992:925).

2.6.8. Difference and similarity factor

Moore and Flanner (1996:64-74) presented two fit factors, difference and similarity factor. Both of these fit factors compare the difference between the percentage drug dissolved per unit time for a test and reference formulation.

Equation 2.6 (calculation of the difference factor) approximates the percentage error between two curves. The percentage error is zero when the test and reference profiles are identical and increases proportionally with the dissimilarity between the two profiles. The difference factor has not been used in this study. On the other hand, the value of the similarity factor is 100 when two dissolution profiles are identical and approaches 0 as the dissimilarity increases (Moore & Flanner, 1996:66). According to Moore and Flanner (1996:74) these two fit factors provide an effective means for comparing dissolution profiles and as such holds promise as tools in the optimisation of product development. In fact, the similarity factor has been adopted by the Center for Drug Evaluation and Research (FDA) as a criterion for assessment of the similarity between two *in vitro* dissolution profiles. According to the FDA two dissolution profiles can be considered similar when f_2-values of between 50 and 100 are obtained (Costa & Lobo, 2001:130).

The difference factor can be calculated by equation 2.6 and the similarity factor by equation 2.7

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_T|}{\sum_{t=1}^{n} R_t} \right\} x100\% \qquad \textbf{2.6}$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} w_t (R_t - T_t)^2 \right]^{-0.5} x100 \right\} \qquad \textbf{2.7}$$

where: f_1 = difference factor,

f_2 = similarity factor,

R_t = reference assay at time point *t*,

T_t = test assay at time point *t*

n = number of pull points, and

w_t= optional weight factor.

2.7. Statistical evaluation of the experimental data

A one-way analysis of variance (ANOVA) was done to determine if statistical significant differences existed between the mean mass values of the test compounds in general. A Levene's test was performed to assure equality of variances. In the case of inequality of variances a Welch test was performed. A normal probability plot on the residuals was done to assure that the data was fairly normally distributed (Tabachnick & Fidell 2001). Tukey's test was done to determine which of the test compounds' means differed statistically significantly from the means of each other.

All these statistical procedures mentioned above were also done on the diameter, thickness, crushing strength, disintegration and dissolution values. These procedures were done using Statistica® (StatSoft, Inc. 2007). All tests were done on a 0.05 significant level.

2.8. Summary

The methods for the preparation of different tablet formulations containing lactose monohydrate and microcrystalline cellulose as fillers, Kollidon® VA64 (binder), Ac-di-sol® (disintegrant), magnesium stearate (lubricant) and two different active ingredients (pyridoxine hydrochloride and furosemide) are given. Methods for the characterisation of tablets prepared from the different tablet formulations were also given. These tests included weight variation, friability, crushing strength and disintegration. The methods for the testing of dissolution were also presented.

Chapter 3

THE EVALUATION OF PHYSICAL TABLET PROPERTIES

3.1. Introduction

A process known as powder compression is used to prepare tablets by forcing particles into close proximity to each other. This enables the particles to cohere into a porous, solid specimen of defined geometry. The reduction in volume of a powder when a force is applied can be defined as powder compression (Alderborn, 2007:443).

A fractional factorial design was used to investigate the influence of different formulation variables on the properties of tablets prepared from the different powder mixtures. Twelve different powder formulations were used to prepare tablets. The tablets were evaluated with respect to:

- weight variation,
- crushing strength,
- thickness,
- diameter,
- friability,
- disintegration time, and
- dissolution behaviour of the API (explained in chapter 4).

The chapter deals with the evaluation of tablets prepared from different powder formulations containing the following excipients:

- Avicel® PH-101 or lactose monohydrate as fillers,
- Kollidon® VA64 as binder at three different concentrations (0.75, 1.5 or 3% w/w),
- Ac-di-sol® (0.5% w/w) as disintegrant, and
- Magnesium-stearate (0.5% w/w) as lubricant.

The two active pharmaceutical ingredients used were furosemide (practically insoluble in water) and pyridoxine hydrochloride (soluble in water).

Ac-di-sol® and magnesium-stearate was incorporated extra-granular. For all formulations, tablets were formulated to weigh 250 mg. Tablets with different hardness profiles were manufactured due to two compression settings (CS) at 22 and 24. Flat faced punches of 9 mm in diameter were used to compress the powder formulations (see section 2.4). Table 3.1 shows a tabulated representation of the fractional factorial design employed to investigate the different variables and levels thereof.

Table 3.1: Factorial design illustrating the different formulations.

		Avicel® PH-101		Lactose monohydrate	
		Furosemide	**Pyridoxine hydrochloride**	**Furosemide**	**Pyridoxine hydrochloride**
Compression setting (CS) 22	**Kollidon® VA64 (3.0% w/w)**		**1**	**6**	
	Kollidon® VA64 (1.5% w/w)	**2**			**7**
	Kollidon® VA64 (0.75% w/w)		**3**	**8**	
Compression setting (CS) 24	**Kollidon® VA64 (3.0% w/w)**	**4**			**9**
	Kollidon® VA64 (1.5% w/w)		**5**	**10**	
	Kollidon® VA64 (0.75% w/w)	**12**			**11**

Where applicable, the following acronyms will be used:

Formula	Acronym
1	APB_3S_1
2	AFB_2S_1
3	APB_1S_1
4	AFB_3S_2
5	APB_2S_2
6	LFB_3S_1
7	LPB_2S_1
8	LFB_1S_1
9	LPB_3S_2
10	LFB_2S_2
11	LPB_1S_2
12	AFB_1S_2

Where: A = Avicel® PH-101; L = Lactose monohydrate; B = Binder concentration 1 (0.75% w/w), 2 (1.5% w/w) or 3 (3.0% w/w); F = Furosemide; P = Pyridoxine hydrochloride; S = stroke length 1 (22) and 2 (24)

Tablets could be prepared from all formulations except formulation 12. In the case of formulation 12, the powder did not flow into the die evenly and resulted in a variable filling volume rendering unsatisfactory tablets. It was noticed, when performing the tableting procedures, that the die did not fill evenly and the resulting tablets were very soft, crumbling with the slightest touch to it. A reason for this phenomenon may be the fact that smaller granules was obtained from the sieving process, rendering a larger fraction of finer particles in the powder, resulting in poor powder flow (Staniforth & Aulton, 2007:169). The smaller particles could be caused by the low binder concentration (0.75% w/w) rendering poor granule formation.

3.2. Tablet weight variation

Table 3.2 illustrates the average weight, SD and %RSD of the different tablet formulations. Tablet weight variation plays a crucial part in influencing the variation of active ingredient content of tablets. The tablets that were compressed from the different powder mixtures were evaluated and compared. The aim of the tableting process was to keep the weight constant at 250 mg per tablet. Wet granulation increases the flowability of a powder – the reason being the use of a liquid binder (Kollidon® VA64) – which coats the individual powder particles, causing adherence to each other leading to the formation of agglomerates, called granules (Sheth, *et al,.* 1980:114). Mixtures 7 and 9 (see table 3.2) exhibited a standard deviation (SD) of more than 7.49 mg and 7.84 mg respectively, which means these mixtures exhibited poorer flow compared to that of the other mixtures – resulting in larger variation in tablet weight.

Table 3.2: The average weight of the tablets prepared according to BP guidelines.

Formulation	Average weight variation			
	n	Mean	Std. Dev.	% RSD
1	20	248.80	2.22	0.89
2	20	247.93	2.49	1.00
3	20	252.04	2.90	1.15
4	20	242.20	5.03	2.08
5	20	260.61	4.93	1.89
6	20	247.12	3.60	1.46
7	20	262.38	7.49	2.85
8	20	250.91	3.49	1.39
9	20	259.27	7.84	3.02
10	20	254.96	4.97	1.95
11	20	254.66	2.37	0.93

All formulations exhibited %RSD-values of less than 5% (see table 3.2). Not more than 2 individual masses deviated from the average mass by more than 5% for tablets with a weight of 250 mg or more. Therefore, tablet weight variation complied with the standards of the BP (2012). The results of the weight variation therefore indicated acceptable flow properties. The latter implies that the variation in drug content should be within acceptable limits.

3.3. Crushing strength and friability

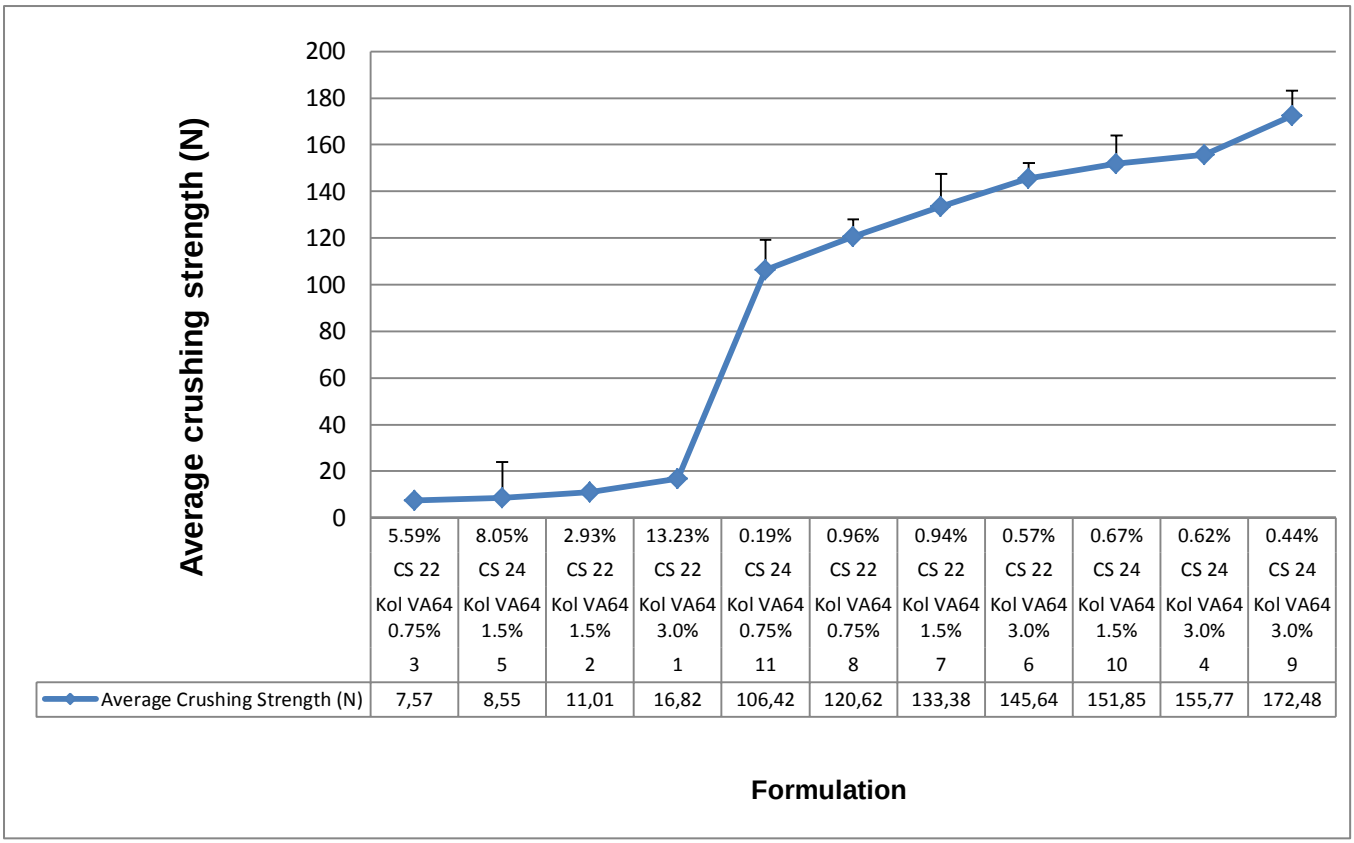
The mechanical strength of a tablet, which can be evaluated in terms of friability and crushing strength, plays an important role as one of the parameters for characterising the mechanical behaviour of tablets. During processing and handling, a minimum mechanical strength should be sustained when potential loading are encountered (Fell & Newton, 1970a:689). Crushing strength and friability tests were conducted as described in sections 2.5.2 and 2.5.3, respectively. In table 3.3, the results obtained for friability and crushing strength are presented. In table 3.4, the results for tablet thickness are presented. In fig. 3.1, an illustration of the average crushing strength of the tablets are presented.

Table 3.3: The crushing strength and %-friability results of tablets prepared from different powder formulations.

Formulation	Crushing Strength (N)			%-Friability
	n	Mean	Std. Dev.	
1	10	16.82	1.35	2.93
2	10	11.01	0.80	5.59
3	10	7.57	0.91	8.05
4	10	155.77	15.43	0.19
5	10	8.55	1.07	13.23
6	10	145.64	7.25	0.44
7	10	133.38	12.70	0.67
8	10	120.62	12.15	0.96
9	10	172.48	14.06	0.62
10	10	151.85	10.68	0.57
11	10	106.42	6.53	0.94

Table 3.4: The average thickness of tablets prepared from different powder formulations.

Formulation	Thickness (mm)		
	n	Mean	Std. Dev.
1	10	3.94	0.01
2	10	4.25	0.03
3	10	4.58	0.02
4	10	2.60	0.03
5	10	4.68	0.02
6	10	2.24	0.03
7	10	2.40	0.06
8	10	2.27	0.02
9	10	2.42	0.06
10	10	2.29	0.03
11	10	2.32	0.03



	5.59% CS 22 Kol VA64 0.75% 3	8.05% CS 24 Kol VA64 1.5% 5	2.93% CS 22 Kol VA64 1.5% 2	13.23% CS 22 Kol VA64 3.0% 1	0.19% CS 24 Kol VA64 0.75% 11	0.96% CS 22 Kol VA64 0.75% 8	0.94% CS 22 Kol VA64 1.5% 7	0.57% CS 22 Kol VA64 3.0% 6	0.67% CS 24 Kol VA64 1.5% 10	0.62% CS 24 Kol VA64 3.0% 4	0.44% CS 24 Kol VA64 3.0% 9
Average Crushing Strength (N)	7,57	8,55	11,01	16,82	106,42	120,62	133,38	145,64	151,85	155,77	172,48

Fig. 3.1: Illustration of average crushing strength of tablets prepared from different powder formulations.

From table 3.3 and Fig. 3.1 it can be seen that a higher %-friability is accompanied by a lower average crushing strength, indicating lower mechanical tablet strength. Formulations 1, 2, 3 and 5 exhibited similar crushing strength values (average crushing strength below 20 N). They all exhibited %-friability values above 2% (2.93%, 5.59%, 8.05% and 13.23%, respectively), which indicated an unacceptable resistance to friability (British Pharmacopoeia, 2012), and poor resistance to crushing (16.82 ± 1.35 N, 11.01 ± 0.8 N, 7.57 ± 0.91 N and 8.55 ± 1.07 N, respectively). All of the above tablet formulations contained Avicel® PH-101 as filler. According to a study by Lahdenpää et al. (1997:318) standard grade Avicel® PH-101 tends to result in rendering stronger tablets, but this does not comply with what is seen in fig. 3.1. The reason for this might be the fact that three of these tablet formulations had a binder concentration of 1.5% or less, indicating that binder concentration had a prominent influence on the crushing strength of a tablet. Another contributing factor was the compression force employed during tableting. Three of these powder formulations (1, 2 and 3) were compressed at the lower

compression setting (stroke length 22). It is recommended that a higher compression force setting be used for future studies.

Regarding the effect of binder concentration (% w/w), it was evident that the tablet formulations with the highest average crushing strength values (formulation 4, 155.77 ± 15.43 N and formulation 9, 172.48 ± 14.06 N) had the higher Kollidon® VA64 concentration (3% w/w). An increase in binder concentration had a statistically significant effect on the crushing strength (ANOVA, Tukey test, $p < 0.05$). Furthermore, both of these tablet formulations were tableted at the highest compression setting (stroke length 24), which indicates an increase in compression force. An increase in compression force results in particles being moved within closer proximity, enlarging the surface contact area between adjacent particles. This allows for improved binding between adjacent particles, rendering tablets with greater mechanical strength (Parrot, 1981:158-160).

With respect to the thickness of the tablets, the tablets with the lowest value for thickness corresponded with a statistically significant increase (ANOVA, Tukey test, $p < 0.05$) in the average crushing strength. The thickness of tablet formulations 4, 6, 7, 8, 9, 10 and 11 (2.6 mm, 2.24 mm, 2.4 mm, 2.27 mm, 2.42 mm, 2.29 mm and 2.32 mm respectively) were all less than 3 mm and all exhibited average crushing strength values of more than 100 N (155.77 ± 15.43 N, 145.64 ± 7.25 N, 133.38 ± 12.7 N, 120.62 ± 12.15 N, 172.48 ± 14.06 N, 151.85 ± 10.68 N and 106.42 ± 6.53 N respectively). From the above mentioned results the following conclusions were made:

- An increase in %-friability, is accompanied by a decrease in average crushing strength.
- An increase in binder concentration, results in an increase in average crushing strength.
- An increase in compression force, results in an increase in average crushing strength.
- An increase in tablet thickness is accompanied by a decrease in average crushing strength.

3.4. Disintegration time

The disintegration time was determined according to the method described in section 2.4.5 and the results are presented in table 3.5. In fig. 3.2, an illustration of the average disintegration time as a function of the average crushing strength are presented. A graphical presentation of the average disintegration time can be seen in fig. 3.3.

Table 3.5: The average disintegration time (seconds) of tablets prepared from different powder formulations.

Formulation	Disintegration time (s)		
	n	mean	std. dev.
1	18	11.78	6.32
2	18	9.56	2.18
3	18	10.11	1.78
4	18	24.67	9.73
5	18	12.33	3.99
6	18	558.22	26.20
7	18	347.33	91.52
8	18	58.56	5.29
9	18	499.50	19.53
10	18	280.22	22.26
11	18	153.78	9.88

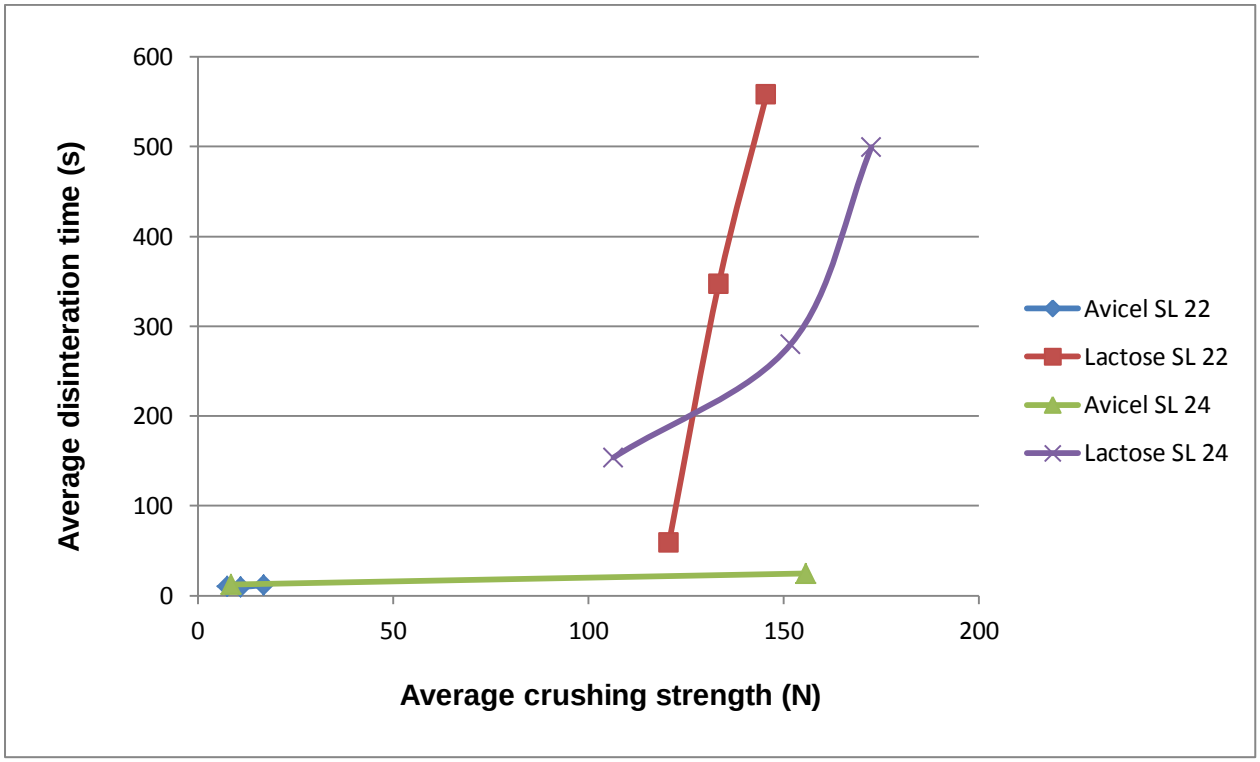
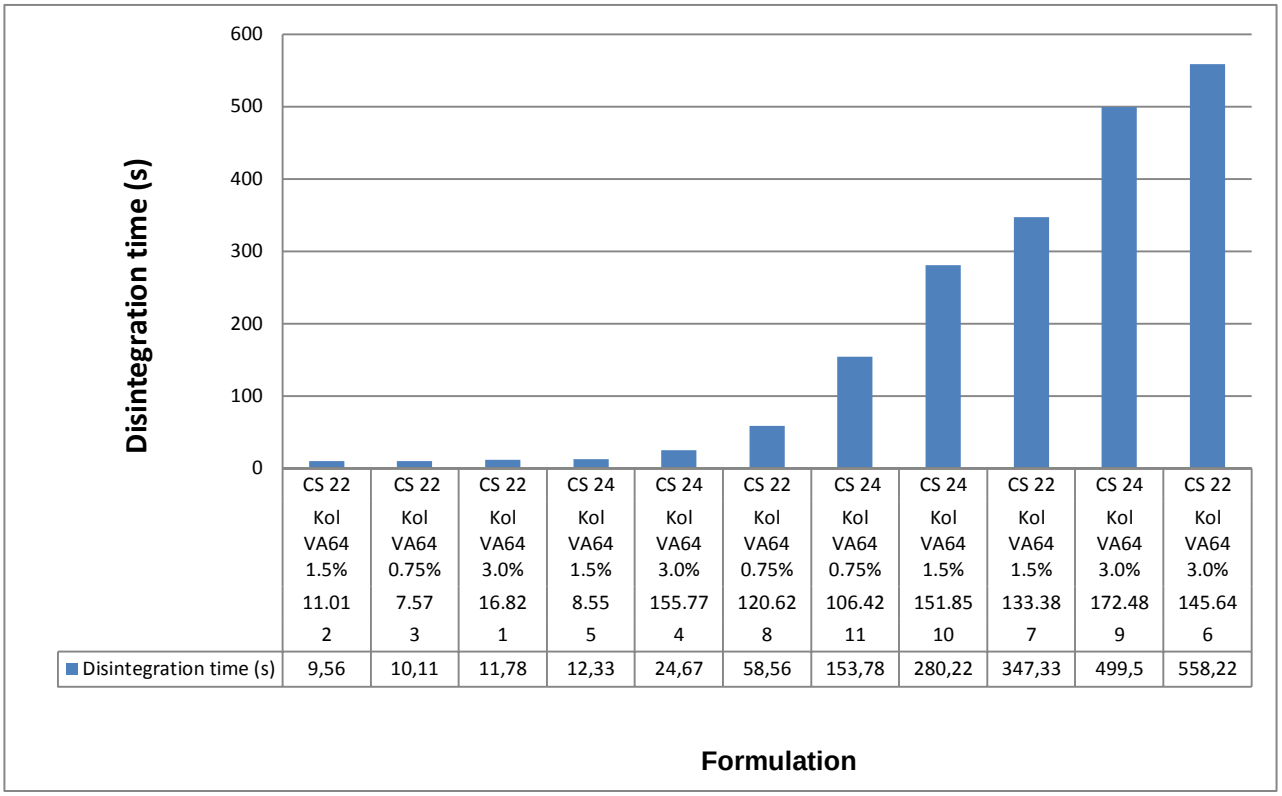


Fig. 3.2: Illustration of the average disintegration time (s) compared to the average crushing strength (N) of Avicel® PH-101 and lactose monohydrate containing tablet formulations compressed at two compression settings (22 and 24).



	CS 22 Kol VA64 1.5% 11.012	CS 22 Kol VA64 0.75% 7.573	CS 22 Kol VA64 3.0% 16.821	CS 24 Kol VA64 1.5% 8.555	CS 24 Kol VA64 3.0% 155.774	CS 22 Kol VA64 0.75% 120.628	CS 24 Kol VA64 0.75% 106.4211	CS 24 Kol VA64 1.5% 151.8510	CS 22 Kol VA64 1.5% 133.387	CS 24 Kol VA64 3.0% 172.489	CS 22 Kol VA64 3.0% 145.646
Disintegration time (s)	9,56	10,11	11,78	12,33	24,67	58,56	153,78	280,22	347,33	499,5	558,22

Fig. 3.3: Illustration of average disintegration time (seconds) of tablets prepared from different powder formulations.

It was evident from fig. 3.2 that an increase in crushing strength results in an increase in disintegration time. Fox *et al.* (1963:260) and Parrot (1981:161) have shown in their studies that an increase in compression force lead to an increase in disintegration time. These researchers attributed the increase in disintegration time to a decrease in capillary porosity due to an increase in compression force. In section 3.3 it was concluded that an increase in compression force, resulted in an increase in crushing strength. Therefore, it could be said that an increase in compression force is associated with an increase in disintegration time and an increase in compression force probably decreased capillary porosity. Due to a decrease in capillary porosity, water penetration was impeded, causing an increase in disintegration time. As seen in fig. 3.3, the formulation that exhibited the longest average disintegration time (558.22 ± 26.20 s) was compressed at compression setting 22. This phenomenon shows that in this study, compression force was not the only factor influencing the disintegration time of the tablets. All six tablet formulations with the highest average disintegration times contained lactose as filler which influenced the disintegration process of the tablets. In agreement with the

disintegration results, all the formulations that contained lactose monohydrate as filler, also exhibited higher average crushing strength values compared to the Avicel® PH-101 containing formulations, except for tablet formulation 4 which contained Avicel® PH-101, but also contained 3.0% w/w binder concentration and was compressed at compression setting 24.

Furthermore, the formulations with the longest disintegration times (>300 sec) all had a Kollidon® VA64 binder concentration escalating from 1.5% (w/w) to 3.0% (w/w). This means that the binder concentration had a prominent influence on the average disintegration time of the tablet formulations. As seen and hypothesised, in section 3.3, an increase in binder concentration caused an increase in average crushing strength, probably rendering tablets with a decreased porosity. Therefore water penetration into the tablets was impeded and, a prolonged disintegration time resulted. The above mentioned formulations showed a statistically significant increase in the disintegration time (ANOVA, Tukey test, $p < 0.05$) because of the increase in binder concentration.

Considering formulations 1 – 5, it is clear that all these formulations exhibited average disintegration times of less than 30 seconds (11.78 ± 6.32 sec, 9.56 ± 2.18 sec, 10.11 ± 1.78 sec, 12.33 ± 3.99 sec and 24.67 ± 9.73 sec, respectively). This can possibly be attributed to the low average crushing strength values. Furthermore, three of these formulations were compressed at the lowest compression setting of 22 adding to the softness of the tablets. No clear correlation with regard to binder concentration was observed for these formulations. However, all of these tablet formulations had one common factor, and that was Avicel® PH-101 as filler. Avicel® PH-101 possesses a low bulk density (0.37 g/cm^3) and was incorporated in these tablet formulations at a higher proportion than the other excipients. Therefore, Avicel® PH-101 has the tendency to generate tablets with greater porosity resulting in water entering the tablet matrix freely, decreasing the disintegration time of the tablets (Sheth, *et al*. 1980:122). Furthermore, due to the low density, it is possible that the particles was not as close to each other as was the case with the lactose (0.64 g/cm^3) containing formulations. The net result being a lower binding strength and tablets exhibiting lower average crushing strength values.

The moisture content can somewhat affect the mechanical strength and flowability of MCC. Water molecules act as a plasticiser when the moisture content of MCC is above 5%, drastically affecting the visco-elastic and mechanical properties of MCC, resulting in lower tensile strength of MCC tablets. New surface areas of particles during tabletting cannot be generated by the plastic deformation of MCC. The decrease of contact area for bonding is accompanied by an increase of particle size of MCC products and results in lower tensile strength of tablets resulting in softer tablets, rendering fast disintegration of tablets (Amidon & Houghton, 1995:924; Doelker, 1993:2460).

3.5. Conclusion

Tablets from powder mixtures containing different concentrations of Kollidon® VA64 (0.75, 1.5 and 3 % w/w) were successfully prepared and evaluated with respect to weight variation, friability, crushing strength, thickness, diameter and disintegration time.

All formulations exhibited %RSD-values of less than 5% (see table 3.2). Not more than 2 individual masses deviated from the average mass by more than 5% for tablets with a weight of 250 mg or more. Therefore, tablet weight variation complied with the standards of the BP (2012). The results of the weight variation therefore indicated acceptable flow properties. The last mentioned, implies that the variation in drug content should be within acceptable limits.

A decrease in average tablet hardness led to tablets with low friability, indicating decreasing mechanical strength. Formulations 1, 2, 3 and 5, which all contained Avicel® PH-101 as filler, exhibited a %-friability of more than 2%, which indicated an unacceptable resistance to friability. The other formulations showed acceptable resistance to friability.

Regarding the crushing strength it can be concluded that the binder concentration had a significant influence on the increase in the average crushing strength. Tablet formulation 4 and 9 exhibited average crushing strength values of, 155.77 ± 15.43 N and 172.48 ± 14.06 N, respectively and this coincided with a Kollidon® VA64 concentration of 3 % (w/w) which was the highest concentration used in this study. Both these tablet formulations were compressed at the highest compression setting

(stroke length 24) and it was shown that an increase in compression force resulted in a statistical significant increase in average crushing strength. Not all formulations exhibited acceptable friability, and therefore, it cannot be said that all formulations exhibited sufficient mechanical strength (friability and crushing strength).

From the average disintegration times of the different tablet formulations, it was observed that an increase in binder concentration resulted in an increase in disintegration time. It was also noted that the compression force played a role, but depended on the filler used, seeing that the tablet with the longest disintegration time was compressed at the lower of the two compression settings but contained lactose monohydrate as filler. Therefore, it was found that both the binder concentration and the filler used had the greatest influence on the disintegration times. Another tendency was found regarding the filler used. Lactose monohydrate rendered tablets with much longer disintegration times compared to the Avicel® PH-101 containing tablet formulations. The reason for this is the fact that Avicel® PH-101 consists of a low bulk density (0.37 g/cm^3) which possibly resulted in high porosity encouraging the entering of water into the tablet matrix freely, decreasing the disintegration time. All formulations exhibited acceptable disintegration times within 15 minutes.

Chapter 4

DISSOLUTION BEHAVIOUR OF TABLETS CONTAINING PYRIDOXINE HYDROCHLORIDE AND FUROSEMIDE AS ACTIVE INGREDIENTS

4.1. Introduction

The process of dissolution is a key factor with regard to the pharmaceutical availability of an active ingredient. Dissolution can be defined as the process where molecules or ions are transferred from a solid state into a solution. The underlying principal of this process is that it is controlled by the relative affinity between the molecules of the solid substance and those of the solvent (Aulton, 2007:17).

The dissolution rate can be influenced by the following factors:

- physicochemical properties of the drug,
- formulation components,
- the manufacturing process, and
- packaging and storage (Peng *et al.* 2007:90).

The rate of drug dissolution is directly proportional to the surface area of the drug particles that is in contact with the surrounding medium (the effective surface area), according to the general dissolution equation (see equation 2.8) which was derived from the Noyes-Whitney (1897) equation.

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{DAC_S}{h} \qquad \textbf{2.8}$$

Where (d*m*/d*t*) is the rate of mass transfer of solute molecules or ions through a static diffusion layer, *D*, the diffusion coefficient, *A*, the area available for molecular or ionic migration, C_S, the saturation solubility and *h* represents the thickness of the boundary layer (Aulton, 2007:19).

It can be assumed that factors influencing the contact area between the drug and the surrounding medium, may have an effect on the rate and extent of drug dissolution. Through the manipulation of process variables and the choice of excipients and their concentration, drug release and dissolution can be optimised (Lambrechts, 2008:73). From the results of the previous chapter it is evident that the binder concentration, as

well as the compression force and tablet hardness had an effect on the disintegration of the tablets prepared from different formulations. Drug dissolution can be significantly influenced by tablet properties such as the disintegrant and disintegration process; type and concentration of binder; the filler and its solubility; and also the solubility of the active ingredient.

Whether the influence of these factors on disintegration is going to be reflected in a difference in the pharmaceutical availability of the active ingredients needs to be investigated with dissolution studies.

4.2. Dissolution studies for tablets containing pyridoxine hydrochloride

The dissolution profiles of tablets containing Kollidon® VA64 as binder and a good water soluble drug, pyridoxine hydrochloride, at two compression settings (stroke length 22 and 24) were determined as discussed in section 2.5. Two dissolution parameters were calculated from the dissolution data. These were DR_i (indicating the initial rate of drug dissolution) and AUC (representing the extent of drug dissolution) (see section 2.6.7), which could be used to describe the dissolution behaviour of the drugs. The calculated DR_i and AUC-values for the different formulations are reported in table 4.1. The similarity factor-values are presented in table 4.2.

Table 4.1: The initial rate (DR_i) and extent of dissolution (AUC) of pyridoxine hydrochloride from tablets prepared from different powder formulations.

Formulation	Filler	Binder [ ] (% w/w Kollidon® VA64)	Compression setting	DR_i ($\mu g.cm^{-3}.min^{-1}$)	Standard Deviation (DR_i)	AUC ($\mu g.cm^{-3}.min$)	Standard Deviation (AUC)
1	Avicel® PH-101	3	22	2.19	0.05	2548.84	66.32
3	Avicel® PH-101	0.75	22	2.22	0.15	2620.82	197.07
5	Avicel® PH-101	1.5	24	2.25	0.05	2652.58	77.05
7	Lactose	1.5	22	1.95	0.10	2536.68	63.77
9	Lactose	3	24	1.40	0.03	2396.52	26.43
11	Lactose	0.75	24	2.22	0.05	2575.18	49.07

The dissolution profiles of pyridoxine hydrochloride containing tablets, produced from the different tablet formulations in 0.1 M HCl at 50rpm are presented in fig. 4.1.

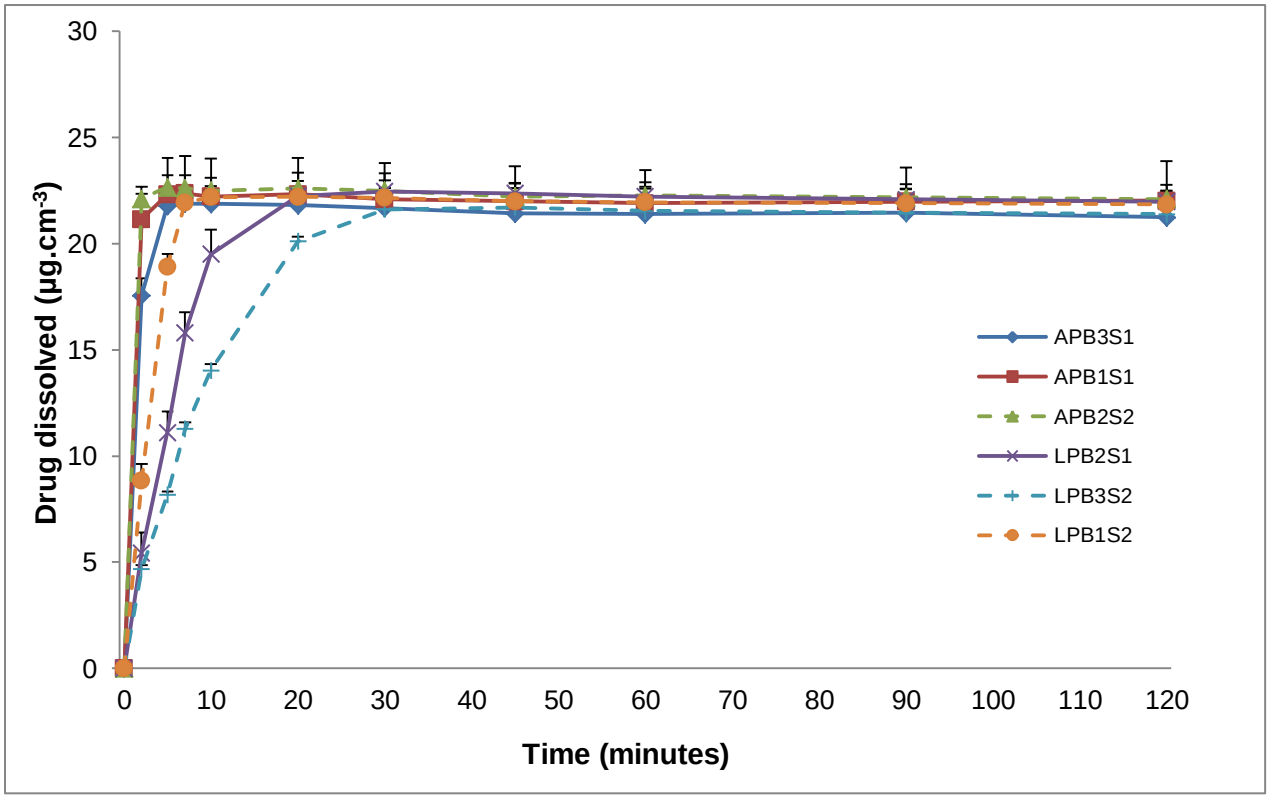


Fig.4.1: The dissolution profiles of pyridoxine hydrochloride in 0.1 M HCl at 50 rpm from tablets prepared from different tablet formulations.

From fig. 4.1 it is evident that the dissolution profiles of tablet formulations 1, 3 and 5 correlated with the disintegration results (<15s) seen in section 3.4. These formulations exhibited average DR_i values of 2.19 ± 0.05, 2.22 ± 0.15 and 2.25 ± 0.05 µg.cm^{-3}.min^{-1}. This phenomenon could be attributed to the fact that pyridoxine hydrochloride is a good water soluble drug and the short disintegration times of the tablets (<15 s). According to a study by Lamprechts (2008:82), it was found that the higher the binder concentration, the slower the DR_i and smaller the AUC-values. These formulations exhibited approximately 90% dissolution within 5 minutes. When compacted masses disintegrate into smaller particles, an increase in the available surface area for dissolution takes place as the disintegration process progresses (Aulton, 2007:20). When tablets disintegrate at a fast rate e.g. <15 s, the surface area available increases rendering conditions for a fast initial rate of drug dissolution, explaining why these formulations resulted in 90% dissolution within 5 minutes. The filler used (Avicel® PH-101) is practically insoluble in water and rendered tablets that were mechanically poor in strength and resulted in rapid disintegration (see section 3.4). It can be stipulated that the filler (Avicel® PH-101) used did not have a direct

influence on the dissolution of the active ingredient, but indirectly influenced dissolution due to the effect on the hardness of the tablets, resulting in lower mechanical strength and quick disintegration. Considering the average AUC-values (2548.84 ± 66.32, 2620.82 ± 197.07 and 2652.58 ± 77.05 $\mu g.cm^{-3}.min$, respectively) of tablet formulations 1, 3 and 5, it can be seen that formulation 1 exhibited the lowest average AUC-value (2548.84 ± 66.32 $\mu g.cm^{-3}.min$). This indicated that the extent of drug dissolution was smaller from this formulation. The difference was statistically significant (ANOVA, Tukey test, $p < 0.05$). This phenomenon can possibly be attributed to the higher binder concentration of 3.0% (w/w) in this formulation. Although these tablets disintegrated within 15 seconds, it is possible that the granules did not disintegrate completely due to the disintegrant being incorporated extra-granular, decreasing available surface area resulting in decreased dissolution of the pyridoxine hydrochloride.

The last three remaining tablet formulations (7, 9 and 11) containing pyridoxine hydrochloride as active ingredient showed similar results compared to the other formulations. Formulation 9, containing 3% w/w Kollidon® VA64 as binder possessed a DR_i and AUC-value of 1.40± 0.03 $\mu g.cm^{-3}.min^{-1}$ and 2396.52 ± 26.43 $\mu g.cm^{-3}min$, respectively. The DR_i and AUC-values were the lowest of all formulations tested containing pyridoxine hydrochloride as active ingredient. As seen in section 3.4 it was concluded that the tablet formulations containing lactose monohydrate as filler delivered much harder and longer disintegrating tablets compared to those containing Avicel® PH-101 as filler. The average disintegration time of tablet formulation 9 (499.50 ± 19.53 s) correlated well with the dissolution profile proving that an increase in disintegration time resulted in decreasing the amount of drug dissolved over time. This phenomenon can possibly be explained by the 3% w/w Kollidon® VA64 binder concentration present and that the tablet was compressed at compression setting 24, where an increase in binder concentration and a higher compression force resulted in an increase in tablet hardness, increasing disintegration time, resulting in a statistically significant decrease in the extent of drug dissolution (ANOVA, Tukey test, $p < 0.05$) over the dissolution time of 2 hours. Tablet formulation 7 also showed a slower rate of dissolution compared to tablet formulations 1, 3, 5 and 11. It had a binder concentration of 1.5% w/w and was compressed at the lowest compression setting (22). Tablet formulation 11

showed a similar rate of dissolution (2.22 ± 0.05 μg.cm^{-3}.min^{-1}) to the first three tablet formulations (1, 3 and 5). It contained the lowest binder concentration (0.75% w/w) and was compressed at the higher of the two compression settings (24). Compared to tablet formulations 7 and 9, it was the softer tablet (average crushing strength value, 106.42 ± 6.53 N; friability, 0.94 %) and could explain why it had a faster dissolution rate.

Table 4.2: The similarity factor values (±SD) of pyridoxine hydrochloride containing tablet formulations compared to one another.

	Similarity factor (f_2)				
	Formula 3	**Formula 5**	**Formula 7**	**Formula 9**	**Formula 11**
Formula 1	62.58± 0.31	51.66± 2.52	31.10± 1.99	24.90± 0.33	43.85± 1.66
Formula 3		62.23± 12.82	28.08± 2.45	23.06± 0.68	37.50± 1.73
Formula 5			34.39± 1.85	20.54± 1.01	34.39± 1.85
Formula 7				48.12± 6.14	40.66± 4.17
Formula 9					29.82± 0.41

All the pyridoxine hydrochloride containing tablet formulations were compared to one another to obtain similarity factor (f_2) values. Formulations 1, 3 and 5 (62.58± 0.31, 51.66± 2.52 and 62.23± 12.82 respectively) rendered f_2-values of more than 50, which reflects that tablets from these formulations exhibited similar dissolution profiles (see section 2.6.8). Regarding the last three tablet formulations 7, 9 and 11 it can be seen that the dissolution profiles were not similar to one another as the f_2-values for the dissolution profiles were less than 50. The disintegration times varied extensively for these formulations (347.33 ± 91.52, 499.50 ± 19.53 and 153.78 ± 9.88 s respectively) raising the possibility that all the granules did not disintegrate completely thereby influencing dissolution. The binder concentrations were also different for each of these tablet formulations (1.5%, 3.0% and 0.75% w/w respectively) rendering tablets with different mechanical strengths (see section 3.3). However, it should be taken into consideration that the similarity factor does not take into consideration the shape of the curve and the unequal spacing between the sampling points (Costa & Lobo, 2001:130).

4.3. Dissolution studies for tablets containing furosemide

The dissolution profiles of tablets containing Kollidon® VA64 as binder and a sparingly water soluble drug, furosemide, at two compression settings (stroke length 22 and 24) were determined as descussed in section 2.5. Two dissolution parameters were obtained from the dissolution data. These are DR_i (indicating the initial rate of drug dissolution) and AUC (representing the extent of drug dissolution) (see section 2.6.7), which could be used to describe the overall dissolution behaviour of the drug. The calculated DR_i and AUC-values for the different formulations are reported in table 4.3. The similarity factor values are presented in table 4.4.

Table 4.3: The initial rate (DR_i) and extent of dissolution (AUC) of furosemide from tablets prepared from different powder formulations.

Formulation	Filler	Binder [ ] (% w/w Kollidon® VA64)	Compression setting	DR_i ($\mu g.cm^{-3}.min^{-1}$)	Standard Deviation (DR_i)	AUC ($\mu g.cm^{-3}.min$)	Standard Deviation (AUC)
2	Avicel® PH-101	1.5	22	0.76	0.03	1419.31	29.14
4	Avicel® PH-101	3	24	0.22	0.07	1018.62	59.74
6	Lactose	3	22	0.54	0.02	1433.20	19.40
8	Lactose	0.75	22	0.94	0.06	1528.07	21.96
10	Lactose	1.5	24	0.87	0.01	1517.53	9.07

The dissolution profiles of furosemide tablets, produced from the different tablet formulations containing Kollidon® VA64 (0.75, 1.5 and 3% w/w) as binder using two different compression settings (22 and 24) and two different fillers (Avicel® PH-101 and lactose monohydrate) in 0.1 M HCl at 50 rpm are presented in fig. 4.2.

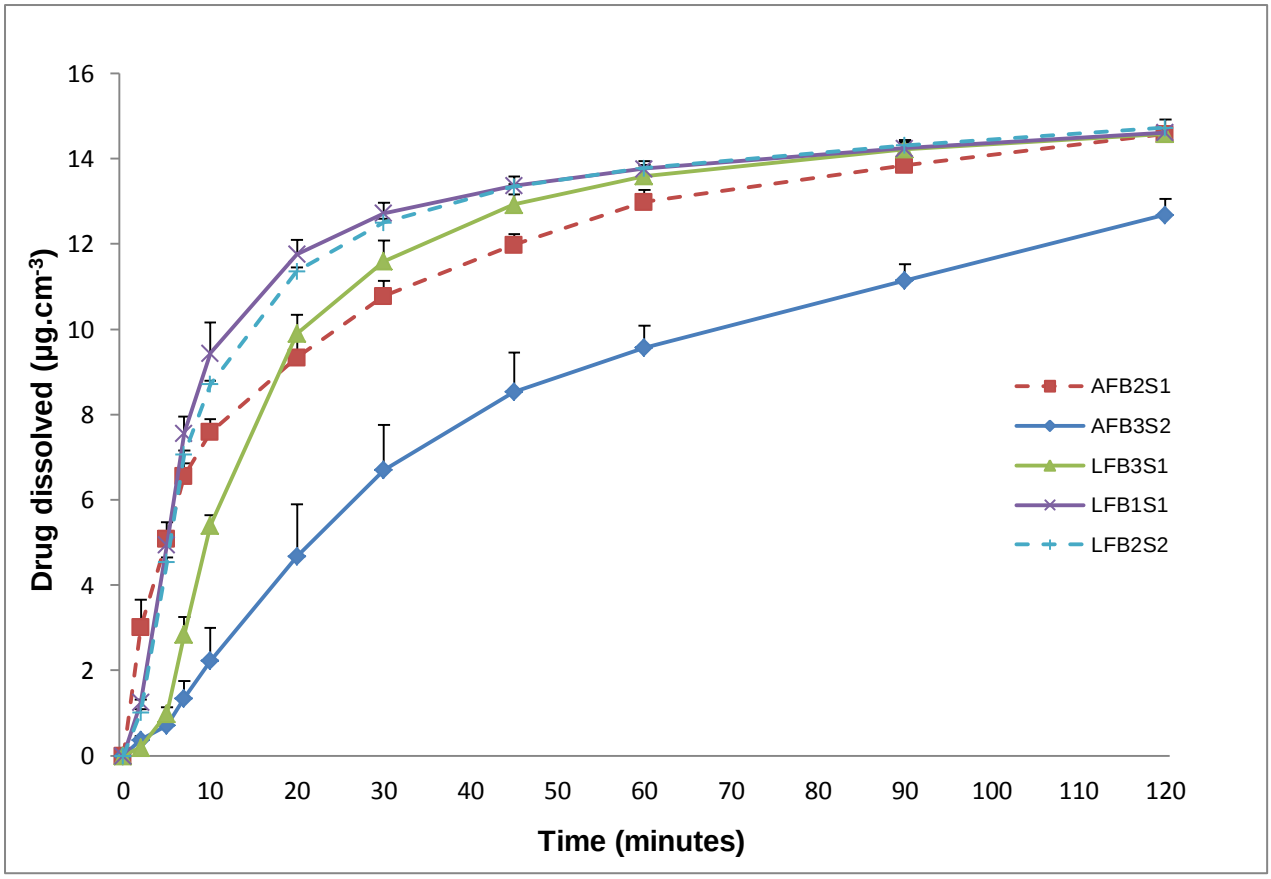


Fig.4.2: The dissolution profiles of furosemide in 0.1 M HCl at 50 rpm of tablets prepared from different tablet formulations.

It was evident from table 4.2 that tablet formulation 4 exhibited the lowest DR_i and AUC-values (0.22 ± 0.07 µg.cm^{-3}.min^{-1}; 1018.62 ± 59.74 µg.cm^{-3}.min). The slow DR_i as well as the lower extent of drug dissolution might be attributed to the binder concentration (Kollidon® VA64, 3% w/w) in combination with the fact that the tablets of formulation 4 were compressed at compression setting 24. The combination of these two factors resulted in tablets with an average crushing strength value of 155.77 ± 15.43 N, indicating the effect of the binder and the compression setting. However, the tablets of formulation 4 exhibited an average disintegration time of 24.67 ± 9.73 seconds. This implied that the slower DR_i and lower extent of drug dissolution cannot be attributed to a slow disintegration time of the tablets. However, it should be kept in mind that the disintegrant (Ac-di-sol®) was incorporated extra-granular. This can explain the fast disintegration time of the tablets, however, the granules that were produced by the granulation process did not contain any disintegrant and due to the binder concentration, the break-up of the granules was negatively affected. The larger granules of formulation 4 therefore, exhibited a

smaller surface area exposed to the dissolution medium (0.1 M HCl) compared to the other formulations. Furthermore, microcrystalline cellulose is insoluble in water and furosemide is poorly soluble in water. Therefore, the combined effect of the binder, the insolubility of mictocrystalline cellulose and the poor solubility of furosemide all contributed to the dissolution behaviour of the tablets of formulation 4.

It is interesting to note that although the tablets of formulation 6 also contained Kollidon® VA64 in a concentration of 3% w/w, this formulation exhibited a higher DR_i and AUC-value (0.54 ± 0.02 $\mu g.cm^{-3}.min^{-1}$ and 1433.20 ± 19.40 $\mu g.cm^{-3}.min$, respectively) compared to formulation 4. Formulation 6, however, was compressed at compression setting 22 and contained lactose monohydrate as filler. The tablets of formulation 6 had an average crushing strength of 145.6 ± 7.25 N. The average crushing for these two formulations (Formulation 4 and 6) was therefore comparable, however, lactose monohydrate is partially soluble in water and this behaviour can therefore improve the dissolution of furosemide due to improved granule break-up. Formulations 8 and 10 exhibited the highest DRi and AUC values. These values were 0.94 ± 0.06$\mu g.cm^{-3}.min^{-1}$; 1528.07 ± 21.96 $\mu g.cm^{-3}.min$ and 0.87 ± 0.01$\mu g.cm^{-3}.min^{-1}$; 1517.53 ± 9.07 $\mu g.cm^{-3}$, respectively. Formulation 8 and 10 were compressed at compression setting 22 and 24 and contained Kollidon® VA64 at a concentration of 0.75 and 1.5% w/w, respectively, indicating that a binder concentration above 3% w/w and the solubility of the filler had a significant influence on the dissolution behaviour of furosemide. An increase in binder concentration resulted in a statistically significant decrease in the extent of drug dissolved (ANOVA, Tukey test, $p < 0.05$).

Table 4.4: The similarity factor values (±SD) of furosemide containing tablet formulations compared to one another.

	Furosemide containing tablets			
	Formula 4	**Formula 6**	**Formula 8**	**Formula 10**
Formula 2	38.75 ± 3.60	50.88 ± 1.08	58.81 ± 2.42	61.17 ± 2.64
Formula 4		41.85 ± 3.07	33.06 ± 2.29	34.31 ± 2.66
Formula 6			48.00 ± 2.02	51.07 ± 0.49
Formula 8				85.70 ± 10.07

All the furosemide containing tablet formulations were compared to one another with respect to the dissolution profiles of the different tablet formulations by means of a similarity factor (f_2). It was evident from the results in table 4.4 that the comparison of tablet formulations 2, 6, 8 and 10 (50.88 ± 1.08, 58.81 ± 2.42, 61.17 ± 2.64, 51.07 ± 0.49 and 85.70 ± 10.07, respectively) rendered similar dissolution profiles as the f_2-values were all above 50 (see section 2.6.8). The dissolution profile of formulation 4 was not similar to any of the dissolution profiles of the other furosemide containing formulations. This was due to the fact that formulation 4 exhibited the slowest initial rate of dissolution (DR_i) and the lowest extent of drug dissolved of all the formulations containing furosemide as active ingredient (see table 4.3). This phenomenon could be explained by the fact that there could be a significant interaction between the binder, stroke length as well as the filler.

4.4. Conclusion

It was found that the tablets containing pyridoxine hydrochloride as active ingredient exhibited better drug dissolution compared to tablets containing furosemide. AUC-values ranged from 1018.62 ± 59.74 to 1528.07 ± 21.96 $\mu g.cm^{-3}$.min for furosemide and 2396.52 ± 26.43 to 2652.58 ± 77.05 $\mu g.cm^{-3}$.min for pyridoxine hydrochloride. This can in part be attributed to the fact that pyridoxine hydrochloride is water soluble while furosemide is practically insoluble in water. Regarding the different tablet formulations containing pyridoxine hydrochloride it was concluded that formulations 1, 3 and 5 rendered faster initial rates of dissolution due to the use of Avicel® PH-101 as filler which contributed to the softness of the tablets at the compression settings (22 and 24) employed in this study. Their AUC-values were higher than that of formulation 9 meaning more of the drug dissolved over time and this could be explained due to the fact that formulations 1, 3 and 5 rendered tablets with low crushing strengths and quick disintegration times. The results obtained from table 4.2 confirmed that tablet formulations 1, 3 and 5 showed similar dissolution profiles with f_2-values higher than 50. Tablet formulations 7 and 9 had the lowest DR_i-values of the pyridoxine hydrochloride containing tablet formulations and this can possibly be related to the higher mechanical strength of the tablets. Regarding the extent of drug dissolved it was found that harder tablets resulted in longer disintegration times in turn rendering a lower extent of drug dissolved over the time period of the dissolution studies.

Regarding the tablet formulations containing furosemide as active ingredient, it was evident that a Kollidon® VA64 concentration of 3% w/w had a detrimental effect on the dissolution of furosemide. This could possibly be attributed to the fact that the disintegrant was incorporated extra-granular. The net effect was that although the tablets disintegrated quickly (< 30 seconds for formulation 4), the granules did not disintegrate quickly thereby affecting dissolution of furosemide negatively. The use of lactose monohydrate as filler seemed to render better dissolution for furosemide compared to Avicel® PH 101 as filler, possibly due to the partial solubility of lactose monohydrate in water compared to the insolubility of furosemide in water.

The disintegration process of tablets goes hand in hand with the dissolution process and results have shown that the establishment of rapid contact between drug

particles and the surrounding medium proves to be necessary for dissolution to take place. Disintegration does not assure drug dissolution, but when this process is prolonged, slower dissolution rates can be obtained resulting in a low rate and extent of drug dissolution.

Overall, the dissolution results obtained from preparing tablets with a good water soluble drug (pyridoxine hydrochloride) and a drug that is practically insoluble (furosemide), using Kollidon® VA64 as binder in three different concentrations (0.75, 1.5 and 3% w/w) with a water soluble filler (lactose monohydrate) and water insoluble filler (microcrystalline cellulose) compressed at two different stroke lengths (22 and 24) was useful and the following can be concluded:

- An increase in binder concentration led to a decrease in the extent of drug dissolved (AUC).
- The filler used had an indirect effect on the dissolution of the active ingredient depending on the aqueous solubility of the filler and the effect on the mechanical strength of the tablets.
- Tablets with a high average crushing strength value rendered longer average disintegration times influencing the extent of drug dissolution (AUC).
- Tablets containing pyridoxine hydrochloride as active ingredient rendered higher and larger DR_i and AUC-values than that of furosemide – mainly because of the fact that pyridoxine hydrochloride is water soluble and furosemide practically insoluble in water.

Chapter 5

SUMMARY AND FUTURE PROSPECTS

5.1. Summary

About 80% of pharmaceutical preparations are in the form of tablets which makes it a very popular choice as dosage form. One of the oldest techniques for the granulation process is wet granulation. It is still widely used today even though the main drawbacks of this process are cost, energy and labour intensity. Despite this drawback, it is a very popular choice of granulation still used in the pharmaceutical industry, especially when a high dose of active ingredient is required. Direct compression on the other hand is usually ineffective when using high dose active ingredients, because of the major concern of binding properties.

Lactose monohydrate and Avicel® PH-101 were used as fillers in this study with Kollidon® VA64 at three different concentration levels (0.75, 1.5 or 3% w/w) as binder to manufacture granules using wet granulation. Ac-di-sol® as disintegrant and magnesium stearate as lubricant were incorporated extra-granular and mixed with the dried granulate. Using two different compression settings (22 and 24), tablets were compressed on a single station tablet press using 9 mm flat faced punches keeping the weight of the tablet constant. The tablets were evaluated in terms of weight variation, mechanical strength (crushing strength and friability) and disintegration. Dissolution studies were conducted on tablets containing furosemide and pyridoxine hydrochloride as model drugs. Two dissolution parameters, namely DR_i and AUC were calculated.

All formulations exhibited %RSD-values of less than 5% with regard to weight variation. Not more than 2 individual masses deviated from the average mass by more than 5% for tablets with a weight of 250 mg or more. Therefore, tablet weight variation complied with the standards of the BP (2012). The results of the weight variation therefore indicated acceptable flow properties. The last mentioned, implies that the variation in drug content should be within acceptable limits.

Decreases in tablet hardness led to tablets with low friability and decreased average crushing strength values of the tablets in general. Formulations 1, 2, 3 and 5, which

all contained Avicel® PH-101 as filler, exhibited a %-friability of more than 2%, which indicated an unacceptable resistance to friability. The other formulations exhibited acceptable resistance to friability.

Regarding the crushing strength it can be concluded that the binder concentration had a significant influence on the increase in the average crushing strength. It was shown that an increase in compression force caused a statistically significant increase in the average crushing strength. Not all formulations exhibited acceptable friability, and therefore, not all formulations exhibited sufficient mechanical strength (friability and crushing strength).

From the average disintegration times of the different tablet formulations, it was observed that an increase in binder concentration resulted in an increase in average disintegration time. It was also noted that the compression force played a role, but depended on the filler used, seeing that the tablet with the longest disintegration time was compressed at the lower of the two compression settings but contained lactose monohydrate as filler. In this study it was seen that the binder concentration had the most significant influence on the average disintegration times. Furthermore, the type of filler also influenced disintegration. Lactose monohydrate rendered tablets with much longer disintegration times compared to the Avicel® PH-101 containing tablet formulations. This can possibly be attributed to the fact that Avicel® PH-101 possesses a low bulk density (0.37 g/cm^3) which resulted in low tablet porosity encouraging the entering of water into the tablet matrix, decreasing the disintegration time. All formulations exhibited acceptable average disintegration times within 15 minutes.

Overall, from the dissolution results obtained from preparing tablets with a good water soluble drug (pyridoxine hydrochloride) and a practically water insoluble drug (furosemide), using Kollidon® VA64 as binder in three different concentrations (0.75, 1.5 or 3% w/w) with a water soluble filler (lactose monohydrate) and water insoluble filler (microcrystalline cellulose) compressed at two different stroke lengths (22 and 24), the following could be concluded:

- An increase in binder concentration led to a decrease in the extent of drug dissolution (AUC).

- The filler used had an indirect effect on the dissolution of the active ingredient depending on the aqueous solubility of the filler and the effect the filler had on the mechanical strength of the tablets.
- Tablets with a high mechanical strength rendered longer disintegration times influencing the extent of drug dissolution (AUC).
- Tablets containing pyridoxine hydrochloride as active ingredient rendered higher and larger DR_i and AUC-values respectively, than that of furosemide – mainly because of the fact that pyridoxine hydrochloride is water soluble and furosemide practically insoluble in water.

5.2. Future prospects

In this study, a water soluble and insoluble filler (lactose monohydrate and microcrystalline cellulose) together with a binder at three different concentrations (0.75, 1.5 and 3% w/w) were employed to produce granules by means of wet granulation. Also included was a sparingly water soluble drug (furosemide) and a good water soluble drug (pyridoxine hydrochloride) to evaluate the effect of formulation variables on the dissolution behaviour of a good water soluble and poor soluble drug. From the results of this study, the following formulation variables can be studied in future to give insight into the functionality of excipients and the effect on the pharmaceutical availability of active ingredients:

- A variety of water soluble and insoluble active ingredients to investigate whether the influence of formulation variables affect the dissolution of these drugs to the same extent.
- A variety of other binders (e.g. hydroxypropylmethyl cellulose, starch) to investigate whether the same results considering the different tablet properties will be obtained.
- Different ratios of disintegrant with regard to intra- and extra-granular distribution to investigate the influence on granulate break-up.
- Different fillers to investigate the influence on filler type and solubility on active ingredient dissolution.

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ANNEXURE A

Results for the evaluation of the 11 different tablet formulations with regard to tablet weight variation, crushing strength, thickness, diameter, disintegration time and friability.

Table A-1: *Tablet analysis of Avicel® PH-101, pyridoxine, Kollidon® VA64 (3.0% w/w) and compression setting 22.*

Tablets	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Crushing Strength (N)	Disintegration time (sec)
1	248.60	3.93	10.06	15.10	2
2	249.50	3.95	10.08	16.30	5
3	251.50	3.94	10.07	16.80	7
4	251.10	3.93	10.07	16.30	7
5	248.00	3.92	10.08	15.90	9
6	252.70	3.95	10.10	15.90	12
7	248.00	3.93	10.07	18.80	2
8	247.40	3.94	10.07	15.90	5
9	247.90	3.94	10.07	18.40	9
10	244.10	3.94	10.06	18.80	12
11	251.60				17
12	245.10				22
13	249.50				14
14	248.50				16
15	246.30				17
16	249.90				20
17	248.70				16
18	246.90				20
19	249.50				
20	251.20				
Average	248.80	3.94	10.07	16.82	11.778
Standard deviation	2.2231	0.01	0.01	1.35	6.320
%RSD	0.89%	0.00%	0.00%	0.08%	53.66%

Table A-2: *Tablet analysis of Avicel® PH-101, furosemide, Kollidon® VA64 (1.5% w/w) and compression setting 22.*

Tablets	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Crushing Strength (N)	Disintegration time (sec)
1	247.00	4.22	10.01	11.40	7
2	246.80	4.20	10.00	11.80	8
3	251.20	4.27	10.02	10.60	8
4	247.50	4.27	10.00	9.80	10
5	247.90	4.28	10.01	10.60	10
6	249.80	4.25	10.05	11.00	10
7	248.20	4.26	10.04	11.80	6
8	248.80	4.25	10.03	10.20	6
9	251.70	4.26	10.01	10.60	9
10	248.00	4.23	10.02	12.30	9
11	248.00				10
12	248.50				10
13	249.20				9
14	249.20				9
15	242.00				12
16	247.80				13
17	243.40				13
18	249.40				13
19	250.50				
20	243.70				
Average	247.93	4.25	10.02	11.01	9.556
Standard deviation	2.4866	0.03	0.02	0.80	2.175
%RSD	1.00%	0.01%	0.00%	0.07%	22.76%

Table A-3: *Tablet analysis of Avicel® PH-101, pyridoxine, Kollidon® VA64 (0.75% w/w) and compression setting 22.*

Tablets	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Crushing Strength (N)	Disintegration time (sec)
1	253.60	4.57	10.01	6.90	9
2	255.30	4.57	10.00	7.40	9
3	248.10	4.56	10.00	6.50	11
4	255.30	4.57	10.02	7.80	11
5	252.40	4.59	9.99	6.10	11
6	250.80	4.59	10.06	9.00	11
7	253.00	4.59	10.02	7.40	8
8	255.60	4.59	10.04	8.60	8
9	252.00	4.55	10.02	7.80	9
10	254.60	4.60	10.03	8.20	9
11	246.30				12
12	251.80				12
13	248.40				7
14	253.40				9
15	252.70				9
16	250.10				11
17	255.80				13
18	249.50				13
19	254.50				
20	247.60				
Average	252.04	4.58	10.02	7.57	10.111
Standard deviation	2.8991	0.02	0.02	0.91	1.779
%RSD	1.15%	0.00%	0.00%	0.12%	17.59%

Table A-4: *Tablet analysis of Avicel® PH-101, furosemide, Kollidon® VA64 (3.0% w/w) and compression setting 24.*

Tablets	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Crushing Strength (N)	Disintegration time (sec)
1	252.00	2.58	10.03	141.80	16
2	239.10	2.60	10.04	153.60	25
3	243.10	2.59	10.00	190.00	28
4	240.20	2.63	10.03	164.30	34
5	239.80	2.57	10.00	147.10	42
6	245.50	2.60	10.01	147.50	52
7	244.80	2.56	10.00	135.30	17
8	236.30	2.61	10.01	165.90	21
9	242.00	2.64	10.03	160.20	21
10	238.70	2.63	10.02	152.00	24
11	254.80				24
12	239.00				24
13	235.30				14
14	243.30				16
15	239.80				16
16	237.50				21
17	245.10				21
18	247.90				28
19	238.90				
20	240.80				
Average	242.20	2.60	10.02	155.77	24.667
Standard deviation	5.0283	0.03	0.01	15.43	9.732
%RSD	2.08%	0.01%	0.00%	0.10%	39.45%

Table A-5: *Tablet analysis of Avicel® PH-101, pyridoxine, Kollidon® VA64 (1.5% w/w) and compression setting 24.*

Tablets	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Crushing Strength (N)	Disintegration time (sec)
1	263.90	4.64	10.00	6.10	11
2	256.00	4.68	10.04	8.60	15
3	261.10	4.68	10.05	9.00	15
4	257.10	4.68	10.03	8.60	17
5	259.70	4.68	10.05	7.80	17
6	266.10	4.68	10.04	8.60	17
7	253.90	4.73	10.05	9.40	12
8	259.90	4.69	10.05	8.60	12
9	261.80	4.68	10.04	10.20	14
10	263.30	4.68	10.05	8.60	15
11	255.70				15
12	263.40				16
13	263.80				4
14	268.60				6
15	264.20				8
16	247.30				8
17	263.80				10
18	265.00				10
19	258.50				
20	259.00				
Average	260.61	4.68	10.04	8.55	12.333
Standard deviation	4.9323	0.02	0.02	1.07	3.985
%RSD	1.89%	0.00%	0.00%	0.12%	32.31%

Table A-6: *Tablet analysis of lactose monohydrate, furosemide, Kollidon® VA64 (3.0% w/w) and compression setting 22.*

Tablets	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Crushing Strength (N)	Disintegration time (sec)
1	248.70	2.29	10.04	135.30	549
2	247.70	2.21	10.05	144.20	555
3	253.80	2.20	10.04	146.30	565
4	253.10	2.28	10.06	152.80	572
5	245.70	2.24	10.05	137.70	578
6	239.50	2.23	10.04	153.20	582
7	244.90	2.28	10.05	155.30	507
8	247.00	2.24	10.06	136.50	548
9	244.90	2.23	10.05	149.60	556
10	252.20	2.20	10.05	145.50	559
11	243.60				580
12	245.50				592
13	247.30				512
14	246.50				524
15	252.80				533
16	244.30				561
17	245.70				574
18	244.00				601
19	247.50				
20	247.60				
Average	247.12	2.24	10.05	145.64	558.222
Standard deviation	3.6037	0.03	0.01	7.25	26.197
%RSD	1.46%	0.01%	0.00%	0.05%	4.69%

Table A-7: *Tablet analysis of lactose monohydrate, pyridoxine, Kollidon® VA64 (1.5 % w/w) and compression setting 22.*

Tablets	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Crushing Strength (N)	Disintegration time (sec)
1	258.10	2.40	10.05	127.10	275
2	258.80	2.38	10.06	117.30	290
3	263.50	2.45	10.06	125.90	293
4	267.30	2.40	10.05	157.70	300
5	271.50	2.46	10.03	133.20	308
6	271.30	2.42	10.05	136.50	336
7	275.80	2.35	10.05	139.30	244
8	260.60	2.51	10.05	136.10	306
9	253.20	2.28	10.05	115.60	311
10	253.00	2.37	10.05	145.10	320
11	268.40				320
12	269.00				388
13	259.80				275
14	267.50				319
15	252.70				524
16	269.00				529
17	254.70				546
18	266.50				368
19	252.30				
20	254.50				
Average	262.38	2.40	10.05	133.38	347.333
Standard deviation	7.4868	0.06	0.01	12.70	91.519
%RSD	2.85%	0.03%	0.00%	0.10%	26.35%

Table A-8: *Tablet analysis of lactose monohydrate, furosemide, Kollidon® VA64 (0.75% w/w) and compression setting 22.*

Tablets	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Crushing Strength (N)	Disintegration time (sec)
1	249.40	2.26	10.05	110.70	50
2	248.80	2.27	10.05	114.40	53
3	250.50	2.29	10.05	116.90	58
4	257.50	2.31	10.04	127.10	58
5	249.10	2.30	10.04	141.00	63
6	255.80	2.25	10.05	138.90	71
7	248.60	2.29	10.03	105.80	54
8	250.10	2.27	10.05	111.10	56
9	253.60	2.26	10.05	114.00	57
10	249.70	2.24	10.06	126.30	61
11	250.40				61
12	247.30				63
13	245.80				48
14	249.60				59
15	249.40				59
16	255.50				59
17	248.90				62
18	254.40				62
19	257.20				
20	246.60				
Average	250.91	2.27	10.05	120.62	58.556
Standard deviation	3.4871	0.02	0.01	12.15	5.294
%RSD	1.39%	0.01%	0.00%	0.10%	9.04%

Table A-9: *Tablet analysis of lactose monohydrate, pyridoxine, Kollidon® VA64 (3.0% w/w) and compression setting 24.*

Tablets	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Crushing Strength (N)	Disintegration time (sec)
1	254.10	2.42	10.04	164.70	483
2	261.50	2.45	10.05	152.00	487
3	259.30	2.56	10.05	158.90	490
4	256.90	2.37	10.04	183.10	494
5	252.80	2.42	10.05	175.70	497
6	251.40	2.42	10.06	187.10	515
7	271.30	2.36	10.03	159.80	459
8	264.60	2.36	10.05	190.40	488
9	251.00	2.41	10.04	188.00	493
10	264.20	2.40	10.05	165.10	493
11	256.20				503
12	252.60				505
13	257.60				488
14	274.50				508
15	259.60				509
16	260.80				509
17	249.80				514
18	253.40				556
19	256.10				
20	277.60				
Average	259.27	2.42	10.05	172.48	499.500
Standard deviation	7.8413	0.06	0.01	14.06	19.528
%RSD	3.02%	0.02%	0.00%	0.08%	3.91%

Table A-10: *Tablet analysis of lactose monohydrate, furosemide, Kollidon® VA64 (1.5% w/w) and compression setting 22.*

Tablets	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Crushing Strength (N)	Disintegration time (sec)
1	257.50	2.27	10.05	139.30	245
2	257.80	2.27	10.05	157.30	251
3	251.70	2.31	10.05	155.70	259
4	246.40	2.34	10.06	169.20	275
5	254.30	2.27	10.04	160.60	287
6	253.40	2.31	10.04	156.10	313
7	270.40	2.26	10.04	135.70	270
8	255.20	2.29	10.06	154.90	278
9	259.40	2.28	10.06	150.40	286
10	253.30	2.32	10.04	139.30	303
11	254.90				314
12	254.00				317
13	255.50				247
14	249.60				265
15	252.40				277
16	247.40				279
17	254.80				283
18	257.20				295
19	256.30				
20	257.70				
Average	254.96	2.29	10.05	151.85	280.222
Standard deviation	4.9747	0.03	0.01	10.68	22.257
%RSD	1.95%	0.01	0.00	0.07	7.94%

Table A-11: *Tablet analysis of lactose monohydrate, pyridoxine, Kollidon® VA64 (0.75% w/w) and compression setting 24.*

Tablets	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Crushing Strength (N)	Disintegration time (sec)
1	256.90	2.29	10.04	99.30	140
2	253.20	2.30	10.05	107.10	150
3	253.80	2.31	10.06	106.20	150
4	253.30	2.36	10.06	100.50	159
5	257.50	2.34	10.04	114.40	161
6	258.90	2.29	10.04	102.20	175
7	251.50	2.30	10.07	98.10	145
8	251.90	2.34	10.06	117.30	149
9	255.60	2.34	10.06	107.50	153
10	258.30	2.34	10.05	111.60	155
11	253.10				159
12	255.40				175
13	254.00				142
14	256.60				144
15	251.70				148
16	256.10				148
17	254.10				156
18	250.30				159
19	255.90				
20	255.00				
Average	254.66	2.32	10.05	106.42	153.778
Standard deviation	2.3676	0.03	0.01	6.53	9.885
%RSD	0.93%	0.01	0.00	0.06	6.43%

Table A-12: *Friability results for 11 different tablet formulations.*

Formula	Mass 1 (g)	Mass 2 (g)	Friability (%)
1	2.5015	2.4283	2.93%
2	2.4683	2.3302	5.59%
3	2.5167	2.3140	8.05%
4	2.4254	2.4207	0.19%
5	2.5814	2.2399	13.23%
6	2.4611	2.4502	0.44%
7	2.6362	2.6185	0.67%
8	2.5091	2.4850	0.96%
9	2.6274	2.6111	0.62%
10	2.5832	2.5686	0.57%
11	2.5501	2.5262	0.94%

ANNEXURE B

Dissolution results of 11 different tablet formulations containing a mixture of 2 fillers (microcrystalline cellulose and lactose monohydrate), 2 active ingredients (pyridoxine and furosemide), Kollidon® VA64 in three different concentrations (0.75, 1.5 and 3.0% w/w) as binder using 2 different compression settings (22 and 24).

Table B-1.1: *Average concentration drug dissolved for tablets containing Avicel® PH-101, pyridoxine, Kollidon® VA64 (3.0% w/w) compressed at compression setting 22.*

Time	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average [ ] (µg.cm^{-3})	Standard deviation	%Relative standard deviation
0	0	0	0	0	0	0	0
2	17.4192	17.3119	16.8149	18.7048	17.5627	0.8056	4.5872
5	21.5162	21.5491	21.3565	22.6873	21.7773	0.6125	2.8124
7.5	21.5143	21.7261	21.5994	22.7187	21.8897	0.5595	2.5560
10	21.6063	21.6696	21.5556	22.6598	21.8728	0.5267	2.4082
20	21.6440	21.6864	21.4221	22.4800	21.8081	0.4627	2.1215
30	21.3211	21.6620	21.3739	22.3248	21.6705	0.4613	2.1285
45	20.6390	21.4420	21.4572	22.1219	21.4150	0.6067	2.8333
60	20.5507	21.5939	21.3813	22.0396	21.3914	0.6240	2.9170
90	20.4340	21.7566	21.6613	21.9390	21.4477	0.6856	3.1965
120	20.3345	21.5058	21.2759	21.8680	21.2461	0.6548	3.0818

Table B-1.2: *Initial drug dissolved (DR_i) and extent of drug dissolved (AUC) for tablets containing Avicel® PH-101, pyridoxine, Kollidon® VA64 (3.0% w/w) compressed at compression setting 22.*

	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average (µg.cm^{-3})	Standard deviation	%Relative standard deviation
DR_i (µg.cm^{-3})	2.161	2.167	2.156	2.266	2.187	0.053	2.408
AUC (µg.cm^{-3})	2464.508	2562.707	2542.797	2625.342	2548.838	66.315	2.602

Table B-2.1: *Average concentration drug dissolved for tablets containing Avicel® PH-101, furosemide, Kollidon® VA64 (1.5% w/w) compressed at compression setting 22.*

Time	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average [ ] (µg.cm^{-3})	Standard deviation	%Relative standard deviation
0	0	0	0	0	0	0	0
2	3.4376	2.0766	3.0500	3.4634	3.0069	0.6484	21.5631
5	4.8554	5.5004	4.6541	5.3056	5.0789	0.3914	7.7056
7.5	6.7529	6.7631	6.1396	6.5906	6.5615	0.2922	4.4532
10	7.8234	7.7369	7.1591	7.6334	7.5882	0.2964	3.9062
20	9.7632	8.8562	9.0494	9.6788	9.3369	0.4518	4.8389
30	11.1220	10.4734	10.4693	11.0422	10.7767	0.3542	3.2863
45	12.2784	11.8037	11.7396	12.0857	11.9768	0.2511	2.0961
60	13.3320	12.7713	12.7419	13.0957	12.9852	0.2814	2.1667
90	14.0615	13.7018	13.6822	13.9514	13.8492	0.1872	1.3515
120	14.7350	14.4550	14.4620	14.6459	14.5745	0.1388	0.9524

Table B-2.2: *Initial drug dissolved (DR_i) and extent of drug dissolved (AUC) for tablets containing Avicel® PH-101, furosemide, Kollidon® VA64 (1.5% w/w) compressed at compression setting 22.*

	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average (µg.cm^{-3})	Standard deviation	%Relative standard deviation
DR_i (µg.cm^{-3})	0.782	0.774	0.716	0.763	0.759	0.026	3.383
AUC (µg.cm^{-3})	1451.399	1397.350	1392.060	1436.420	1419.307	29.139	2.053

Table B-3.1: *Average concentration drug dissolved for tablets containing Avicel® PH-101, pyridoxine, Kollidon® VA64 (0.75% w/w) compressed at compression setting 22.*

Time	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average [ ] (µg.cm^{-3})	Standard deviation	%Relative standard deviation
0	0	0	0	0	0	0	0
2	20.9567	20.1491	20.6227	22.8835	21.1530	1.2003	5.6744
5	21.6699	20.8254	21.9138	24.8082	22.3043	1.7331	7.7705
7.5	21.6510	20.9493	21.9521	24.9095	22.3655	1.7473	7.8124
10	21.5605	20.6985	21.8621	24.7745	22.2239	1.7704	7.9664
20	21.9375	20.7524	21.8287	24.7662	22.3212	1.7155	7.6855
30	21.4208	20.6647	21.7012	24.5746	22.0903	1.7130	7.7547
45	21.3871	20.6190	21.5540	24.4121	21.9931	1.6633	7.5628
60	21.2527	20.7328	21.3948	24.2174	21.8994	1.5713	7.1751
90	21.2918	20.8550	21.3911	24.3523	21.9726	1.6035	7.2977
120	21.1457	20.9511	21.2031	24.8018	22.0254	1.8540	8.4177

Table B-3.2: *Initial drug dissolved (DR_i) and extent of drug dissolved (AUC) for tablets containing Avicel® PH-101, pyridoxine, Kollidon® VA64 (0.75% w/w) compressed at compression setting 22.*

	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average (µg.cm^{-3})	Standard deviation	%Relative standard deviation
DR_i (µg.cm^{-3})	2.156	2.070	2.186	2.477	2.222	0.153	6.899
AUC (µg.cm^{-3})	2542.932	2470.904	2557.365	2911.058	2620.565	197.320	7.530

Table B-4.1: *Average concentration drug dissolved for tablets containing Avicel® PH-101, furosemide, Kollidon® VA64 (3.0% w/w) compressed at compression setting 24.*

Time	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average [ ] (µg.cm^{-3})	Standard deviation	%Relative standard deviation
0	0	0	0	0	0	0	0
2	0.2589	0.3706	0.4081	0.4556	0.3733	0.0838	22.4528
5	0.6882	0.5747	0.9449	0.6418	0.7124	0.1619	22.7208
7.5	1.6541	1.0182	1.7289	0.9882	1.3474	0.3987	29.5938
10	2.4846	1.5768	3.1990	1.6474	2.2269	0.7681	34.4896
20	5.2439	3.6394	6.1165	3.6913	4.6728	1.2168	26.0403
30	7.2819	5.6351	7.8685	6.0065	6.6980	1.0518	15.7033
45	8.9854	7.5703	9.5902	7.9862	8.5330	0.9216	10.8006
60	10.3332	9.4528	9.2312	9.2727	9.5725	0.5162	5.3925
90	11.6394	11.1075	11.1105	10.7188	11.1441	0.3780	3.3920
120	12.6970	12.8588	13.0178	12.1688	12.6856	0.3686	2.9053

Table B-4.2: *Initial drug dissolved (DR_i) and extent of drug dissolved (AUC) for tablets containing Avicel® PH-101, furosemide, Kollidon® VA64 (3.0% w/w) compressed at compression setting 24.*

	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average (µg.cm^{-3})	Standard deviation	%Relative standard deviation
DR_i (µg.cm^{-3})	0.248	0.158	0.320	0.165	0.223	0.067	29.869
AUC (µg.cm^{-3})	1072.584	974.089	1067.593	960.192	1018.614	59.742	5.865

Table B-5.1: *Average concentration drug dissolved for tablets containing Avicel® PH-101, pyridoxine, Kollidon® VA64 (1.5% w/w) compressed at compression setting 24.*

Time	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average [ ] (µg.cm^{-3})	Standard deviation	%Relative standard deviation
0	0	0	0	0	0	0	0
2	21.8067	22.8656	22.2233	21.5543	22.1125	0.5729	2.5908
5	22.3906	23.3806	22.7850	22.0809	22.6593	0.5606	2.4739
7.5	22.4103	23.3756	22.7142	21.9671	22.6168	0.5916	2.6158
10	22.1744	23.2322	22.7368	21.8382	22.4954	0.6154	2.7356
20	22.2745	23.6062	22.6781	21.8124	22.5928	0.7626	3.3754
30	22.1561	23.6025	22.5419	21.6725	22.4933	0.8206	3.6481
45	22.0137	23.0202	22.3234	21.4906	22.2120	0.6391	2.8774
60	22.5005	22.9016	22.2188	21.4349	22.2639	0.6196	2.7832
90	22.2125	22.9375	22.1538	21.3689	22.1682	0.6411	2.8919
120	22.1765	22.9045	22.0549	21.2869	22.1057	0.6623	2.9962

Table B-5.2: *Initial drug dissolved (DR_i) and extent of drug dissolved (AUC) for tablets containing Avicel® PH-101, pyridoxine, Kollidon® VA64 (1.5% w/w) compressed at compression setting 24.*

	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average (µg.cm^{-3})	Standard deviation	%Relative standard deviation
DR_i (µg.cm^{-3})	2.217	2.323	2.274	2.184	2.250	0.053	2.369
AUC (µg.cm^{-3})	2645.894	2748.476	2655.874	2560.059	2652.576	77.053	2.905

Table B-6.1: *Average concentration drug dissolved for tablets containing lactose monohydrate, furosemide, Kollidon® VA64 (3.0% w/w) compressed at compression setting 22.*

Time	Bowl 1 [ ] ($\mu g.cm^{-3}$)	Bowl 2 [ ] ($\mu g.cm^{-3}$)	Bowl 3 [ ] ($\mu g.cm^{-3}$)	Bowl 4 [ ] ($\mu g.cm^{-3}$)	Average [ ] ($\mu g.cm^{-3}$)	Standard deviation	%Relative standard deviation
0	0	0	0	0	0	0	0
2	0.1289	0.0722	0.4048	0.1464	0.1881	0.1479	78.6322
5	1.0134	0.8930	1.1816	0.8584	0.9866	0.1460	14.7939
7.5	3.0712	3.0760	2.9978	2.2162	2.8403	0.4176	14.7035
10	5.2438	5.3037	5.3225	5.7466	5.4041	0.2308	4.2705
20	10.4296	9.3672	9.8928	9.9160	9.9014	0.4338	4.3816
30	11.6171	11.3205	12.2692	11.1732	11.5950	0.4859	4.1906
45	12.8012	12.9631	13.2394	12.7082	12.9280	0.2328	1.8008
60	13.4986	13.7563	13.7650	13.3500	13.5925	0.2035	1.4971
90	14.0773	14.3165	14.4327	14.0654	14.2230	0.1815	1.2758
120	14.4900	14.6430	14.7316	14.4672	14.5830	0.1261	0.8649

Table B-6.2: *Initial drug dissolved (DR_i) and extent of drug dissolved (AUC) for tablets containing lactose monohydrate, furosemide, Kollidon® VA64 (3.0% w/w) compressed at compression setting 22.*

	Bowl 1 [ ] ($\mu g.cm^{-3}$)	Bowl 2 [ ] ($\mu g.cm^{-3}$)	Bowl 3 [ ] ($\mu g.cm^{-3}$)	Bowl 4 [ ] ($\mu g.cm^{-3}$)	Average ($\mu g.cm^{-3}$)	Standard deviation	%Relative standard deviation
DR_i ($\mu g.cm^{-3}$)	0.524	0.530	0.532	0.575	0.540	0.020	3.698
AUC ($\mu g.cm^{-3}$)	1428.475	1431.755	1459.573	1412.976	1433.195	19.399	1.354

Table B-7.1: *Average concentration drug dissolved for tablets containing lactose monohydrate, pyridoxine, Kollidon® VA64 (1.5% w/w) compressed at compression setting 22.*

Time	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average [ ] (µg.cm^{-3})	Standard deviation	%Relative standard deviation
0	0	0	0	0	0	0	0
2	5.7254	6.6793	4.7827	4.5950	5.4456	0.9597	17.6243
5	11.1437	12.4726	10.2996	10.5398	11.1139	0.9729	8.7540
7.5	16.0000	16.5477	14.3850	16.2775	15.8026	0.9711	6.1455
10	19.3698	20.2133	17.9670	20.4955	19.5114	1.1352	5.8183
20	21.8726	22.6637	21.4930	22.9900	22.2548	0.6914	3.1069
30	22.1263	22.8983	21.9243	22.9025	22.4629	0.5119	2.2790
45	22.1334	22.8058	21.8119	22.7173	22.3671	0.4754	2.1254
60	21.9875	22.6179	21.6899	22.5914	22.2216	0.4587	2.0643
90	21.8318	22.4869	21.5270	22.4905	22.0841	0.4835	2.1895
120	21.6909	22.3966	21.4381	22.3957	21.9803	0.4911	2.2344

Table B-7.2: *Initial drug dissolved (DR_i) and extent of drug dissolved (AUC) for tablets containing lactose monohydrate, pyridoxine, Kollidon® VA64 (1.5% w/w) compressed at compression setting 22.*

	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average (µg.cm^{-3})	Standard deviation	%Relative standard deviation
DR_i (µg.cm^{-3})	1.937	2.021	1.797	2.050	1.951	0.098	5.039
AUC (µg.cm^{-3})	2508.361	2593.114	2460.103	2585.158	2536.684	63.773	2.514

Table B-8.1: *Average concentration drug dissolved for tablets containing lactose monohydrate, furosemide, Kollidon® VA64 (0.75% w/w) compressed at compression setting 22.*

Time	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average [ ] (µg.cm^{-3})	Standard deviation	%Relative standard deviation
0	0	0	0	0	0	0	0
2	1.2723	1.1557	1.3115	1.2665	1.2515	0.0669	5.3493
5	4.7592	4.8261	5.1712	5.0576	4.9535	0.1934	3.9037
7.5	8.1130	7.2510	7.5071	7.3920	7.5658	0.3795	5.0167
10	10.3253	8.7550	8.9851	9.7103	9.4439	0.7148	7.5688
20	12.2340	11.4809	11.5664	11.7631	11.7611	0.3366	2.8624
30	13.0740	12.5610	12.7111	12.5372	12.7208	0.2477	1.9474
45	13.6670	13.1761	13.3121	13.3181	13.3683	0.2096	1.5681
60	13.9633	13.5372	13.7481	13.8058	13.7636	0.1762	1.2803
90	14.4120	14.1078	14.2607	14.1937	14.2435	0.1286	0.9028
120	14.6675	14.6390	14.6202	14.5379	14.6161	0.0557	0.3810

Table B-8.2: *Initial drug dissolved (DR_i) and extent of drug dissolved (AUC) for tablets containing lactose monohydrate, furosemide, Kollidon® VA64 (0.75% w/w) compressed at compression setting 22.*

	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average (µg.cm^{-3})	Standard deviation	%Relative standard deviation
DR_i (µg.cm^{-3})	1.033	0.876	0.899	0.971	0.944	0.062	6.555
AUC (µg.cm^{-3})	1558.401	1505.876	1523.115	1524.869	1528.065	21.965	1.437

Table B-9.1: *Average concentration drug dissolved for tablets containing lactose monohydrate, pyridoxine, Kollidon® VA64 (3.0% w/w) compressed at compression setting 24.*

Time	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average [ ] (µg.cm^{-3})	Standard deviation	%Relative standard deviation
0	0	0	0	0	0	0	0
2	4.4833	4.5771	4.9279	4.6765	4.6662	0.1915	4.1029
5	8.3264	8.2041	8.1926	7.9734	8.1741	0.1469	1.7969
7.5	11.6748	11.2547	10.8935	11.2674	11.2726	0.3193	2.8324
10	14.3761	13.7872	14.1903	13.7676	14.0303	0.3018	2.1514
20	20.3216	20.1539	20.1817	19.8013	20.1146	0.2214	1.1008
30	21.3262	21.6233	21.8747	21.6106	21.6087	0.2242	1.0375
45	21.2585	22.0007	21.8782	21.6840	21.7053	0.3252	1.4982
60	21.1189	21.8474	21.6862	21.5278	21.5451	0.3126	1.4511
90	21.0143	21.7379	21.6551	21.4601	21.4668	0.3234	1.5065
120	20.9303	21.6210	21.5825	21.4400	21.3935	0.3184	1.4885

Table B-9.2: *Initial drug dissolved (DR_i) and extent of drug dissolved (AUC) for tablets containing lactose monohydrate, pyridoxine, Kollidon® VA64 (3.0% w/w) compressed at compression setting 24.*

	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average (µg.cm^{-3})	Standard deviation	%Relative standard deviation
DR_i (µg.cm^{-3})	1.438	1.379	1.419	1.377	1.403	0.026	1.863
AUC (µg.cm^{-3})	2361.373	2418.169	2415.523	2391.018	2396.521	26.429	1.103

Table B-10.1: *Average concentration drug dissolved for tablets containing lactose monohydrate, furosemide, Kollidon® VA64 (1.5% w/w) compressed at compression setting 24.*

Time	Bowl 1 [ ] ($\mu g.cm^{-3}$)	Bowl 2 [ ] ($\mu g.cm^{-3}$)	Bowl 3 [ ] ($\mu g.cm^{-3}$)	Bowl 4 [ ] ($\mu g.cm^{-3}$)	Average [ ] ($\mu g.cm^{-3}$)	Standard deviation	%Relative standard deviation
0	0	0	0	0	0	0	0
2	1.0773	1.0565	1.0157	0.9073	1.0142	0.0757	7.4661
5	4.3956	4.5530	4.6561	4.5497	4.5386	0.1074	2.3658
7.5	6.9864	7.0247	7.0909	7.1764	7.0696	0.0832	1.1774
10	8.7574	8.6350	8.8083	8.6434	8.7110	0.0856	0.9822
20	11.4508	11.3328	11.4053	11.2503	11.3598	0.0877	0.7720
30	12.5907	12.4878	12.5499	12.3807	12.5023	0.0914	0.7312
45	13.4135	13.3326	13.3659	13.2582	13.3426	0.0653	0.4894
60	13.8218	13.8087	13.8113	13.6823	13.7810	0.0661	0.4794
90	14.2964	14.5000	14.2617	14.1928	14.3127	0.1320	0.9226
120	14.5945	14.8750	14.9155	14.5287	14.7284	0.1952	1.3255

Table B-10.2: *Initial drug dissolved (DR_i) and extent of drug dissolved (AUC) for tablets containing lactose monohydrate, furosemide, Kollidon® VA64 (1.5% w/w) compressed at compression setting 24.*

	Bowl 1 [ ] ($\mu g.cm^{-3}$)	Bowl 2 [ ] ($\mu g.cm^{-3}$)	Bowl 3 [ ] ($\mu g.cm^{-3}$)	Bowl 4 [ ] ($\mu g.cm^{-3}$)	Average ($\mu g.cm^{-3}$)	Standard deviation	%Relative standard deviation
DR_i ($\mu g.cm^{-3}$)	0.876	0.864	0.881	0.864	0.871	0.007	0.851
AUC ($\mu g.cm^{-3}$)	1518.875	1524.927	1521.876	1504.443	1517.530	9.068	0.598

Table B-11.1: *Average concentration drug dissolved for tablets containing lactose monohydrate, pyridoxine, Kollidon® VA64 (0.75% w/w) compressed at compression setting 24.*

Time	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average [ ] (µg.cm^{-3})	Standard deviation	%Relative standard deviation
0	0	0	0	0	0	0	0
2	9.1568	8.9948	7.8823	9.2875	8.8304	0.6433	7.2847
5	19.3626	18.7216	18.1111	19.4314	18.9067	0.6192	3.2751
7.5	21.8474	21.6743	22.4321	21.7837	21.9344	0.3394	1.5474
10	21.9680	21.9402	23.0161	21.8280	22.1881	0.5553	2.5028
20	22.1004	21.9217	23.0080	21.8145	22.2112	0.5442	2.4501
30	21.9689	22.0304	22.9217	21.7159	22.1592	0.5262	2.3748
45	21.8187	21.9186	22.6931	21.5655	21.9990	0.4860	2.2093
60	21.8475	21.7737	22.5905	21.6007	21.9531	0.4373	1.9921
90	21.7995	21.7062	22.5164	21.5736	21.8989	0.4219	1.9268
120	21.7746	21.6306	22.4452	21.5106	21.8402	0.4175	1.9117

Table B-11.2: *Initial drug dissolved (DR_i) and extent of drug dissolved (AUC) for tablets containing lactose monohydrate, pyridoxine, Kollidon® VA64 (0.75% w/w) compressed at compression setting 24.*

	Bowl 1 [ ] (µg.cm^{-3})	Bowl 2 [ ] (µg.cm^{-3})	Bowl 3 [ ] (µg.cm^{-3})	Bowl 4 [ ] (µg.cm^{-3})	Average (µg.cm^{-3})	Standard deviation	%Relative standard deviation
DR_i (µg.cm^{-3})	2.197	2.194	2.302	2.183	2.219	0.048	2.168
AUC (µg.cm^{-3})	2563.125	2554.215	2646.898	2536.499	2575.184	49.073	1.906

Table B-12.1: *Standard curve used for dissolution studies from tablet formulations containing pyridoxine as active ingredient.*

Dilutions:

Volume (ml)	Standard volume (ml)	[ ] (µg.ml)	Abs 1	Abs 2	Abs 3	Average Abs
1	250	**5.02**	0.2180	0.2186	0.2186	**0.2184**
2	250	**10.05**	0.4489	0.4495	0.4497	**0.4494**
3	250	**15.07**	0.6615	0.6630	0.6630	**0.6625**
4	250	**20.10**	0.8871	0.8878	0.8883	**0.8877**
5	250	**25.12**	1.1222	1.1251	1.1237	**1.1237**

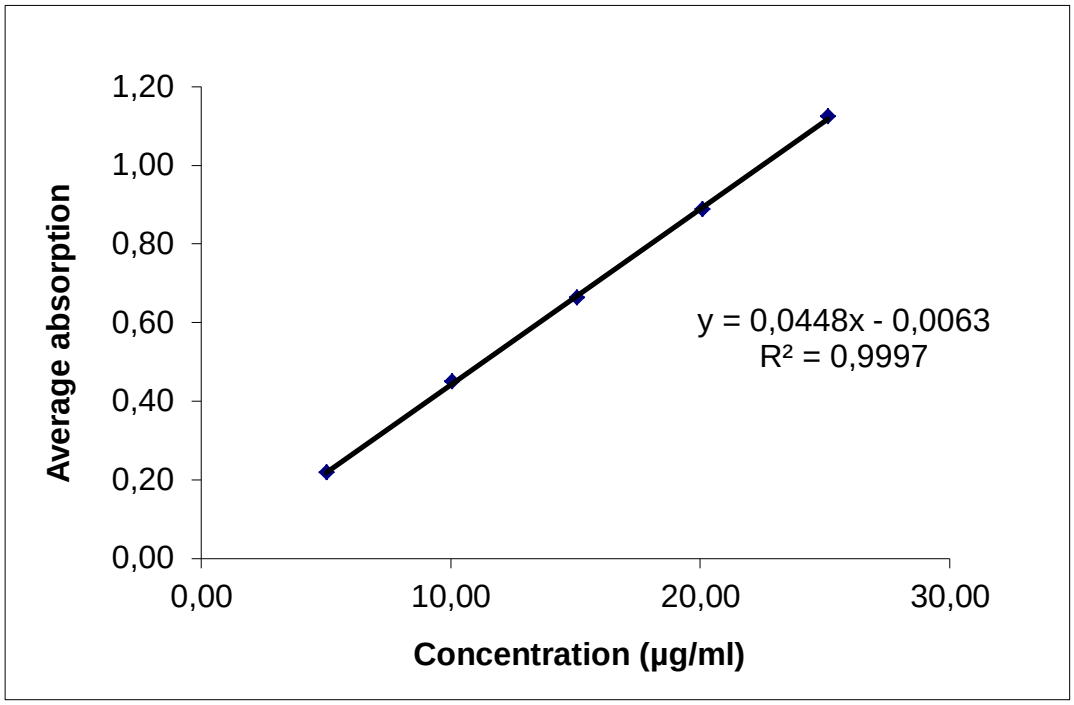

Figure 12.1: *Standard curve for dissolution studies from tablets containing pyridoxine as active ingredient.*

Table B-12.2: *Standard curve used for dissolution studies from tablet formulations containing furosemide as active ingredient.*

Dilutions:

Volume (ml)	Standard volume (ml)	[ ] (µg.ml)	Abs 1	Abs 2	Abs 3	Average Abs
1	250	**4.06**	0.2529	0.2544	0.2544	**0.2539**
2	250	**8.11**	0.5024	0.5044	0.5043	**0.5037**
3	250	**12.17**	0.7362	0.7383	0.7383	**0.7376**
4	250	**16.22**	0.9886	0.9907	0.9907	**0.9900**
5	250	**20.28**	1.2266	1.2274	1.2283	**1.2274**

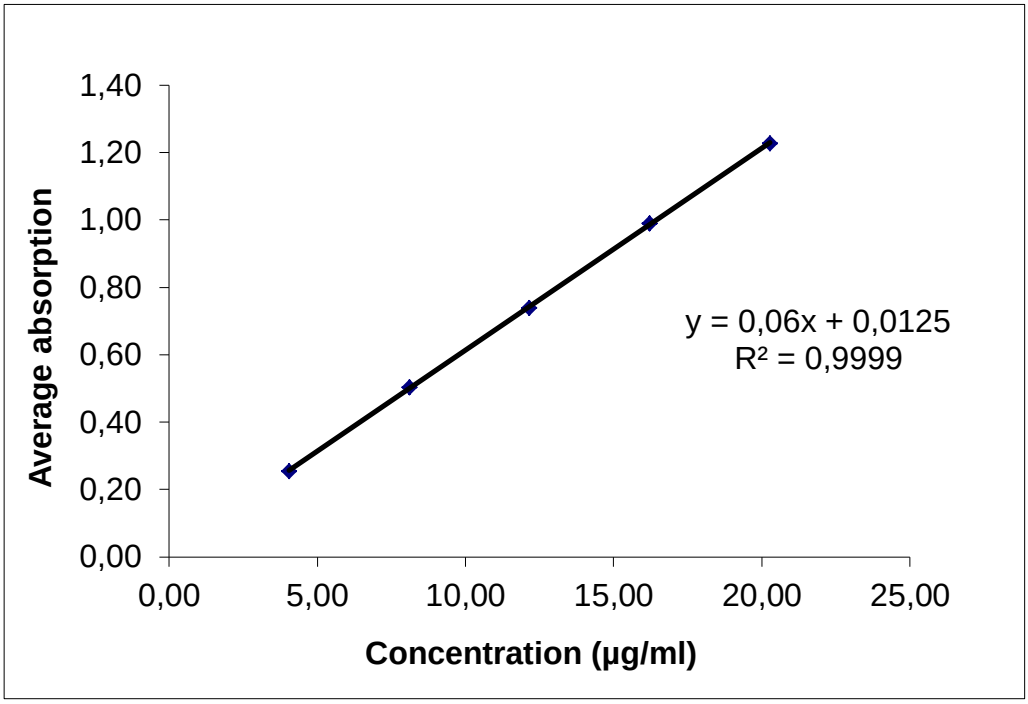

Figure 12.2: *Standard curve for dissolution studies from tablets containing furosemide as active ingredient.*