Investigation into the influence of different Kollidon® polymers on the properties of powder mixtures intended for tableting

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I thank the Lord for the opportunity He granted me to advance in excellence. Without His grace I could not have completed this study. He blessed me and loved me unconditionally, filling my life with opportunities. To Him all the glory!

'Trust in the Lord with all your heart

and lean not on your own understanding;

in all your ways acknowledge him

and he will make your paths straight.'

Proverbs 3:5

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Investigation into the influence of different Kollidon® polymers on the properties of powder mixtures intended for tableting

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INTRODUCTION, AIM AND OBJECTIVES

Today tablets as a dosage form still account for over 80% of drug administration to man. This can be attributed to the cost-effectiveness, convenience of administration, stability and ease of manufacturing. Two common manufacturing methods namely, direct compression and wet granulation are employed in the pharmaceutical industry. Manufacturing solid dosage forms such as tablets by means of wet granulation is one of the oldest and more traditional methods of producing satisfactory solid dosage forms, and is still commonly used today (Rajniak *et al.*, 2007:92). Despite the disadvantages of wet granulation, advantages of this method include prevention of segregation of powder constituents, increased flow properties and increased compaction characteristics (Summers & Aulton, 2002:365-366).

The selection of fillers and excipients is essential in the pharmaceutical formulation process. This often serves as the matrix around which success or failure of the formulation revolves. The properties of formulations generally depend on the physicochemical properties of the filler since it often comprises over 80% of the tablet. The additives (e.g. binders, disintegrants, lubricants and glidants) not only affect the physical properties of the tablet, but can also play a major role in the disintegration of the tablet and dissolution of the drug, affecting the bioavailability of it. It is, therefore, vital to choose the correct filler and excipients for formulation. Some fillers are not compressible (e.g. lactose), and binders are implemented to produce compressible fillers intended for tableting.

Wet granulation is a size enlargement process of converting small-diameter solids (typically powders) into larger diameter agglomerates to generate a specific size, improve flow properties and to produce a powder with specific characteristics such as dissolution rates, granule strength, apparent bulk density and to ensure composition uniformity (Rajniak *et al.*, 2007:92). To produce a compressible powder by means of granulation a binder should be incorporated in the formulation. The binder is included to render granules suitable for compression. Therefore, binder properties are essential. The binder type and properties will influence the characteristics of the prepared granules and these properties will influence tablet properties. It is therefore essential to select a suitable binder for the required properties of the desired formulation.

Polyvinylpyrrolidone (PVP) is most commonly used in the pharmaceutical industry as binder. Polyvinylpyrrolidone (PVP) and derivatives thereof are marketed as Kollidon® and is manufactured by BASF. Examples of binders in the Kollidon® range include Kollidon® 30, VA64 and 90F that differ remarkably in terms of their physicochemical properties (Bühler 2003:17-20).

Aim and objectives

The aim of this study was to evaluate and compare selected binders in the Kollidon® range with regard to their influence on powder and tablet properties.

To accomplish the aim of the study the following objectives were set:

1. Conduct a literature study on the manufacturing of tablets with an emphasis on wet granulation and the use of binders.

2. Preparation of compressible powders (granulates) by using three different Kollidon® polymers at three different concentration levels.

3. Characterization of the powders (granulates) with regard to flow properties.

4. Manufacturing of tablets from the different powder mixtures at two different compression settings, namely stroke length 1 and 4.

5. Evaluation of the tablets with regard to weight variation, mechanical strength (crushing strength and friability) and disintegration.

6. Investigation of the influence of an active ingredient on tablet properties.

In chapter 1, a literature overview of wet granulation as a manufacturing process will be given. In chapter 2 the experimental methods used in this study are described. Chapter 3 deals with the results regarding the powder properties of the different formulations and is followed by chapter 4 in which the properties of the placebo tablets prepared from the different powder mixtures are discussed. Dissolution data and the discussion thereof are given in chapter 5 and the study concludes with a summary and future prospects in chapter 6.

ABSTRACT

INVESTIGATION INTO THE INFLUENCE OF DIFFERENT KOLLIDON® POLYMERS ON THE PROPERTIES OF POWDER MIXTURES INTENTED FOR TABLETING

α-Lactose monohydrate is one of the oldest fillers used for production of solid dosage forms. Lactose was used as filler in this study, as it is readily available and relatively cheap. Lactose is not directly compressible, but it was one of the first fillers to be modified or co-processed into a direct compressible filler. Tablettose® and Ludipress® are examples of co-processed lactose based powders intended for direct compression. Lactose possesses unacceptable powder flow properties and this is one of the reasons why co-processed powders were developed. One of the great advantages of lactose is that it is water soluble, therefore, not influencing the solubility of the active ingredient incorporated in the tablet.

To determine the efficacy of the different binders (Kollidon® 30, VA64 and 90F), wet granulation was used to prepare granules from lactose. Wet granulation is used to enlarge powder particles, producing bigger agglomerates (granules) with better flow properties (because of the spherical shape) and compressibility to produce solid dosage forms. As binders, Kollidon® 30, VA64 and 90F were employed. The binders were used at three concentration levels (3, 6 and 10% w/w) to produce granules by means of wet granulation. Granules were prepared using ethanol as granulating fluid for Kollidon® 30 and VA64, and distilled water for Kollidon® 90F. Granules from the 10% w/w Kollidon® 90F formulation could not be prepared, as the wet powder mass could not be screened through the sieve. The granules obtained were dried in an oven for a specific time and at a specific temperature depending on the binder in question. A second step of granulation took place and the granules obtained were mixed with the disintegrant (1% w/w Explotab®) and the lubricant (0,5% w/w magnesium stearate). The disintegrant was incorporated in a 50 : 50 ratio (intra-granular : extra-granular). All the powders were mixed in a Turbula® mixer. The quantity of disintegrant and lubricant was kept constant for all formulations as this was not variables for this study.

During the initial phase of the study the physical properties (flow properties and compressibility) of the powder mixtures produced with the different binders (Kollidon® 30, VA64 and 90F) were evaluated to establish the influence of the binder. All the formulations exhibited acceptable powder flow properties and compressibility.

Tablets were compressed at two compression settings (stroke length 1 and 4) from the different powder mixtures. Two compressions settings were used to determine how the

different binders would react under different external pressures. The die volume of the tablet press was kept constant. The physical properties of the obtained tablets were evaluated with respect to tablet weight variation (%RSD), mechanical strength (crushing strength and friability) and disintegration. Tablets produced from Kollidon® 90F powder mixtures exhibited shortcomings in terms of disintegration as it exceeded the disintegration time limit of twenty minutes (in house specification). Results with regard to the mechanical properties of the tablets from all three binders employed, proved that there was no significant benefit by increasing binder concentration.

Kollidon® VA64 proved to be the most favorable binder in terms of disintegration. It was, therefore, selected and a compressible powder containing furosemide was prepared by means of wet granulation. Tablets were manufactured at the same concentration levels as previously mentioned and evaluated with respect to tablet weight variation (%RSD), mechanical strength (crushing strength and friability), disintegration and dissolution. Incorporation of furosemide had no detrimental effect on the weight variation as well as the mechanical strength (crushing strength and friability) of the tablets produced from the different formulations. However, disintegration behavior was negatively affected by the incorporation of the active ingredient. Only the tablets produced from the 3% w/w powder mixtures containing furosemide compressed at compression setting 1, exhibited disintegration below twenty minutes (disintegration time limit). Dissolution of furosemide (model drug representing sparingly water soluble drugs) from tablets produced from different powder mixtures (3, 6 and 10% w/w) of Kollidon® VA64 was determined in 0.1 M HCl for 90 minutes. Dissolution results were compared in terms of initial dissolution rate (DR_i) and extent of dissolution (AUC). At compression setting 1, all three formulations (3, 6 and 10% w/w) exhibited similar dissolution profiles. However, dissolution results revealed significant differences in the rate (DR_i) and extent (AUC) of furosemide dissolution between the 3% w/w and both the 6 and 10% w/w formulations. Tablets prepared at higher compression levels for both the 6 and 10% w/w concentration level exhibited poor dissolution profiles. The higher compression force caused a decrease in tablet porosity and as a result the disintegration time was prolonged. Water penetrated the tablet matrix to a lesser extent and disintegration was negatively influenced. This, in combination with the hydrophobic nature of furosemide, is the probable cause for the poor dissolution behavior of the 6 and 10% Kollidon® VA64 formulations at compression setting 4. The dissolution results indicated that disintegration is not an absolute prerequisite for dissolution, as tablets from the 6 and 10% w/w formulations did not disintegrate, but still exhibited dissolution, depending on the compression force. Dissolution results also indicated the dependency of the extent of drug dissolution (AUC) on the initial dissolution rate (DR_i), indicating the importance (although not

an absolute prerequisite) of establishing rapid contact between drug particles and the surrounding dissolution medium.

UITTREKSEL

'n ONDERSOEK NA DIE INVLOED VAN VERSKILLENDE KOLLIDON® POLIMERE OP DIE EIENSKAPPE VAN POEIERS WAT BESTEM IS VIR TABLETTERING

Laktose is een van die oudste en mees algemeen gebruikte vulstowwe in die vervaardiging van tablette. Redes vir die gewildheid van laktose sluit in: die koste-effektiwiteit, wateroplosbare gedrag en algemene beskikbaarheid daarvan. Laktose beskik egter nie oor goeie vloei-eienskappe en saampersbaarheid nie en was om hierdie rede ook een van die eerste vulstowwe wat gemodifiseer is om 'n direksaampersbare vulstof te lewer. Voorbeelde hiervan is Ludipress® en Tablettose®. Ten spyte van die ontwikkeling van direksaampersbare vulstowwe, word laktose en natgranulering algemeen in die farmaseutiese nywerheid gebruik in die vervaardiging van tablette.

Natgranulering is 'n arbeidsintensiewe en tydrowende vervaardigingsproses, maar is ten spyte hiervan steeds 'n algemene vervaardigingsproses wat te wyte is aan voordele soos verbeterde vloei-eienskappe en beter saampersbaarheid van veral hoë dosis geneesmiddels. Die insluiting van 'n bindmiddel tydens natgranulering is essensieël om agglomerasie van poeierdeeltjies te verseker, aangesien die vorming van granules fundamenteel is in die natgranuleringsproses.

In hierdie studie is α-laktose monohidraat as vulstof en natgranulering as vervaardiginsmetode gebruik. Ten einde die effektiwiteit van bindmiddels te ondersoek, is drie verskillende polimere in die Kollidon®-reeks, naamlik Kollidon® 30, VA64 en 90F by drie verskillende konsentrasies (3, 6 en 10% m/m) gebruik. As oplosmiddel is etanol vir Kollidon® 30 en VA64 gebruik terwyl gedistilleerde water vir Kollidon® 90F gebruik is. Na die eerste granuleringstap is die granulaat in oonde gedroog vir bepaalde tye en sekere temperature, afhangend van die bindmiddel. Die granules wat verkry is na die tweede granuleringstap is vermeng met Explotab® in 'n 50 : 50 verhouding (intragranuêr : ekstragranulêr) asook magnesiumstearaat. Die konsentrasies van beide die Explotab® (1% m/m) en magnesiumstearaat (0.5% m/m) was konstant in al die formulerings aangesien dit nie as veranderlikes in hierdie studie ingesluit is nie. Die poeiers is gekarakteriseer en vergelyk in terme van vloeigedrag en saampersbaarheid. Hierdie poeiers is gebruik om plasebotablette te vervaardig met 'n konstante matrysvolume by twee verskillende persdrukke, naamlik persdrukstelling 1 en 4. Die tablette van die verskillende poeierformules is geëvalueer ten opsigte van massavariasie, meganiese sterkte (breeksterkte en afsplyting) asook disintegrasie. Op grond van hierdie resultate is Kollidon®

VA64 as bindmiddel gekies en furosemied is as geneesmiddel ingesluit om die invloed van 'n swak wateroplosbare geneesmiddel op die eienskappe van die bindmiddel en die tablette te ondersoek.

Resultate met betrekking tot die vloeigedrag van die verskillende poeierformules het getoon dat al die poeiers oor aanvaarbare vloei-eienskappe beskik het en dat al drie bindmiddels vergelykbare resultate gelewer het.

Oor die algemeen het 'n verhoging in persdruk gelei tot 'n verhoging in die gemiddelde breeksterkte van tablette. Hierdie tendens is opgemerk by al drie bindmiddels. Vir beide Kollidon® 30 en 90F het 'n verhoging in bindmiddelkonsentrasie gelei tot 'n verhoging in die gemiddelde breeksterkte van tablette. Hierteenoor het 'n vehoging in bindmiddelkonsentrasie geen statisties betekenisvolle invloed gehad op die breeksterkte van Kollidon® VA64-tablette nie. Al drie bindmiddels het plasebotablette met voldoende meganiese sterkte by 'n 3% m/m konsentrasie gelewer. 'n Verhoging in persdruk het ook gelei tot verlengde gemiddelde disintegrasietye vir al drie bindmiddels. Die gemiddelde disintegrasietyd vir al die Kollidon® 90F formules was langer as twintig minute (disintegrasielimiet).

Dissolusieresultate het getoon dat die insluiting van 'n swak wateroplosbare geneesmiddel (furosemied), selfs teen 'n lae dosis (40 mg) 'n betekenisvolle invloed op bindmiddelgedrag en gevolglik tableteienskappe gehad het. Uit die resultate was dit duidelik dat die tempo (DR_i) en omvang (AUC) van furosemied betekensvol beïnvloed is. Die resultate het ook getoon dat disintegrasie nie 'n absolute voorvereiste vir dissolusie is nie.

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Chapter 1

THE EFFICACY OF BINDERS USED IN WET GRANULATION – A LITERATURE REVIEW

1.1 Introduction

Today it is still remarkable that tablets account for over 80% of drug administration to man. This can be attributed to the cost-effectiveness, convenience of administration, stability and ease of manufacturing.

The use of solid dosage forms can be traced to arabic medical literature. It started when particles were compressed between ebony rods, and a hammer was used to apply force at the one end. A patent was granted to William Brockedon for a machine which could compress powders between two cylindrical punches. It consisted of a piece of metal with a hole (the die) in it. The punches were inserted; one at a constant depth with a fixed volume. The other punch was inserted from the top and a hammer was used to apply the compacting force. This invention caught the attention of pharmaceutical companies (Armstrong, 1988:648; Rubenstein, 1988:304).

Tablets as a dosage form offers several advantages and these include:

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

1.2 Wet granulation

Tableting by means of wet granulation is one of the oldest and more traditional methods of producing satisfactory solid dosage forms and is still most commonly used today. Wet granulation is a size enlargement process of converting small-diameter solids (typically powders) into larger diameter agglomerates to generate a specific size, improve flow properties and to produce a powder with specific characteristics such as dissolution rates, granule strength, apparent bulk density and to ensure composition uniformity (Rajniak *et al.*, 2007:92).

Processing takes place in one of two types of closed granulating systems: fluid bed granulators or high-shear mixers. These techniques differ technically on the mode of solid agitation and fundamentally, on the mode of granule growth. In fluid bed granulation, the powder mixture is maintained as a fluidized bed by flow of air injected upwards through the bottom screen of the granulator. The binder solution is usually sprayed from above the powder bed, in a direction opposite to the air flow. Other spraying directions can be used on the same equipment for solid coating. The granules result from the adhesion of the solid particles to the liquid droplets that come into contact with the bed. Partial drying by the fluidizing air occurs continuously during granulation. The process continues until all the powder has been agglomerated and it needs to be stabilized as far as moisture balance is concerned. The equilibrium may not be constant, because the moisture content of the granules could increase slightly during the process, and the trajectories of the particles may change with changes in the density of the agglomerated powder bed. Complete drying is quickly achieved in the hot air stream when binder spraying is stopped (Faure *et al.*, 2001:269).

In high-shear granulation, an impeller maintains the powder in agitation in a closed vessel and the binder solution is sprayed from the top. As the liquid droplets disperse in the powder, they form the first nuclei of the future granules. The agitation forces prevent the development of large agglomerates, because they would be too fragile to sustain shear. However, as mixing and spraying proceed, the existing agglomerates undergo densification, whereby the internalized binder is squeezed out to the surface of the wet agglomerates. This has two consequences, namely: it makes the agglomerates harder and their surface more adhesive, and hence, granule growth enters a new more sufficient phase. The process is stopped somewhere in this phase before an excess of liquid or excessive densification provokes a phase inversion, i.e. slurry or uncontrollable growth. The drying step traditionally takes place after transferring the damp mass into another piece of equipment (fluid bed dryer), but the use of single-pot technology (drying in place) is now spreading. The granules formed are understandably denser than those obtained in fluid bed granulation (Faure *et al.*, 2001:270).

According to the operating conditions and the physicochemical properties of the primary particles and binder solution, the evolution of granule properties during granulation is controlled by three processes, namely: coating, growth (agglomeration) and attrition (breakage). During coating, a liquid binder solution is sprayed onto the powder to form a layer of liquid surrounding a particle. This mechanism is observed when wetted particles become dry before their collision or the cohesive strength between the wetted particles is weaker than the breakup forces induced by the particle-particle collisions in the fluidized

bed. During agglomeration, large particles or granules are produced by smaller particles adhering to one another via liquid bridges. Liquid bridges are formed as wetted particles coalesce. Strong solid bridges that hold a granule together develop from the liquid bridges during the subsequent drying step. It has also been suggested that even though some pharmaceutical excipients may be somewhat soluble in the granulating liquid, polymeric binders are still required to assure appropriate granule strength. Excipients that are strongly soluble in the liquid binder play a major role in the formation and strength of solid bridges inside a granule (Rajniak *et al.*, 2007:93).

The rate of granule growth by agglomeration is proportional to the collision frequency between particles present in the granulator and the fraction of collisions that are successful, i.e. the fraction of collisions that lead to coalesce rather than rebound (Thielman *et al.*, 2008:160-161).

For a collision to be successful, two conditions must be met:

1. the particles must contact each other at a binder-wet region, and
2. the viscous binder layer in this region must be able to dissipate the kinetic energy of the particles.

Depending on the surface energy, a liquid binder droplet deposited on a smooth particle will either spread completely and form a film coating (total wetting case), or in case of partial wetting, take the shape of a spherical cap whose base radius, a, and height, h, can be related to the volume, V, and contact angle, θ, by the following equations (Thielman *et al.*, 2008:161), if we assume the droplet size to be relatively small compared to the particle size and, therefore, neglect the curvature of the particle surface:

$$a = \left[\frac{3V}{\pi}\frac{\sin^3\theta}{2-3\cos\theta+\cos^3\theta}\right]^{1/3} \quad \text{and} \quad h = a\left[\frac{1-\cos\theta}{\sin\theta}\right] \qquad \textbf{1.1}$$

The dependence of a and h on θ is plotted in fig. 1.1. As can be seen, for a fixed binder volume, a hydrophobic particle (i.e. larger contact angle, θ) will have a smaller fraction of its surface covered by the liquid than a hydrophilic one, and therefore smaller probability of coming into contact with another particle with a wet region during a certain number of random collisions. On the other hand, if it does come into contact with another particle with a binder-wet area, the local thickness of the liquid layer will be larger than for a corresponding hydrophilic particle, and so will its ability to dissipate the kinetic energy of the impact. An illustration of the liquid configuration on a hydrophilic and a hydrophobic particle is shown in fig. 1.2. The critical conditions for the dissipation of kinetic energy by a viscous

layer of given thickness (so-called viscous coalescence) have been derived in the form of the Stokes number, defined as:

$$St_v = \frac{2mu_0}{3\pi\mu d^2} \qquad \textbf{1.2}$$

where m is the particle mass, u_0 is the collision velocity, μ is the viscosity of the liquid, and d is the particle diameter.

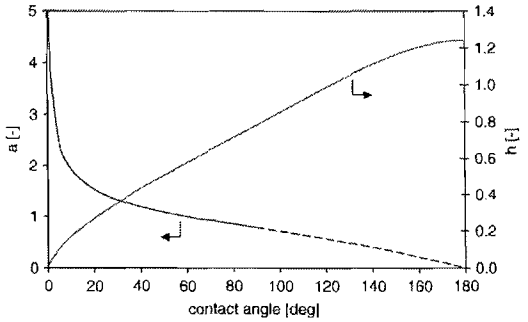


Fig. 1.1: Dependence of the base radius, *a*, and the height, *h*, of a spherical cap with a nominal volume of $V = 1$, on contact angle (Thielman *et al.*, 2008:161).

In the case of a collision between particles of unequal size, the reduced mass and radius respectively, are used rather than m and d:

$$m = \frac{2m_1m_2}{m_1 + m_2} \qquad \text{and} \qquad d = \frac{2d_1d_2}{d_1 + d_2} \qquad \textbf{1.3}$$

A collision is deemed successful if the Stokes number is below a critical value (the critical Stokes number, St_v^*):

$$st_v^* = \left(1 + \frac{1}{e}\right)\ln\left(\frac{h}{h_a}\right) \qquad \textbf{1.4}$$

where e is the coefficient of restitution, h is the thickness of the binder layer at the collision point, and h_a is the characteristic size of surface aspherities. The value of the Stokes number determines whether coating or granulation occurs, and the maximum granule size that can still lead to coalescence for a given volume of binder with certain viscosity (Thielman *et al.*, 2008:161). Of specific interest in present research, is the influence of the particle surface properties on the agglomeration rate, which Thielman *et al.* (2006:161) interpreted in terms of the dependence of the critical Stokes number on contact angle, via the binder layer thickness , i.e. the combination of equation 1.1 and 1.4.

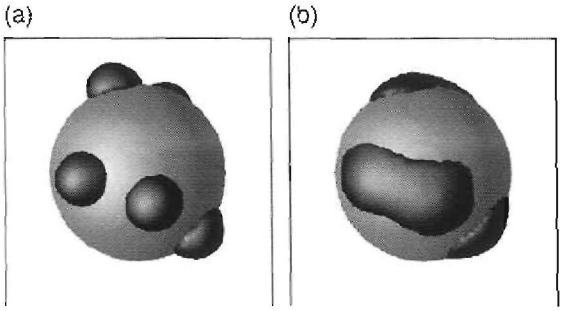


Fig. 1.2: Illustration of liquid droplet morphologies on a spherical particle with a contact angle of 75° (a) and 15° (b). The binder volume and the initial position of the droplets were the same. The final liquid configuration was obtained by a volume-of-fluid (VOF) simulation (Thielman *et al.*, 2008:161).

The selection of an appropriate polymeric binder to agglomerate drug with excipients is a critical issue in the development of high-shear wet granulation processes for pharmaceutical tablet systems. During the wet granulation phase, the surface energy of the drug particles has an impact on the ability of the binder solution to spread across the surface of the particles. The same surface energy also influences the strength of the adhesion of the drug to the dry binder. Both factors will determine how well the drug is incorporated into the granules.

It is well known that granulation behavior can be rather sensitive to the properties of the primary solid particles. Even different batches of nominally the same material can granulate differently and a considerable amount of time is often spent on identifying granulation conditions (binder type and level, temperature etc.). It would be desirable if quantitative or qualitative guidelines were available for the selection of robust granulation process conditions based on a set of particle physicochemical properties that can be measured on a small scale sample during the early phase of the formulation and process development cycle (Thielman *et al.*, 2008:160).

The change in granulation behavior when a new solid material is introduced can be caused by several factors such as:

- different materials will generally possess different surface properties (surface energy and wetting characteristics),
- different particle morphology,
- density, and
- size distribution (Thielman *et al.*, 2008:160).

1.2.1 Granulators

Granulation takes place in mainly one of two types of closed granulating systems: high-shear mixers (see fig. 1.3) or fluid bed granulators (see fig. 1.4).

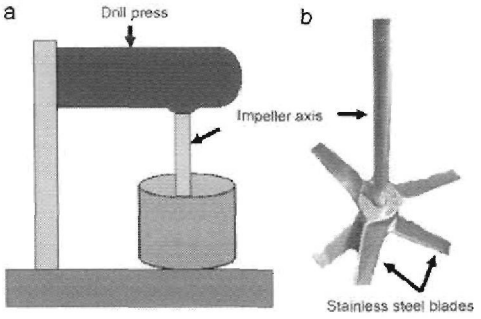


Fig. 1.3: Illustration of a high-shear mixer (a) and the impeller (b) (Realpe & Velázquez, 2007:1604).

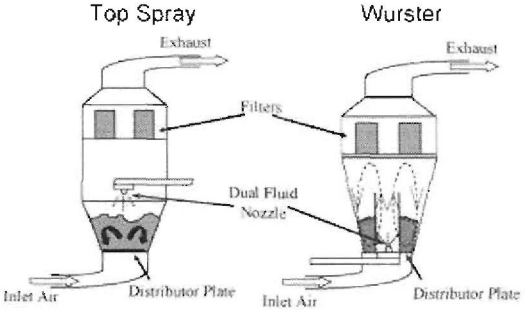
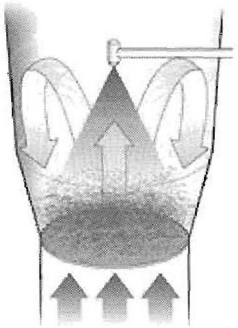


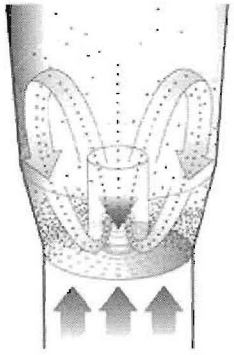
Fig. 1.4: Illustration of a fluidized bed granulator. Comparison of top-spray vs. Wurster fluid bed granulator (Rajniak *et al.*, 2007:93).

The two techniques differ technically on the mode of solid agitation and fundamentally on the mode of granule growth. Fig. 1.3 displays a schematic illustration of a laboratory-scale high-shear mixer. High-shear mixers operate on the same principle as a Kenwood® chef mixer. The impeller motor sits on top, rotating vertically at the desired selected speed. Usually stainless steel is used for the blades on the impeller axis. Liquid binder must be added manually. Peristaltic pumps are usually used with a nozzle and the binder solution is added at a fixed rate (Realpe & Velázquez, 2007:1604). Homogenization of the powder mixture can be ensured by using a NIR spectrometer. Powders would then be mixed until the spectrum no longer changes respective to the previous one. Powders are mixed at a fixed rate and fixed time. Samples can be extracted at different times to obtain the desired spectra. Wet granules are transferred to a fluid-bed dryer or oven to be dried (Faure *et al.*, 2001:270). In fluid bed granulation the powder mix is maintained as a fluidized bed by flow of air injected upwards through the bottom screen of the granulator (see fig. 1.5). The

binding solution is sprayed from above the powder bed in a direction opposite to the air flow. Other spraying directions can be used on the same equipment for solid coating (Wurster). The granules result from the adhesion of the solid particles to the liquid droplets that come into contact with the bed. Partial drying by the fluidizing air occurs continuously during granulation. The process continues until all the powder has been agglomerated and it needs to be stabilized as far as moisture balance is concerned. The equilibrium may not be constant, because the moisture content of the granules could increase slightly during the process, and the trajectories of the particles may change with changes in the density of the agglomerated powder bed. Complete drying is quickly achieved in the hot air stream when binder spraying is stopped (Faure *et al.*, 2001:269). The difference between top spray and the Wurster (bottom spray) is the direction of inlet of air and binder solution (see fig. 1.5).



Principle:
Batch fluid bed granulation,
Top spray



Principle:
Batch fluid bed granulation,
Bottom spray (Wurster)

Fig. 1.5: Illustration of fluid bed granulators (Rajniak *et al.*, 2007:93).

A third, but older and more time consuming granulation method can be used. The desired quantity of powder is weighed, and then mixed with the other excipients. A mortar and pestle are used to knee the mixture in the presence of the binder solution until a uniform/homogenic product is obtained. The wetted powder is then extruded through a steel grid of selected size. The granules are placed in an oven to dry for a specific time and temperature. When the desired humidity content is obtained a second granulation takes place and the large granules are extruded through a smaller grid. The final product is obtained. However, this technique can only be used on small scale wet granulation formulations.

The popularity of wet granulation is understandable when considering the compaction process. When a powder is compressed in the die, the different processes can be separated as follows (Khan & Rhodes, 1973:3):

- rearrangement – where particles move within the die cavity to occupy void spaces that exist between particles.

- deformation – when particles can no longer rearrange themselves, the material will start to deform elastically.

- compaction – when the elastic limit of the material is exceeded, the material will deform either plastically or destructively (fragmentation). Either mechanism can occur and is dependent upon the material's characteristics, compaction speed, particle size and compaction pressure. Plastic deformation will aid bonding because it increases the contact area between the particles and fragmentation produces new surfaces that also favor strong bonding.

- relaxation – once the compression force is withdrawn from a compressed mass, the compact will undergo relaxation and if these elastic forces exceed the tensile strength of the tablet, then the tablet integrity will fail.

Successful tablets can be produced when the right balance of the brittle fracture and plastic behavior within the compression mix can be achieved, which in turn, depends on the compression characteristics of the excipients and the drug substance.

Table 1.1 presents the differences and similarities between wet granulation, dry granulation and direct compression methods. Regardless which one of the three methods are employed, mixing and milling would be the first step in the process.

Table 1.1: A comparison of the typical unit operations involved in traditional wet granulation, dry granulation and direct compression (Shangraw, 1989:195-246).

Wet Granulation	Dry Granulation	Direct Compression
1. Milling and mixing of drugs and excipients	1. Milling and mixing of drugs and excipients	1. Milling and mixing of drugs and excipients
2. Preparation of binder solution	2. Compression into slugs or roller compression	2. Compression of tablets
3. Wet massing by addition of binder solution or granulating solvent	3. Milling/screening of slugs/compacted powder	
4. Screening wet masses	4. Mixing with lubricant and disintegrant	
5. Drying of the wet granules	5. Compression of tablets	
6. Screening of the dry granules		
7. Blending with lubricants and disintegrant to produce "running powder"		
8. Compression of tablets		

1.2.2 Limitations of wet granulation

As any pharmaceutical process, wet granulation has certain limitations, such as:

- an expensive process – labor intensive, time consuming, lots of equipment, energy and space requirements,
- loss of material during different steps of the process,
- stability is a concern for moisture and thermolabile drugs,
- multiple processing steps add complexity and make validation and control difficult, and
- an inherent limitation of wet granulation is that any incompatibility between formulation components are aggravated (ANON, 2006a:www.pharmpedia.com).

1.2.3 Advancements in granulation

All the advancements were fundamentally derived from traditional wet granulation.

Steam Granulation

This method is a modification of the wet granulation process. Steam is used as binder solvent instead of water. Benefits include:

- higher distribution uniformity,
- higher diffusion rate into powders,
- more favorable thermal balance during drying step,
- granules are more spherical,
- steam possess large surface area,
- better dissolution rate of the drug,
- process times are shorter, and
- steam is sterile.

However, thermolabile drugs cannot be subjected to this process (ANON, 2006a:www.pharmpedia.com).

Melt Granulation / Thermoplastic Granulation

A melted binder is added during granulation to produce granules. The binder occurs in the solid state at room temperature, but melts in temperature ranges of 50-80 °C. The melted binder acts as a liquid binder. No drying is necessary since dry granules are obtained when cooling to room temperature. This technique is useful when granulating with water sensitive excipients or drugs (ANON, 2006a:www.pharmpedia.com).

Foam Granulation

Liquid binders are added as aqueous foam. This technique has several benefits over spray (wet) granulation. Benefits include:

- less binder is required than with spray granulation,
- requires less water to wet granulate,
- rate of addition of foam is greater than the rate of addition of sprayed liquids,
- no over wetting,
- useful in water sensitive and thermolabile formulations,
- reduced drying time,
- uniform distribution of binder, and
- reduced manufacturing time (ANON, 2006a:www.pharmpedia.com).

1.2.4 Wettability of pharmaceutical solids

Knowledge of wettability and surface energies of pharmaceutical solids is important in the rational design of pharmaceutical formulations. Information of this type can provide indications about interfacial interactions and compatibility among formulation components, thus allowing excipients to be selected on a rational basis. Different techniques are employed to assess the wettability and surface energy of powders, such as:

- the contact angle method,
- the floatation method,
- isothermal microcalorimetry, and
- inverse gas chromatography (Zhang *et al.*, 2002:547).

The contact angle method via sessile drop is commonly used to obtain surface energy data, but this technique has shortcomings associated with drop penetration, solid dissolution and

surface change upon compression. Zhang *et al.* (2002:547) also found that it was difficult to apply the contact angle method to hydrophilic powders where the contact angle is low and drop penetration is fast. The floatation method and isothermal microcalorimetry are not widely used in the pharmaceutical industry and irregular particle shape of solids limits the application of the floatation method. Microcalorimetry is sensitive to surface properties of powders via heat of adsorption. It is not readily applicable to drug compounds since they are usually hydrophobic and possess low surface areas. More recently inverted gas chromatography (ICG) has been demonstrated to be a useful method for characterization of powders. The advantage of this technique is that the powder can be probed in its natural state avoiding problems occurring with contact angle. However, inverted gas chromatography (ICG) is labor intensive and does not give surface energy data that can assess interactions of solids (Zhang *et al.*, 2002:547).

1.3 Direct compression

The use of direct compression as manufacturing process is increasing in the pharmaceutical industry. It can be attributed to the time saving and economical benefits of this process. The term direct compression refers to the process which involves compressing tablets directly from a powder blend of active ingredient and suitable excipients (disintegrants, lubricants, glidants and fillers) into a stable solid form. Direct compression can only be achieved when the powder has certain properties like adequate flow properties and compressibility. It is absolutely essential that every excipient must be selected very carefully as this choice would contribute to the final product's success. Many drugs cannot be directly compressed, therefore, special attention must be given to the choice of selected excipients (Armstrong, 1988:647; Rubenstein, 1988:307). The properties of each and every raw material and the process by which these materials are blended become extremely critical to the compression stage of tableting. Direct compression is a unique manufacturing process, requiring new approaches to excipient selection, blending and compressibility (Shangraw, 1989:196).

Direct compression offers the following advantages:

- Economical – Savings occur in different areas including shorter processing times, thus reduced labor costs, fewer manufacturing steps and equipment, less process validation and lower consumption of electricity.

- Drugs are not subjected to heat and moisture, an advantage when working with thermolabile and waterlabile drugs.

- Probably one of the least recognized advantages is the optimization of tablet disintegration, in which each primary drug particle is liberated from the tablet mass and is available for dissolution. The granulation process, wherein small particles with a large surface area are "glued" into larger agglomerates, is in direct opposition to the principle of increased surface area for rapid dissolution (Battista & Smith, 1962:21; Fox *et al.*, 1963:260).

- As seen in table 1.1 it is a very simple process, requiring few manufacturing steps. Therefore, errors can be minimized and products maximized.

- Saving space by using less equipment (Sheth *et al.*, 1980:148).

As with wet granulation, direct compression also has its limitations:

- The limited dilution potential of fillers or binders available and the poor flow properties of the powder mixture are the main problems with this method of tablet production.

- Furthermore, segregation of the drug can occur, debating the uniformity of low dose drugs (Schmidt & Rubensdörfer, 1994a:2899). Direct compression blends are subjected to unblending in postblending handling steps. The lack of moisture in the blends may give rise to static charges that can also lead to unblending. Differences between particle size, or density between drug and excipient particles, can also lead to unblending in the hopper or the feed frame of the tablet press (Shangraw, 1989:200).

- Direct compression fillers are often costlier than fillers used in granulation because co-processing is necessary.

- Physical properties and functional specifications are more critical. Properties of raw materials must be defined and carefully controlled.

- Limitations in producing colored tablets.

- Greater dust problems.

- More sensitive to lubricant softening and over mixing than granulations.

The ideal direct compression vehicles should be:

- able to produce tablets containing a proportion of non-compressible material,
- free flowing,
- able to improve the compressibility of poorly compressible drugs,
- capable of being reworked with no loss of flow or compressibility, and
- able to promote rapid disintegration (Armstrong, 1988:648)

Table 1.2 presents a detailed comparison of the differences and similarities of direct compression and wet granulation as formulation processes.

Table 1.2: A detailed comparison between direct compression and wet granulation.

	Direct Compression	Wet granulation
Compression	Potential problem for high dose drugs	Harder tablets for poorly compressible substances
Flow properties	Many formulations may require a glidant Cannot be used for high-dose micronized drugs	Excellent in most cases
Particle Size	Smaller with narrower range	Larger with great range
Content uniformity	Segregation may occur in mass transport, hopper and feed frame	Massing and drying included
Mixing	Low shear with ordered blending	High or low shear
Lubricant	Minimal blending with magnesium stearate	Less sensitive to lubricant softening and over-blending
Disintegrant	Lower levels usually necessary because no granules present	Often problems with granules
Dissolution	No wetting Dissolution may be slower if larger size drug crystals used Generally faster than wet granulation	Drug wetted during processing Drug dissolution from granules may be problematic Generally slower than direct compression
Costs	Increase in raw material costs and their quality control	Increase in equipment, labor, time, process validation and energy
Flexibility of formulation	Properties of raw materials must be carefully defined	Granulation covers raw materials' flaws
Stability	No heat No moisture Dissolution rate rarely changes	Problems with heat or moisture Dissolution rate decreases with time
Tableting speed	May require lower speed	May be faster
Dust	More dusty	Less dusty
Color	Pastel only (Lakes only)	Deep or pastel (dyes or lakes)

1.4 Required properties of mixtures intended for tableting – factors influencing tablettability

There are three essential requirements for powders intended for compression:

1. compressibility,
2. flow properties, and
3. anti-adherence.

If these three standards are not met, successful tablets cannot be produced. Unfortunately, there are few powders/substances that meet these requirements. Therefore, preliminary mixing and/or granulation are necessary to obtain these specific properties in order to successfully produce tablets that meet the specific requirements (Armstrong, 1988:247-249).

1.4.1 Compressibility

Compression in general is regarded as the reduction in bulk volume of a powder, exerting the gaseous phase to produce a solid product. Consolidation is the increase in mechanical strength of the material resulting in particle-particle interactions. After years of studies and experiments it is still not possible to predict with absolute certainty how some materials will respond during compression (Rubenstein, 1988:306).

Compression usually involves repacking and rearranging of particles. Under high compression forces, rearrangement becomes a problem and particles will undergo deformation. When the pressure load is removed, deformation is reversible, to a large extend. If the powder acts like rubber, it is said to be elastic. When shear strength is less than tensile strength, it resembles plastic deformation. If tensile strength exceeds shear strength, particles may be fractured. Smaller particles will fill up air spaces and this usually occurs in hard particles (Marshall, 1986:72). De Boer *et al.* (1986:148) defined fragmentation as the formation of smaller, discrete particles from initial grain.

1.4.2 Flow properties

It is essential to produce tablets with uniform/constant weight. This can only be achieved if the powder mixture intended for tableting possesses the necessary flow properties. Adequate flow properties are necessary to transport the powder through the hopper into the die. When a powder mixture exhibits unsatisfactory flow, tablets with different weights would be obtained and active ingredient variation would occur. Flow properties of powder mixtures can be improved by vibrations, incorporation of glidants, spray drying and granulation (Rubenstein, 1988:306).

Pharmaceutical powders can be classified as free flowing or cohesive. Changes in particle size, density, shape, electrostatic charge, texture and moisture significantly affect the flow properties. Generally, flow properties are determined by a combination of (i) material properties (particle size, size distribution, shape, packing density and surface properties), and (ii) operating conditions (moisture, temperature, static charge and history of applied stress) (Kachrimanis *et al.*, 2005:72-73).

Surface roughness plays a major role and leads to poor flow due to friction and cohesiveness. The presence of moisture can also result in poor flow because particles have a tendency to stick together. This problem can be minimized by drying. Very small particles also tend to have poor flow properties, whereas bigger spherical particles result in better flow. Shapes of particles are critical because spherical particles would flow better than cubic particles (Martin *et al.* 1983:517).

Martin *et al.* (1983:518) found that if granule size is reduced, the variation in tablet weight decreases. If granule size is further reduced, the granules flow less freely resulting in an increase in weight variation. When powder flow is impaired, tablets with uniform drug dosages cannot be produced.

Design, operation and quality assurance in many industrial processes involving granular material rely heavily upon the ability to quantitatively determine the propensity of powders to flow (Santomaso *et al.*, 2003:2857). However, free flowing powders are known to easily segregate by size when used with a polydispersed particle size distribution (PSD). The opposite is the case of cohesive or poorly flowing powders. Consequently, being able to qualify flow properties of granular material is crucial to prevent future problems during the production process (Santomaso *et al.*, 2003:2857).

There are different techniques to determine the flow properties of a powder. It can be classified under methods that directly observe the behavior of the granular material during flow in the consolidated state and those that determine flow properties expected to be connected with the flow ability in its loose packed state (indirect methods). Indirect methods refer to static and dynamic angle of repose, and discharge time, under given circumstances. The propensity to pack is another flow ability index used to describe the behavior of loosely packed powders. An external force field, e.g. gravity, can promote higher packing of granules, which occurs through relative particle motion. Note that compaction here refers to reduction of inter-particle voidage without affecting original particle shape. A comparison among different degrees of packing can be a measure of the difficulties experienced by the particles to rearrange their positions in the bed and hence to macroscopically flow (Santomaso *et al.*, 2003:2857).

Packing is usually quantified by apparent (bulk) density and tapped density. *Aerated density* is meant to be the lowest degree of packing under gravity. It can be determined by allowing the powder to settle by gravity. *Poured density* is most widely used and referred to as apparent density. Both aerated and poured density aim at achieving a condition of loose and random particle packing with air spaces still intact between particles. *Tap density*, on the other hand, is obtained by vibration of the collecting container in order to produce the highest packing prior to compaction (Santomaso *et al.*, 2003:2858).

The compressibility of a powder is commonly indicative of the flow properties and is often expressed using Carr's index. The higher the value of Carr's index, the more difficult it is for the powder to flow. Another commonly used technique to indicate powder flow is to measure the time it takes an amount of powder to flow through a funnel with a fixed orifice (Abdul *et al.*, 2007:1)

1.4.3 Anti-adherence

Many excipients and fillers exert strong adhesive properties toward the materials/steel used in the dies and punches of a tablet press. The result is sticking to punches and dies. When punches are not properly polished/buffed and cleaned regularly, a film on the punch face could develop. Film forming could also occur in high humidity and when lubrication is inadequate. Picking is an advanced stage of sticking. Pieces/portions of the compressed tablet are lifted or picked out, adhering to the punch face. Incorrect glidant use, damp granulations (improperly dried) and punches with incorrect logo designs could be reasons for sticking and picking when a powder is compressed. Serious sticking during ejection can lead to chipping of the tablet, leading to rough edges. It also gives rise to the lower punch not moving freely, abiding in the die causing stress on punches and the tablet press; and consequently leading to tablet weight variations. Damage of punches, dies and the tablet press can also occur. Anti-adherents, lubricants and glidants are implemented to overcome these problems (Banker & Anderson, 1986:313; Peck *et al.*, 1989:110-112; Marshall & Rudnic, 1991:383). Shah and Mlodozeniec (1977:1381) found that, when implementing magnesium stearate as lubricant, the duration of mixing had major effects upon tablet disintegration. Powder mixtures blended at longer times yielded tablets with longer disintegration times. This phenomenon may be attributed to the formation of hydrophobic surfaces developed by the lubricant, upon mixing.

1.5 Pharmaceutical excipients for tableting

1.5.1 Fillers

The active ingredient in tablets usually constitutes such a small percentage of the overall tablet weigh that it is impossible to compress tablets only containing the active ingredient. On the other hand, most active ingredients are not compressible. To overcome these problems, substances namely fillers, are added to formulations to reach tablettable weights. One of the functions of a filler is to act as a carrier of the active ingredient in tablets. Other functions include:

- provision of certain characteristics such as: delayed, controlled and slow release of the active ingredient out of the tablet matrix and site specific delivery,
- improved powder flow to minimize weight variation,
- enable direct compression,
- improved disintegration, and
- provision of certain binding properties.

Most of the fillers produced today are directly compressible such as: Ludipress®, Tablettose® and Avicel®. However, lactose is still extensively used in wet granulation.

The perfect filler should:

- be chemically and physiologically inert,
- be non-hygroscopic,
- be biocompatible,
- possess good biopharmaceutical properties (be water soluble and hydrophilic),
- possess good technical properties (compressibility and flow properties),
- have acceptable taste,
- be cheap,
- not interfere with active ingredient bioavailability, and
- possess a good pressure-hardness profile (Khan *et al.*, 1973:3).

1.5.2 Fillers intended for direct compression

1.5.2.1 Microcrystalline cellulose (Avicel®)

In a survey conducted within the pharmaceutical industry, many formulation scientists ranked microcrystalline cellulose as the most useful filler for direct compression. Its popularity can be attributed to its excellent compression ability at low pressures, high dilution potential and superior disintegration properties (Bolhuis & Lerk, 1973:474). Microcrystalline cellulose is purified, partially de-polymerized cellulose, which is prepared by treating cellulose with mineral acids, producing bundles of needle-like micro crystals. The substance is a white, crystalline powder composed of agglomerated porous particles (Mathur, 1994:84).

Commercially, microcrystalline cellulose is available as Avicel®. Avicel® is non-fibrous, free-flowing, inert and possesses a high surface area. Avicel® can be compressed into very hard tablets and still disintegrate immediately when placed in water. These tablets also possess low friability because of their hardness (Battista & Smith, 1962:21). Avicel® can be used as a filler, binder, disintegrating agent and lubricant in solid dosage form formulations. Microcrystalline cellulose possesses excellent flow properties although the particle size is very small. Avicel® is mainly used in direct compression formulations (Fox *et al.*, 1963:161).

Avicel® appears in many different grades for usage in direct compression. The different Avicel® grades differ from each other by particle size, particle shape, flow properties and moisture content. The average particle size, range from about 20 µm (PH 105) to about 200 µm (PH 200). The most common Avicel® PH grades, like PH 101 and PH 102, contain no more than 5% moisture. Most of the Avicel® PH grades are not regarded as free flowing, but PH 200 has been designed to exhibit better flow properties. Extremely strong tablets can be obtained with Avicel®, however, such tablets disintegrate quickly when placed in water as a result of the destruction of the cohesive forces between particles (Niskanen & Yliruusi, 1996:179). The excellent disintegration times of Avicel® can be explained by the capillary pores that exist in a compressed tablet. Water can enter the matrix of the tablet easily by means of the capillaries, breaking hydrogen bonding between adjacent particles (Fox *et al.*, 1963:260).

1.5.2.2 Ludipress®

This filler is co-processed and contains an incorporated filler (93,4% w/w α-lactose monohydrate), binder (3,2% w/w polyvinylpyrrolidone) and disintegrant (3,4% w/w crosspovidone). Ludipress® is included in this discussion, because it is a lactose-based co-processed filler and lactose was used in this study. The material consists of spherical particles made up of small crystals with smooth surfaces. Ludipress®, therefore, has

excellent flow properties (Schmidt & Rubendörfer, 1994b:2901). Unfortunately, a lubricant must be incorporated in the formulation of tablets to reduce the friction during the tableting process (Plaizier-Vercammen & Van Der Bossche, 1992:975). In general, formulations containing Ludipress® exhibits longer disintegration times than Avicel® formulations. To overcome this, a disintegrant can be incorporated in formulations containing Ludipress® (Schmidt & Rubensdörfer, 1994b:2901).

1.5.3 Fillers suited for wet granulation

1.5.3.1 Lactose

Lactose is one of the most cost effective fillers used today and it is readily available. It is a very popular filler and widely used in the pharmaceutical industry. Lactose is a white powder with a sweet taste. It is a disaccharide consisting out of two elementary sugars namely galactose and glucose, and it occurs naturally in the milk of mammals, but it can be chemically produced by joining galactose and glucose together. Lactose can be divided into crystalline and amorphous lactose. Crystalline lactose can be divided into two categories based on their water content, namely hydrous and anhydrous lactose. It can be expected that the different forms of lactose would have different physicochemical properties. Hydrous and anhydrous lactose exists in two isomeric forms namely the α-form and β-form (Bolhuis & Lerk, 1973:470; Lerk, 1993:2359-2360; Van Kamp *et al.,* 1986:229-230).

Lerk (1993:2359) classified the different forms of lactose as shown in table 1.3.

Table 1.3: The different forms of lactose (Lerk, 1993:2359).

Crystalline		**Amorphous**
Hydrous	**Anhydrous**	
• α-lactose monohydrate • α-crystals	• Unstable α-lactose • Stable α-lactose • β-lactose	

1.5.3.2 Hydrous lactose

α-Lactose monohydrate in the hydrous state is commercially available and is produced below temperatures of 93 ℃ by means of crystallization from an over saturated solution. This form of lactose exhibits, in direct compression, poor binding, but coarse sieve fractions exhibit excellent flow. The excellent flow properties are the reason why α-lactose

monohydrate is being used in direct compression systems (Bolhuis & Lerk, 1973:470; Van Kamp *et al*,. 1986:229-230; Lerk, 1993:2360; Van der Voort Maarschalk & Bolhuis, 1998:28). Spray-drying can be used to improve binding of particles (Gunsel & Lachman, 1963:182). One problem of hydrous lactose is the discoloration to brown. This occurs in the presence of amine drugs or alkaline substances and is called the Millard reaction due to the presence of water (Goodhart, 1994:257).

1.5.3.3 Anhydrous lactose

From table 1.3, it is evident that α-lactose occurs in both hydrous and anhydrous states, but β-lactose only occurs in the anhydrous state. Anhydrous lactose consists mainly out of β-lactose. β-Lactose is specifically designed for use in direct compression formulations. The β-isomer is obtained at temperatures above 93 °C and no water is incorporated in the crystal structure during crystallization. Thermal dehydration can convert the hydrous form to the anhydrous form. Disintegration is very slow in an anhydrous matrix and is one of the major problems with the anhydrous form. Anhydrous lactose does not undergo the Millard reaction as it contains no internalized crystal water (Goodhart, 1994:257).

1.5.3.4 Amorphous lactose

Quick drying of a lactose solution produces amorphous lactose. Amorphous lactose changes into crystalline lactose when moisture is absorbed under atmospheric conditions. When this form of lactose is heated at elevated temperatures, it is converted into a stable α/β-crystalline compound (Lerk, 1993:2359).

1.5.4 Factors that influence lactose as choice being used as a filler

There exist many advantages for using lactose as filler in formulations including:

- affordability,
- cost-effectiveness,
- easy storage in airtight containers,
- exhibits adequate drug release,
- it is readily soluble in water,
- spray-dried lactose is directly compressible,
- easy to use in the wet granulation industry,
- easy drying,
- it is a stable compound (should be stored in airtight containers),

- specific sieve fractions exhibit good flow properties,
- easily available because of chemical production, and
- lactose discolor to brown – reactions between lactose and active ingredient can easily be observed.

1.5.5 Disintegrants

A general prerequisite for drug bioavailability after oral administration is that the drug must be in solution in the gastrointestinal fluids to be absorbed. For dissolution to take place the drug must be released from the intact tablet. The breaking up of the tablet that comes into contact with water is called disintegration. Disintegration is critical to dissolution and is usually the rate limiting step. It affects bioavailability as well as onset of action and duration of effect of the active ingredient. Conventional dosage forms are divided into disintegrating tablets and non-disintegrating tablets. Disintegrating dosage forms release their active ingredient by breaking down the physical integrity of the tablet, usually made of disintegrating or gas-releasing agents. Non-disintegrating dosage forms are usually made of soluble drugs and excipients that will rapidly dissolve in the gastrointestinal fluids. Most conventional tablet formulations are designed and manufactured to ensure rapid and complete drug release from the tablet matrix, 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. 1.6 displays a schematic presentation of the drug release process from a tablet by disintegration and dissolution (Wells & Rubenstein, 1976:629).

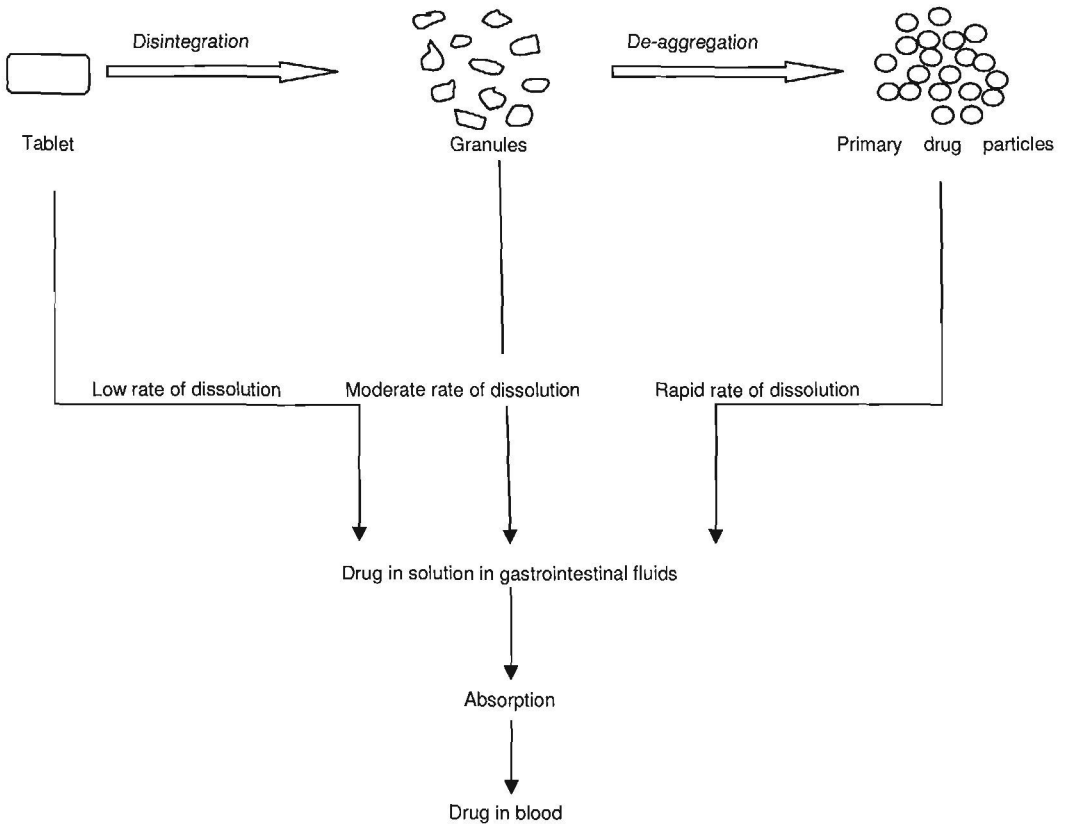


Fig. 1.6: Schematic illustration of the disintegration and dissolution process (Wells & Rubenstein, 1976:629).

A disintegrant is included in formulations to ensure disintegration when the tablet comes into contact with a liquid. Ideally, the tablet should break up into smaller fragments enlarging the surface area, thereby speeding the dissolution process.

Disintegrants mainly have two working mechanisms:

1. Disintegrants that facilitate water uptake into the intact tablet through pores and 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.

2. Disintegrants that will rupture the tablet. Rupturing of tablets occurs when the disintegrant itself swells and breaks the tablet (Alderborn, 2002:406).

Disintegrants are commonly used in direct compression as well as in wet granulation, examples being:

- sodium starch glycolate (Explotab®, Primojel®),
- crosscarmellose sodium (Ac-di-sol®), and
- crosspovidone (Kollidon® CL).

1.5.6 Lubricants

During compression, strong forces may develop between the tablet and the die wall. These forces may lead to friction, which is minimized by adding a lubricant. The function of the lubricant is to ensure that tablet formation and ejection can occur with low friction between the solid and the die wall. Lubricants act by forming an intermediate layer between the tablet surface and the die wall (Shah & Mlodozeniec, 1977:1377).

Usually, solid state lubricants acting as boundary lubricants are used. Magnesium stearate is an example of a boundary lubricant (Marshall & Rudnic, 1991:379). Lubricants acting on a hydrodynamic mechanism, i.e. fluid lubrication, where two moving surfaces are separated by a finite and continuous layer of fluid lubricant is also possible. Since adherence of solid lubricants to the die wall is more than that of fluid lubricants, solid lubricants are more effective and more frequently used (ANON, 2006b:www.pharmpedia.com).

Since lubricants are primarily required to act on the tooling or material interface, lubricants should be incorporated in the final mixing step, after granulation is complete. When hydrophobic lubricants are added to a granulate, they form a coating around the individual particles (granules), which may cause an increase in the disintegration time and a decrease in the drug dissolution rate. The presence of lubricants may also result in a less cohesive and mechanically weaker tablet, because it may interfere with particle-particle bonding (ANON, 2006b:www.pharmpedia.com). Shah and Mlodozeniec (1977:1381) found that the duration of mixing has major effects on tablet disintegration. Longer mixing leads to prolonged disintegration times. This may be attributed to the formation of a hydrophobic surface during mixing.

Surface area is an important parameter influencing lubricant efficiency. Lubricants with a high surface area are more sensitive to changes in mixing time than lubricants with a low surface area. *Therefore lubricant mixing time should be kept to a minimum* (Shah & Mlodozeniec 1977:1381).

Consideration of the tooling used to compress tablets is an important factor when deciding on the type and concentration level of lubricant to be employed. Additional lubricant is often

added to the tablet formulations that are to be compressed with curved face punches. Furthermore, the amount of lubricant increases as the particle size of the granulation decreases, but its concentration should not exceed 1% w/w (ANON, 2006b:www.pharmpedia.com).

Inadequate lubrication produces binding which can result in tablet machine strain and can lead to damage of lower punch heads, lower cam track, die seats and the tooling itself. When lubrication is inadequate, tablets are often scratched on the sides and/or exhibit fractured top edges. With excessive binding to the die wall, the tablet may be cracked and fragmented by ejection.

Lubricants can be classified according to their water solubility i.e. water insoluble and water soluble. Selection of the lubricant depends partly on the mode of administration, type of tablet, desired disintegration and dissolution properties, physicochemical properties of granules or powder and cost (ANON, 2006b:www.pharmpedia.com).

1.5.7 Glidants

Glidants are added to the formulation to improve the flow properties of the powder mixture which is to be fed into the die cavity and aid in particle rearrangement within the die during the early stages of compression. Starch is an example of a glidant and is popular because it possesses disintegration properties as well. Talc is another example, but its concentration should be limited, because it has a retardant effect on the dissolution-disintegration profile (ANON, 2006b:www.pharmpedia.com).

Silaceous materials like colloidal silica i.e. Syloid®, pyrogenic silica (0.25%), hydrated sodium silioaluminate (0.75%) are also successfully used to induce powder flow.

Glidants act by interposing their particles between those of the material and lower the overall interparticulate friction of the system by virtue of their reduced adhesive tendencies. Similar to lubricants, they are required at the surface of feed particles and they should be in a fine state of division and appropriately incorporated in the mixture (ANON, 2006b: www.pharmpedia.com).

1.5.8 Binders

The use of direct compression is restricted mainly to formulations containing a low amount of active ingredient. The properties of the mixture are mainly characterized by the additives in the formulation. When the amount of active ingredient becomes greater, the problem of insufficient binding of the formulation particles arises. It is difficult to obtain strong tablets

that can withstand handling and processing, therefore, binders are used to improve binding in tablets (Nyström *et al.*, 1982; Hwang & Parrott, 1993).

Binders provide necessary bonding properties in formulations. It increases adhesiveness and the mechanical strength of the tablet, but as a result prolong disintegration time and dissolution rate. Usually binders are incorporated in a formulation using wet granulation, but it can be used in direct compression as well. The concentration of binder in a direct compression formulation is usually much higher than in a wet granulation formulation. Binders added as dry powders are generally less effective than when added as solutions (Nyström *et al.*, 1982:209-210).

Polyvinylpyrrolidone (PVP) is most commonly used in the pharmaceutical industry as a binder and coating material in tablets. It can also be applied as a viscosity-increasing agent in liquid formulations. Other examples include:

- alginic acid,
- carboxymethylcellulose codium,
- galenIQ™ (ANON, 2006c:www.aicma.com).

Polyvinylpyrrolidone (PVP) and derivatives are marketed as Kollidon®. The Kollidon® range produced by BASF is the most popular binder used by pharmaceutical companies. All the Kollidon® grades are pharmaceutical pure, free-flowing and white or yellowish-white powders with different particle sizes (Bühler, 2003:17). One of the salient features of the Kollidon® grades is their universal solubility, which extends from extremely hydrophilic solvents (water) to hydrophobic liquids (butanol) (Bühler, 2003:19). Fig. 1.7 displays viscosity curves for all the water soluble grades. The viscosity of aqueous solutions of the Kollidon® grades depends on their average molecular weight. From fig. 1.7 the considerable differences in viscosity between solutions of the different Kollidon® grades in water as function of their concentration can be seen. A 20% w/w aqueous solution of Kollidon® 12PF shows hardly any visible difference to pure water, whereas a 20% w/w solution of Kollidon® 90F in water provides high viscosities between 6 and 25 Pa s (Bühler, 2003:20). The molecular weight of Kollidon® is expressed in terms of its K-value. It is calculated from the relative viscosity in water and always forms part of the commercial name (Bühler, 2003:24). Kollidon® 90F possesses the highest viscosity (300-700 mPa s) and therefore K-value (85-95). This means Kollidon® 90F possesses a high molecular weight.

The viscosity of alcoholic solutions of Kollidon® is significantly higher than that of aqueous solutions (Bühler, 2003:26).

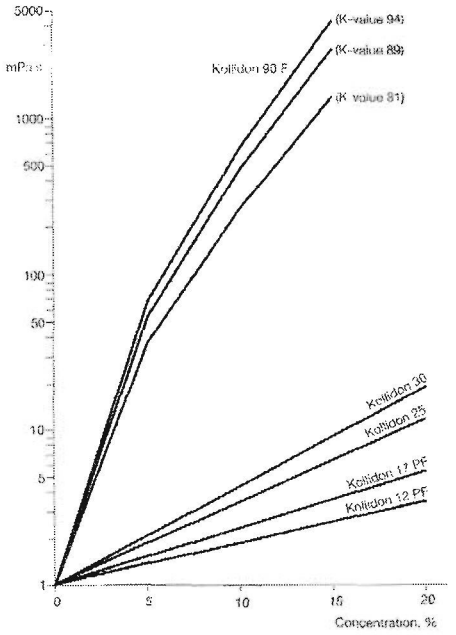


Fig. 1.7: Viscosity curves for the water soluble Kollidon® grades (Bühler 2003:21).

1.5.8.1 General properties of the Kollidon® range

Characteristics of the Kollidon® range include the following:

- solubility in all conventional solvents,
- adhesive and binding power,
- film formation,
- affinity to hydrophilic and hydrophobic surfaces,
- ability to form complexes,
- availability in different average molecular weights, and
- thickening properties (Bühler, 2003:78).

1.5.8.2 Main applications of povidone in the pharmaceutical industry

Povidone is widely used in the pharmaceutical industry, mostly for its binding properties in tablets. Table 1.4 lists applications for povidone in general.

Table 1.4: Applications of povidone (Bühler, 2003:79).

Function	Pharmaceutical form
Binder	Tablets, capsules and granules
Bioavailability enhancer	Tablets, capsules, granules, pellets and suppositories
Film former	Ophthalmic solutions, tablet cores and medical plastics
Solubilizer	Oral, parenteral and topical solutions
Taste masking agent	Chewing tablets and oral solutions
Suspension stabilizer	Suspensions, dry syrups and instant granules
Lyophilisation agent	Injectables
Hydrophilizer	Medical plastics, sustained release forms and suspensions
Adhesive	Adhesive gels and transdermal systems
Stabilizer	Enzyme in diagnostics
Intermediate	Povidone-Iodine as active ingredient
Toxicity reduction	Injectables and oral preparations

1.5.9 Soluble polyvinylpyrrolidone (Kollidon® 30 & 90F)

As examples of binders, Kollidon® 30, 90F and VA64 were investigated in this study. Therefore, their properties are discussed briefly in this chapter. The soluble grades of Kollidon® (see table 1.5) are obtained by free-radical polymerization of vinylpyrrolidone in water or isopropanol, yielding the chain structure of polyvinylpyrrolidone. Spray-drying is used in the production of all Kollidon® soluble grades with the exception of Kollidon® 90F, which is dried on a roller because of its high molecular weight (Bühler, 2003:31). The current range of soluble Kollidon® differs from each other by their K-values (see table 1.5). In contrast to the soluble grades of Kollidon® (Kollidon® 30 and 90F) the number 64 in the trade name, Kollidon® VA64, is not a K-value, but the mass ratio of the two monomers, vinylpyrrolidone and vinyl acetate (Bühler, 2003:199).

The viscosity of aqueous solutions of the Kollidon® grades depends on their average molecular weight. The viscosity, e.g. of Kollidon® 30 in water at concentrations up to 10% w/w, remains nearly uninfluenced by the change in temperature.

Table 1.5: Typical viscosity values for aqueous solutions of Kollidon® grades (Bühler, 2003:22).

Product	K-value range	Typical viscosity range (mPa s)
Kollidon® 12PF	11-14	1.3-2.3
Kollidon® 17PF	16-18	1.5-3.5
Kollidon® 25	24-27	3.5-5.5
Kollidon® 30	28-32	5.5-8.5
Kollidon® 90F	85-95	300-700

All the Kollidon® grades are hygroscopic substances and depending on the application, this characteristic can be an advantage or disadvantage. Hygroscopicity is an advantage when Kollidon® is implemented as binder or adhesive, and is one of the few parameters that are largely independent of the molecular weight. When Kollidon® is used as film-coating agent, it could be a disadvantage (Bühler, 2003:32-33).

1.5.10 Vinylpyrrolidone-vinyl acetate copolymer (Kollidon® VA64)

Water soluble vinylpyrrolidone-vinyl acetate copolymer contains two monomers in the ratio of 6:4, namely: vinylpyrrolidone and vinyl acetate. It is produced by free-radical polymerization, i.e. the same process used to manufacture the soluble Kollidon® grades. Vinyl acetate is insoluble in water and organic solvents (ethanol or isopropanol) are used for the synthesis of this monomer. As mentioned earlier, the number in the trade name, 64, is not the K-value, but the mass ratio of the two monomers (Bühler, 2003:199).

The hygroscopicity of Kollidon® VA64 depends on the application. When Kollidon® VA64 is used as binder and granulating agent in tablets, a certain degree of hygroscopicity is useful whereas it can be problematic when used as film-coating agent. In general, Kollidon® VA64 absorbs about three times less water than povidone (Kollidon® 30) at a given humidity.

Kollidon® VA64 is almost universally soluble and it can be attributed to the two monomers, vinylpyrrolidone and vinyl acetate. It dissolves in extremely hydrophilic liquids such as water and in hydrophobic solvents such as butanol (Bühler, 2003:201).

The applications of Kollidon® VA64 rely mainly on its good binding and film-forming properties, its affinity for hydrophilic and hydrophobic surfaces and relatively low hygroscopicity.

These properties enable Kollidon® VA64 to be used in:

- the production of granules,
- the production of tablets,
- direct compression,
- film-coating, and
- film-forming processes (Bühler, 2003:224).

1.5.11 Particle size

In the manufacturing of solid dosage forms, the particle size distribution of excipients such as Kollidon® can play a major role. This applies particularly to direct compression, because in wet granulation Kollidon® is dissolved in the appropriate solvent. Important effects of the particle size include:

- a high proportion of fines spoils the flow properties,
- fine particles produce dust,
- a high proportion of coarse particles leads to de-mixing,
- a coarse particle fraction is unevenly distributed in tablets,
- with high-molecular polymers, a large coarse fraction seriously delays dissolution, and
- coarse particles of a binder demonstrate a weaker binding effect in direct compression (Bühler, 2003:30).

1.5.12 Particle structure

As mentioned previously, all soluble grades of Kollidon®, with the exception of roller dried Kollidon® 90F, are spray-dried powders and therefore, possess typical particle structures of this technology. Fig. 1.8 displays spray-dried Kollidon® 30, which consists of hollow and mainly spherical particles. Fig. 1.9 displays the completely different roller dried Kollidon® 90F particle structure (Bühler, 2003:31) and fig. 1.10 displays the particle structure of Kollidon® VA64. The particles are hollow and spherical, like Kollidon® 30, but almost all broken (Bühler, 2003:206).

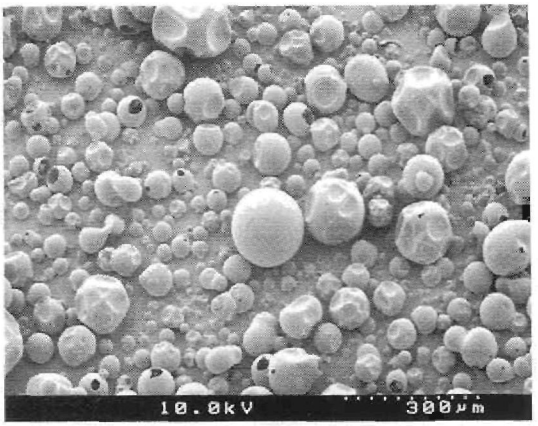


Fig. 1.8: Particle structure of Kollidon® 30 (Bühler, 2003:31).

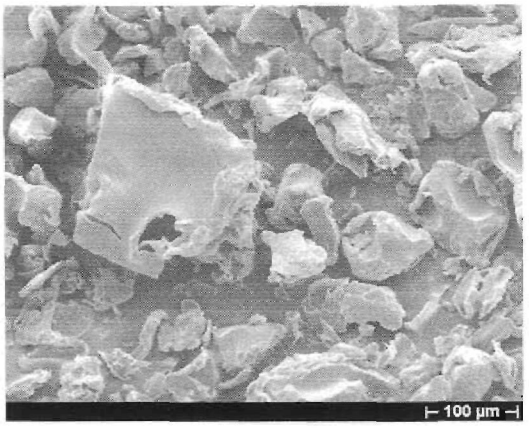


Fig. 1.9: Particle structure of Kollidon® 90F (Bühler, 2003:32).

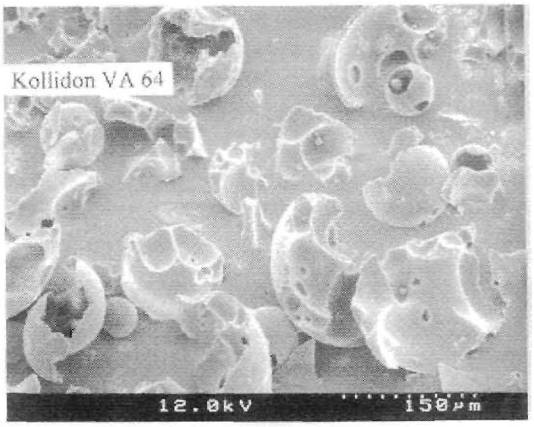


Fig. 1.10: Particle structure of Kollidon® VA64 (Bühler, 2003:206).

1.5.13 Stability and storage

The soluble Kollidon® grades, with exception of Kollidon® 90F, have very good storage stability in the pure form. The lower stability of Kollidon® 90F, compared to other grades, is due to a slow decrease in the K-value. If packaging remains sealed, peroxide levels are lower and the K-value decreases much slower (Bühler, 2003:45-46).

1.6 Factors influencing bioavailability

As discussed in section 1.5.5, disintegration and dissolution are critical to bioavailability. Some of the factors influencing dissolution rates from solid dosage forms are:

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

1.7 Effect of moisture on stability

Moisture has a major effect on the stability of drugs and pharmaceutical excipients. Internal and external moisture are a major problem and must be considered. Daoust & Lynch (1963:26) considered the following reasons:

- Water absorption by drugs and excipients is not always reversible and absorbed moisture may not easily be removed during drying.
- Moisture can affect the way in which a system accepts aqueous granulating solutions.
- The moisture content and rate of moisture uptake are functions of temperature and humidity and should be considered.
- Moisture content in a blend affects the tableting characteristics of the blend.
- Hygroscopicity data can aid in the design of tablet manufacturing areas.

- Moisture-sensitive drugs should not be combined with hygroscopic excipients.
- Packing/storing materials should be chosen to suit the product.

1.8 Mixing

Mixing is a critical step in the production process. Efficient mixing will contribute to ensuring that a patient will be taking the correct dosage of active ingredient each time a tablet is taken. Hence, it is very important to obtain homogeneous powders during the mixing process. Each tablet must be representative of the total mixture, i.e. each tablet must be the same as the previous one.

1.9 Summary and conclusion

Tablets account for about 80% of pharmaceutical preparations and are very popular for its numerous advantages. Wet granulation is the oldest technique used to produce solid pharmaceutical dosage forms, but it is still widely used and is a very popular technique. Drawbacks, however, for this technique are cost, energy and labor intensity. Despite this, it is a commonly used process by many pharmaceutical industries worldwide, especially when certain dosage forms contain a large amount of active ingredient. Direct compression is ineffective when the concentration of active ingredient incorporated in the tablet is high, because binding properties in the tablet becomes a major concern.

Direct compression was developed, but formulations should possess certain properties such as compressibility, flow properties and anti-adherent qualities. It should also favor disintegration of tablets and posses low friability. This opened the next door to develop excipients for direct compression. Despite this, wet granulation is very popular and binders exist that can be used as a dry binder as well as a wet binder. The binder is dissolved in an appropriate solvent to produce a binder solution that is added to a filler such as lactose. Wet massing produce wet granules and the product must be dried. Dry massing is the next step and then mixing with the rest of the excipients. It is a long and time consuming process but very effective to increase powder flow properties.

Chapter 2

EXPERIMENTAL METHODS USED IN THE STUDY

2.1 Introduction

The formulation of a solid dosage form requires precise process control over the preparation of the powder to ensure a homogenic tablet. Different excipients are added to a formulation and care should be taken when adding and mixing the excipients to ensure uniformity to obtain acceptable tablets. This chapter deals with the selection of the drug and excipients as well as the procedures followed to characterize and evaluate the properties of the powders and tablets.

2.2 Materials

2.2.1 Active ingredient

Furosemide (Lot no. 90111045) was the drug of choice. It has a pKa value of 3.6 and this drug exhibits poor dissolution due to low water solubility and water wettability (Boles Ponto & Schoenwald, 1990:305). This may be due to the cohesive properties of the powder particles leading to agglomeration (De Villiers, 1988:39; De Villiers *et al.* 1993:160). For this drug, dissolution is often the rate-determining step during absorption and therefore, disintegration of the tablet definitely affects the rate and extent of dissolution (Marais, 2000:60).

Due to the very cohesive behavior and the resulting influence thereof on dissolution, it was hypothesized that the influence of formulation variables could easily be evaluated with furosemide and this was the reason for selecting furosemide as the model drug for this study.

2.2.2 Filler

Lactose monohydrate was used in this study, because it is water soluble and is one of the oldest and cheapest fillers, still in use today. Lactose was one of the first fillers to be modified into a direct compressible filler. It is readily available and very cost-effective.

2.2.3 Binders

The different binders that were used in the study are shown in table 2.1. The different binders were produced and supplied by BASF (South Africa).

Table 2.1: The different binders used in the study.

Binder	Lot number	Manufacturer
Kollidon® 30	06397736W0	BASF Aktiengesellschaft, Ludwigshafen, Germany
Kollidon® VA64	26460375L0	BASF Aktiengesellschaft, Ludwigshafen, Germany
Kollidon® 90F	39801647G0	BASF Aktiengesellschaft, Ludwigshafen, Germany

The Kollidon® range from BASF was used in the different formulations at different concentration levels (3, 6 and 10% w/w) to determine which binder and concentration thereof proves to be the most effective. Wet granulation was employed to prepare a granulate rendering a compressible powder.

2.2.4 Lubricant

Magnesium stearate (Lot no. 357631169681) is most commonly used in the industry and was employed as lubricant in this study. It accounts for almost 80% of industrially produced solid dosage forms and it is popular because of its ability to reduce friction between punches and the wall of the die during ejection of the tablet. Magnesium stearate is effective in very low concentrations, but care should be taken during formulation, because magnesium stearate is hydrophobic and could influence tablet properties such as the crushing strength, disintegration and dissolution (Shotton & Lewis, 1964:119T; Ganderton, 1969:9S; Shah & Mlodozenic, 1977:1377; Bolhuis *et al.*, 1980:15-16; Sheskey *et al.*, 1995:1). Mixing times can also be influential when formulating with magnesium stearate (Kikuta & Kitamori, 1994:353-354).

2.2.5 Disintegrant

Explotab® (Lot no. 91G27797) was used as disintegrant. Explotab® is a superdisintegrant and ruptures the tablet as soon as it comes in contact with moisture. Disintegrants with fast action are most useful in formulations containing sparingly water soluble drugs and insoluble fillers/binders (Gissinger & Stramm, 1980:189).

2.3 The granulation process

Wet granulation was employed to produce granules which incorporated the different binders. An amount of Lactose monohydrate was weighed and mixed with 50% w/w of the total amount (1% w/w) of Explotab® in a Turbula mixer (Turbula, Type T2C, Serial no. 741130) for five minutes at a mixing speed of 47 rpm. 50% w/w of Explotab® was mixed intra-granular and 50% w/w extra-granular depending on the formulation in question. To prepare the binder solution, a quantity of the binder (Kollidon® 30, VA64 or 90F), depending on the formulation in question, was either dissolved in ethanol (Kollidon® 30 and VA64) or distilled water (Kollidon® 90F). Distilled water was used to wet Kollidon® 90F because ethanol formed an insoluble complex. The binder solution was added to the powder mixtures and knead until a uniform wet mass was obtained with a mortar and pestle. The wet mass was screened through a 30 mesh sieve to produce coarse granules. The coarse granules were dried in an oven at 37 ± 1 °C for 90 minutes. Kollidon® 90F was dried at 50 ± 1 °C for 90 minutes, because distilled water was used in the binder solution instead of ethanol. The dried coarse granules were screened through a 20 mesh sieve to produce finer granules. The finer granules were mixed with the remainder (50% w/w) of the Explotab® and 0,5% w/w magnesium stearate in the Turbula mixer (Turbula, Type T2C, Serial no. 741130) for five minutes at 69 rpm. A slower mixing speed was used in the first mixing step, because lactose exhibits very poor flow and adheres to the walls of the glass container resulting in a non-homogeneous mixture. Mixing in the second step could be done at a higher speed, because the granules exhibited very good flow and did not adhere to the glass wall.

2.4 Powder characteristics

2.4.1 Introduction

As described in section 2.3, wet granulation was implemented to produce granules incorporating the different binders. The granules were mixed with a lubricant and disintegrant producing a compressible powder. After mixing, the properties of the different powders were determined by means of different physical characterization tests. Powder flow is one characteristic of powders and is essential in tableting, because it affects tablet weight variation and in the end the dosage of active ingredient contained in each tablet. Thus, it is absolutely critical for a powder to possess acceptable flow behavior in order to obtain consistent dosages in each tablet. Although there exist different tests, powder properties can be described in terms of angle of repose and flow rate.

2.4.2 Powder density

Density is the weight to volume ratio of a substance. Tapped and poured density are used to define powder density and can be expressed in $g.cm^{-3}$ ($g.ml^{-1}$). Equation 2.1 can be used to calculate density.

$$D = \frac{m}{V} \qquad 2.1$$

Where D is density ($g.cm^{-3}$), m is mass (g) and V volume (cm^{-3}).

2.4.2.1 Bulk density (p_b)

The bulk density of a powder can be defined as the weight to volume ratio it occupies. In this density ratio, the volume of particles as well as the volume of the voids (air spaces) between particles are included. Bulk density is essentially the same as poured density. The bulk volume of each powder was determined using a tared 100 cm^{-3} measuring cylinder. The powder was poured into the cylinder, thus the bulk volume was 100 cm^{-3}. The amount of powder was weighed and the bulk density calculated by equation 2.2.

$$p_b = \frac{w}{V_b} \qquad 2.2$$

Where p_b represents bulk density ($g.cm^{-3}$); w is the weight (g) and V_b is the volume (cm^{-3}) of the powder.

2.4.2.2 Tapped density

Tapped density accounts for the settlement of particles of the powder during handling or vibration. Tapped density was measured for each powder. The powder was poured into a 100 cm^{-3} cylinder and weighed. The cylinder was placed on a vibrating surface (Fritsh® Analsette, Germany, Type 03.502, Serial no. 6331) and vibrated at an amplitude of 7 for ten minutes. The volumes of the powders were noted and the average tapped density for each powder calculated according to equation 2.2.

2.4.2.3 Compressibility index (Carr's Index)

Approximately 100 cm^{-3} of powder was gently poured into a tared graduated cylinder and the initial volume and weight of the material was noted. The cylinder was vibrated until the volume remained constant and the final volume was noted. Lower percent compressibility values represent better flow.

The initial bulk density (D_0) and the final bulk density (D_f) can be calculated. Another method was developed by Carr (British Pharmacopoeia, 2007:A406):

$$\%Compressib\,ility = \frac{D_f - D_0}{D_f} X100 \qquad \textbf{2.3}$$

Where D_f represents final density and D_0 represents initial density.

In table 2.2 the relationship between compressibility and powder flow can be seen.

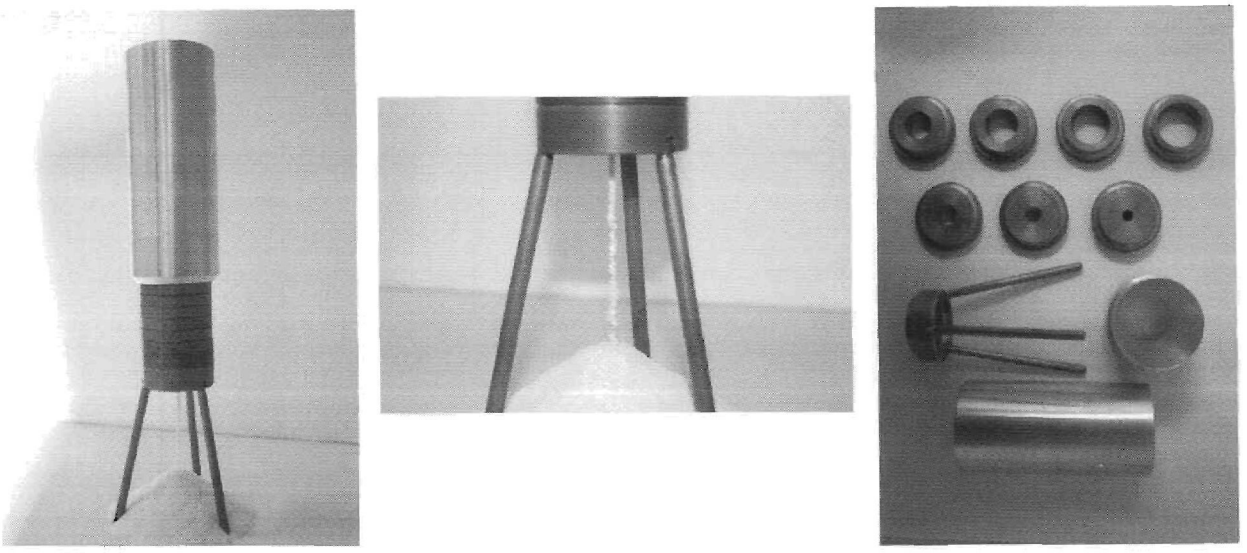
Table 2.2: Relationship between powder flow and %-compressibility (Staniforth, 2000:613).

% Compressibility	Flow Description
5-12	Excellent
12-18	Good
18-23	Fair
23-28	Poor (very fluid powders)
28-35	Poor (very cohesive powders)
35-40	Very poor
>40	Extremely poor

2.4.3 Angle of repose

Angle of repose is one of the indirect methods to qualify flow properties of powders. A particle will start sliding when the angle of inclination is large enough to overcome frictional forces between adjacent particles (Staniforth, 2002:200). Angle of repose has been used because of its relationship with inter-particle cohesion. There are many different methods determining the angle of repose and they may produce different values (Staniforth, 2000:610). A significant disadvantage of angle of repose is the fact that different methods are used as well as the handling of the samples prior to measurement may produce different values. For these reasons, angle of repose tends to be variable and are not always representative of flow under specific conditions (Staniforth, 2000:610). Despite these difficulties, this method continues to be used in the pharmaceutical industry (British Pharmacopoeia, 2007:A405).

The apparatus used, consisted of rings with different orifice sizes (fig. 2.1c) stacked onto each other to form a cylindrical tower (fig. 2.1a) rendering a decrease in orifice size. The diameter of the opening at the bottom was 4 mm. Approximately 100 g of powder was poured into the cylindrical tower (Instrument Makers, Potchefstroom campus, Northwest University).



(a) (b) (c)

Fig. 2.1: Apparatus used to measure angle of repose and flow rate.

The powder had to discharge through the hole (orifice) to form a cone-like heap (fig. 2.1a and b) underneath on a horizontal surface. The cylinder was at a fixed height of 8 cm and the procedure was repeated three times for each powder. The height (*h*) and diameter (*d*) of the discharged heap were measured and using equation 2.4, the angle of repose was calculated.

$$Tan\Phi = \frac{h}{0.5d} \qquad \textbf{2.4}$$

Fig. 2.2 illustrates how the angle of repose was measured and table 2.3 illustrates the relationship between angle of repose and flow properties.

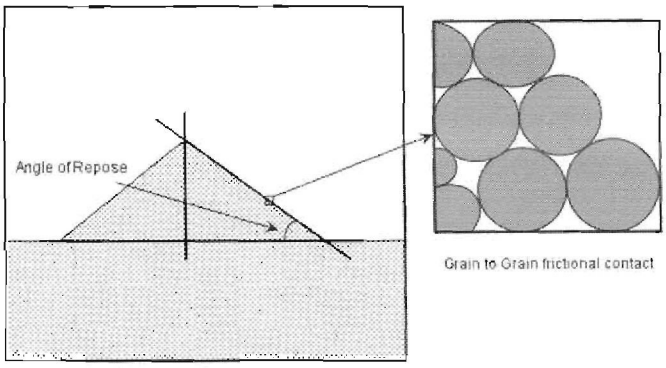


Fig. 2.2: Illustration of measurement of angle of repose.

Table 2.3: The relationship between the angle of repose and flow properties (British Pharmacopoeia, 2007:A405).

Flow Property	Angle of Repose (°)
Excellent	25-30
Good	31-35
Fair – aid not needed	36-40
Passable – may hang up	41-45
Poor – must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

2.4.4 Flow rate

The flow rate of the powder through a fixed orifice (4 mm – same as angle of repose) was measured with the same equipment (see section 2.4.3 and fig. 2.1) by placing it on a scale (Mettler® Toledo, serial no. PB303-S). A computer connected to the apparatus was used to measure the amount of powder discharged in grams per second ($g.s^{-1}$). Balance® Link was the program installed on the computer to determine flow rate. Approximately 25 g of powder was poured into the cylinder closing the orifice gap at the bottom. The time it took for the powder to discharge from the cylinder upon opening of the gap was noted to determine the flow rate through the orifice. The computer calculated the amount of power discharged each second in grams (g). The density of the powder was measured by means of bulk and tapped density, described in section 2.4.2.1-2.4.2.2. The conversion from grams per second ($g.s^{-1}$) to volume per second ($cm^{-3}.s^{-1}$) can be done with equation 2.1.

2.4.5 Particle size distribution

Determination of particle size distribution was done by means of sieve fraction analysis. The openings in the screens are described by a U.S. mesh number which indicates the number of strands per inch. Each sieve is assumed to collect particles of a certain diameter. The particle diameter would be slightly bigger than the screen opening, collecting only the particles bigger than the specific screen opening. Smaller particles fall through the screen onto the sieves with smaller screen sizes.

Approximately 100 g of powder was placed on a selection of sieves to determine sieve fractions of the produced granules. A 500, 425, 300, 250, 180, 125, 106, 90 mesh sieve and the pan were used. After sieving for ten minutes at an amplitude of 6 (Fritsh® Analsette, Germany, Type 03.502, Serial no. 6331), the weight of powder on each sieve was measured.

2.5 Determining tablet properties

2.5.1 Compression of tablets

Tablets were compressed on a Cadmach® (AHMEDABAN-INIA, TYPE: SSF3, Serial No., 105/2/90) single station (eccentric) press (fig. 2.3 illustrates a schematic drawing of a single station tablet press). Flat face punches with a diameter of 8 mm were used. The die volumes for all formulations were kept constant.

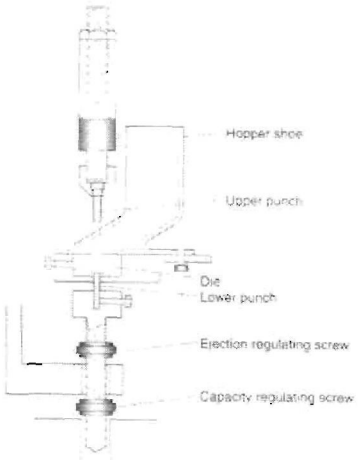


Fig. 2.3: Schematic drawing of a single-station tablet press (Alderborn, 2002:400).

Two different compression settings (stroke length 1 and 4) were used to determine filler compressibility (hardness and friability) and to evaluate how the binders, incorporated in the powder, were influenced by different compression pressures. Compression force was

manipulated by movement of the upper punch. Since the die volume was kept constant, the depth of movement of the upper punch (represented by a number ranging from 0-35, provided on the tablet press) was altered to obtain different compression pressures (stroke length 1 and 4). This ensured higher compression and would represent higher crushing strength values and possibly slower disintegration (see section 2.5.3 and 2.5.5).

The first ten tablets of each batch were ignored and disposed of. The tablets were transferred to glass containers, sealed airtight with Parafilm® and locked tight with screw caps.

2.5.2 Weight variation

Twenty tablets from each formulation were randomly selected and dusted with an art brush and weighed on a Mettler® (Mettler® Toledo, serial no. PB303-S) analytical balance. The average weight, standard deviation (SD) and the percentage relative standard deviation (%RSD) were calculated using equation 2.5.

$$\%RSD = \frac{SD}{Average} X100 \qquad \textbf{2.5}$$

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

2.5.3 Crushing strength

Crushing strength of ten tablets, which was randomly selected, was measured from each formulation using a PHARMA TEST tablet test unit (model PTB 311, Pharma Test, Switzerland).

2.5.4 Friability

For each formulation ten tablets were randomly selected, dusted with an art brush to remove excess dust and then weighed. The ten tablets were placed in the drum of a Roche® Friabilator (see fig. 2.4). The lid was closed and rotation started for four minutes at 25 rpm. After completion, the sample was removed, dusted and weighed.

The %-friability (weight loss) was calculated using equation 2.6.

$$\%friability = \frac{m_1 - m_2}{m_1} X100 \qquad \textbf{2.6}$$

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

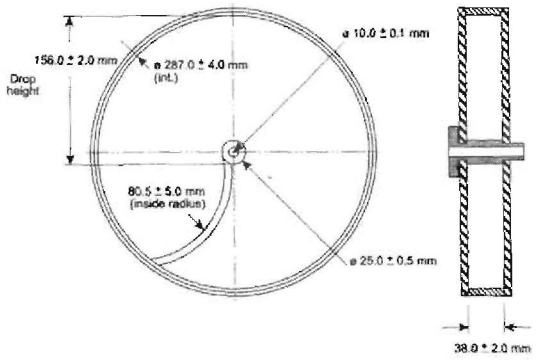
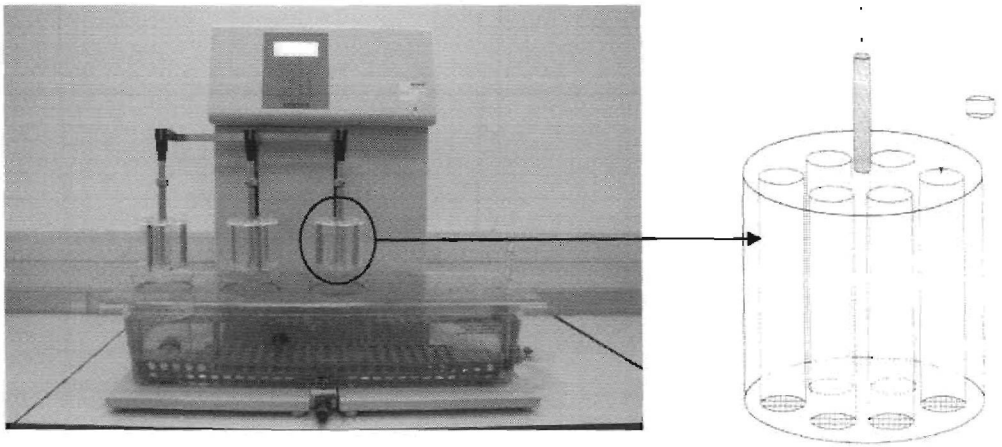


Fig. 2.4: Schematic drawing of the Roche® friabilator (British Pharmacopoeia, 2000:A299).

2.5.5 Disintegration

Disintegration tests were conducted using the standard ERWEKA® GmbH (Type ZT503, Heusenstamm, Germany) test unit filled with distilled water operating at 37 ± 0.5 ℃ and fitted with a thermostat to regulate temperature (see fig. 2.5a). In fig. 2.5b the glass tubes used for disintegration can be seen. For each formulation six tablets were randomly selected and the disintegration times were determined.



(a) (b)

Fig. 2.5: A picture of the ERWEKA® GmbH disintegration unit (a) and the schematic drawing of the disintegration tubes (b) (Alderborn, 2003:419).

2.6 Dissolution studies

2.6.1 Apparatus

Dissolution measurements were done with a six-station dissolution apparatus at 37 ± 0.5 °C (ERWEKA®, model DT6R, Heustenstramm, Germany) using standard USP specified paddles, fitted with a thermostat and variable speed synchronous motor. Fig. 2.6 is an illustration of the paddles used in the study.

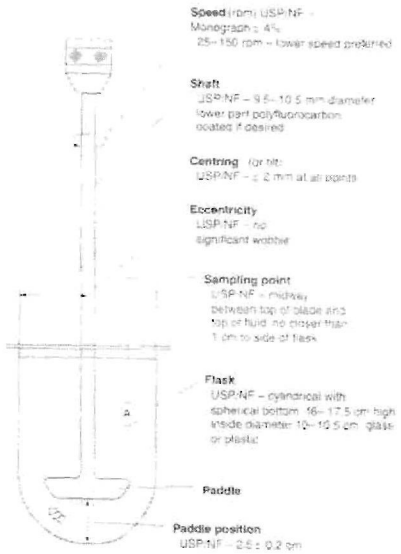


Fig. 2.6: Schematic drawing of dissolution based on rotating paddle method (Alderborn, 2002:421).

2.6.2 Settings and conditions

Furosemide is a weak acidic drug (pKa 3.6). The solubility of this sparingly water soluble drug is pH-dependent. Studies showed that the pH of the dissolution medium played an important role in detecting differences between good and poor formulations (Rubenstein & Price, 1977:5P). Studies from Prasad *et al.* (1982:85) showed that as the pH of the dissolution medium was increased away from the pKa of the drug (i.e. 3.6-3.9), the differences in dissolution decreased and at pH 7.4 it almost disappeared.

Dissolution studies were conducted in 900 cm^3 0.1 M HCl at a temperature of 37 ± 0.5 °C (regulated by the thermostat) and at a rotational speed of 75 rpm (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 motor was started and allowed to reach the required

speed (75 rpm). As soon as the motor reached the required speed, the tablets were introduced and dropped directly into the medium at time zero (t = 0). At times t = 1, 2, 4, 5, 6, 10, 20, 30, 60 and 90 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 through sampling was replaced with an equal amount 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 2.6.6).

The UV-absorbencies of the samples were measured in duplicate at 277 nm against 0.1 M HCl as blank, using a UNICAM-spectrophotometer (model Helios α, Unicam Ltd, Cambridge, UK) fitted with a sipper and 1 cm^3 flow-through quartz cell.

The furosemide concentration in the withdrawn samples was determined from standard curves by means of linear regression.

2.6.4 Standard curve

Standard curves were constructed every day prior to dissolution testing. Standard solutions with concentrations ranging from 2-40 $\mu g.cm^{-3}$ were prepared from a stock solution containing 50 mg furosemide dissolved in ± 70 ml absolute ethanol and made up with 0.1 M HCl to 250 cm^3. The UV-absorbencies of the standard solutions were determined spectrophotometrically at 277 nm against 0.1 M HCl as blank. The absorbencies were plotted against concentration and the best straight line through the data was drawn using linear regression. All standard curves exhibited a Beer's law relationship in the concentration range employed, with correlation coefficients (r^2) > 0.999.

2.6.5 Calculations

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

2.6.6 Dissolution data

The amount of furosemide dissolved ($mg.cm^{-3}$) at each sampling time was calculated using equation 2.7, whereas equation 2.8 was used to calculate the correction for the drug lost through sampling.

$$x = \frac{y^* - c}{1000m} \qquad \textbf{2.7}$$

Where y^* is the corrected absorbency (from equation 2.8); x is the drug concentration ($mg.cm^{-3}$) and m and c are the slope and y-axis intercept respectively obtained from the standard curve.

$$y_n^* = y_n + \frac{V_s}{V_m} \cdot \sum^{n-1} y^* \qquad \textbf{2.8}$$

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 dissolved (in $mg.cm^{-3}$) as function of time (minutes) and are the means of four runs for each formulation.

2.6.7 Dissolution parameters, DR_i and AUC

The initial slope of the dissolution curve between t_0 and t_6 was suggested to be a fair estimate for the initial dissolution rate of furosemide (DR_i) from the different tablet formulations, whereas the area under the dissolution profile up to 90 minutes (AUC) would be an indication of the extent of drug dissolution.

The DR_i ($mg.cm^{-3}.min^{-1}$) of the furosemide from each tablet formulation at the specific compression pressure (stroke length for that formulation) was determined from the slope of the dissolution curve between t_0 and t_6, whereas the AUC ($mg.min.cm^{-3}$) between t_0 and t_{90} was determined using the trapezoidal rule, which is given by equation 2.9.

$$AUC = 0.5X \sum_{t=n}^{t=0} (t_n - t_{n-1})(c_n = c_{n-1}) \qquad \textbf{2.9}$$

Where t_n-t_{n-1} is the time difference between two consecutive sampling times and c_n and c_{n-1} is 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 Statistical evaluation of the experimental data

Statistical analysis was performed using STATISTICA (data analysis software system) version 7 from StatSoft, Inc. (2004) and the SAS system for Windows release 9.1 TS Level 1M0 Copyright© 2002-2005 by SAS Institute Inc. A 95% confidence level ($p < 0.05$) was considered satisfactory for indicating significant differences. A three-way analysis of variance (i.e. ANOVA), followed by two-way and one-way ANOVA's, depending on the interactions between the factors compression force (two levels), binder concentration (three levels) and binder type (two levels). Tukey multiple comparison tests were conducted to compare the three levels of binder concentration (% w/w) and binder type.

2.7 Summary and conclusion

The methods for the preparation of different granulate formulations containing lactose (filler), Kollidon® (binder), Explotab® (disintegrant) and magnesium stearate (lubricant) are given. Methods for the evaluation of powder characteristics in terms of flow rate, angle of repose, compressibility and particle size distribution are also presented. Furthermore, methods for the characterization of tablets prepared from the different granulate (powder) mixtures are also given. These tests included weight variation, mechanical strength (crushing strength and friability) and disintegration. The method for dissolution testing of tablets incorporating furosemide as model drug is also presented.

Chapter 3

CHARACTERIZATION OF POWDER PROPERTIES

3.1 Introduction

To produce tablets successfully, the pharmaceutical process is dependent on the development of suitable excipients that are free-flowing, highly compressible, soluble, physiologically inert and chemically compatible with active ingredients. The physicochemical properties of fillers or binders is the main determinant affecting the physical properties of tablets. Where the filler or binder comprises more than 80% of the tablet composition, these properties mainly determine drug release and the dissolution of the active ingredient. Furthermore, it is well known that the physical properties of the primary particles influence the interaction between particles under load or pressure. It is, therefore, essential to understand and describe particle properties such as shape and size of the filler or binder and how it would affect flow and binding properties of the material.

This chapter deals with powder properties such as angle of repose, powder flow, compressibility and tablet weight variation to determine their inherent physical properties and their contribution to the properties of the tablet. At the end these results are used to evaluate binder properties.

3.2 Powder properties

The powder properties were determined as described in sections 2.4.2-2.4.5 and 2.5.2. Powder mixtures were characterized with respect to the following:

- angle of repose,
- sieve fraction analysis,
- flow rate,
- compressibility (bulk and tapped density), and
- tablet weight variation (%RSD).

3.2.1 The angle of repose

Angle of repose is very useful when determining the flow properties of powders. Particle size, shape and density play a major role when evaluating angle of repose. Cohesion and adhesion of particles influence its ability to flow, as well as the angle of repose. In general, fine particles are more cohesive than coarse particles and exhibit poor flow and also affects the angle of repose. A smaller angle of repose represents better flow and a bigger angle,

usually compromised flow ability. Particle shape can also influence powder flow as well as the angle of repose. Spheres in general exhibit better flow properties than cubic or irregular shapes, but particles of the same size, but with different shapes can markedly influence flow properties and angle of repose. Spheres' surfaces have minimum inter-particle contact and, therefore, exhibit optimal flow (Staniforth, 2002:200-201).

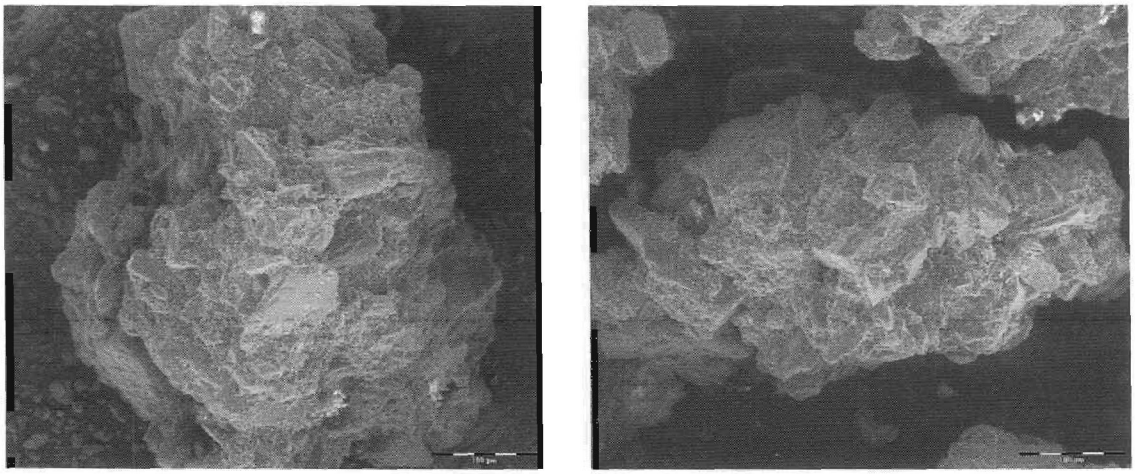
The angle of repose was determined as discussed in section 2.4.3. Table 3.1 presents the results obtained for the different evaluation tests. The formulation containing 10% w/w Kollidon® 90F could not be prepared, due to difficulty during the wet granulation process (The wet powder mass could not be screened through the 30 mesh sieve to produce granules).

Table 3.1: The characteristics of the powders prepared with the different grades of Kollidon® at different concentration levels (% w/w). The values in brackets represent standard deviation (SD) or relative standard deviation (%RSD).

							Compression Setting 1	Compression Setting 4
Concentration (% w/w)	Binder	Angle of Repose (°)	Flow rate ($g.s^{-1}$)	Bulk density ($g.cm^{-3}$)	Tapped density ($g.cm^{-3}$)	% Compressibility	Average tablet weight (%RSD)	
3	Kollidon® 30	39.734 (0.89)	0.397 (0.086)	0.656 (0.02)	0.835 (0.01)	21.500 (0.87)	258.9 (3.69)	259.2 (2.76)
	Kollidon® VA64	38.054 (1.05)	0.481 (0.108)	0.644 (0.00)	0.800 (0.00)	19.667 (0.58)	273.0 (1.00)	273.7 (0.46)
	Kollidon® 90F	40.005 (1.32)	0.448 (0.146)	0.707 (0.01)	0.886 (0.01)	20.167 (0.29)	283.3 (3.38)	278.5 (0.57)
6	Kollidon® 30	38.980 (2.67)	0.413 (0.138)	0.635 (0.01)	0.809 (0.02)	21.500 (0.87)	268.3 (0.74)	257.8 (3.19)
	Kollidon® VA64	38.381 (1.71)	0.510 (0.104)	0.644 (0.00)	0.801 (0.00)	19.667 (0.29)	252.5 (4.23)	258.1 (2.73)
	Kollidon® 90F	39.173 (2.26)	0.753 (0.088)	0.649 (0.01)	0.811 (0.00)	20.000 (1.00)	281.3 (0.79)	266.5 (1.51)
10	Kollidon® 30	39.709 (1.17)	0.525 (0.099)	0.661 (0.01)	0.842 (0.01)	21.500 (0.29)	273.5 (4.63)	284.6 (0.79)
	Kollidon® VA64	39.063 (1.57)	0.490 (0.106)	0.644 (0.01)	0.801 (0.01)	19.667 (0.29)	254.5 (3.56)	245.3 (3.50)
	Kollidon® 90F	*	*	*	*	*	*	*

* The powder containing 10% w/w Kollidon® 90F could not be prepared due to difficulty during the granulation process.

All the formulations exhibited acceptable flow (exhibiting angles in the 36-40° range) as characterized by the angle of repose by the British Pharmacopoeia (2007:A405) (see table 2.3). However, formulations prepared with Kollidon® VA64 exhibited a smaller angle of repose at each binder concentration level (3, 6 and 10% w/w) in comparison to that of the other Kollidon® grades. This can be attributed to the fact that the formulations of Kollidon® VA64 contained granules with a more or less spherical shape (see fig. 3.1a – SEM-images), minimizing the contact area between particles. In contrast with this finding, formulations of Kollidon® 30 exhibited bigger angles of repose, because the granules obtained were irregular and possessed a rectangular shape (see fig 3.1b – SEM-images). These results correlate with findings of Staniforth (2000:604), who suggested that powders consisting of larger particles and uniform particle shape exhibit better flow properties. However, the difference in flow behavior as characterized by angle of repose was not statistically significant (ANOVA, Tukey test, $p > 0.05$).



(a) (b)

Fig. 3.1: The spherical shape of a granule prepared from the powder mixture of 6% w/w Kollidon® VA64 (a), and the rectangular granule shape of powder mixtures prepared with 3% w/w Kollidon® 30 (b).

3.2.2 Sieve fraction analysis

Sieve fraction analysis was conducted to determine the particle size distribution of each formulation. Table 3.3 presents the results of sieve fraction analysis. Results are reported as a percentage (mass on sieve / total mass of powder X 100).

In fig. 3.2-3.4 cumulative distribution frequency diagrams of the different formulations prepared from Kollidon® 30, VA64 and 90F at different concentration levels (3, 6 and 10% w/w) are depicted. All three grades of Kollidon® at the different concentrations rendered

similar results. It was hypothesized that with an increase in binder concentration, a corresponding increase in particle size was to be expected. This was expected because an increase in binder would probably result in stronger binding and, therefore, bigger particles. This hypothesis is confirmed by the cumulative frequency distribution diagrams. In table 3.2 the median particle size for the different binders are reported. These values were obtained form the corresponding cumulative frequency distribution diagrams. For Kollidon® 30 and VA64, the median particle size values confirm the increase in particle size with an increase in binder concentration.

Table 3.2: The median particle size as characterized by sieve fraction analysis for the different binders. The median particle size is reported in terms of sieve size (mesh number). The powder mixture containing 10% w/w Kollidon® 90F could not be prepared due to difficulty during granulation.

Binder Concentration (% w/w)	Kollidon® 30	Kollidon® VA64	Kollidon® 90F
3	260	240	350
6	300	290	340
10	360	330	0

From the cumulative frequency distribution diagrams it is evident that for every concentration (% w/w) employed, Kollidon® VA64 consisted of finer particles than Kollidon® 30 and 90F. Fine particles contribute to a lower compressibility index, rendering a less porous powder and, therefore, a lower degree of tablet weight variation (%RSD). A higher proportion of finer particles can influence powder flow properties negatively, because larger particles tend to flow better (Staniforth, 2000:604). Whether this finer particles of the Kollidon® VA64 mixtures will have a significant effect on tablet weight variation remains to be seen. Kollidon® 90F rendered more coarse particles than Kollidon® 30 and VA64 and whether this will have a significant effect on powder flow needs to be proved.

Table 3.3: Sieve fraction analysis of the powder mixtures of the different Kollidon® polymers.

Average sieve opening	% Weight per sieve								
	3%			6%			10%		
	Kollidon® 30	Kollidon® VA64	Kollidon® 90F	Kollidon® 30	Kollidon® VA64	Kollidon® 90F	Kollidon® 30	Kollidon® VA64	Kollidon® 90F *
0	10.48%	18.27%	12.23%	7.36%	15.59%	13.27%	7.00%	10.99%	None
45	10.65%	8.75%	5.80%	8.89%	6.77%	4.71%	6.46%	6.68%	
98	9.80%	7.36%	5.98%	8.38%	5.57%	5.52%	6.98%	7.14%	
115.5	10.05%	9.18%	6.30%	9.64%	8.12%	7.57%	8.22%	6.72%	
152.5	8.76%	9.08%	7.28%	8.51%	8.49%	7.90%	7.63%	7.61%	
215	6.72%	7.40%	6.22%	7.21%	7.08%	6.40%	6.98%	6.71%	
275	15.14%	14.14%	14.84%	14.83%	15.04%	14.79%	15.17%	15.10%	
362.5	7.41%	6.57%	8.08%	8.78%	7.44%	7.78%	9.17%	8.76%	
462.5	20.99%	19.25%	33.27%	26.40%	25.90%	32.06%	32.39%	30.29%	

* The powder mixture containing 10% w/w Kollidon® 90F could not be prepared due to difficulty during granulation.

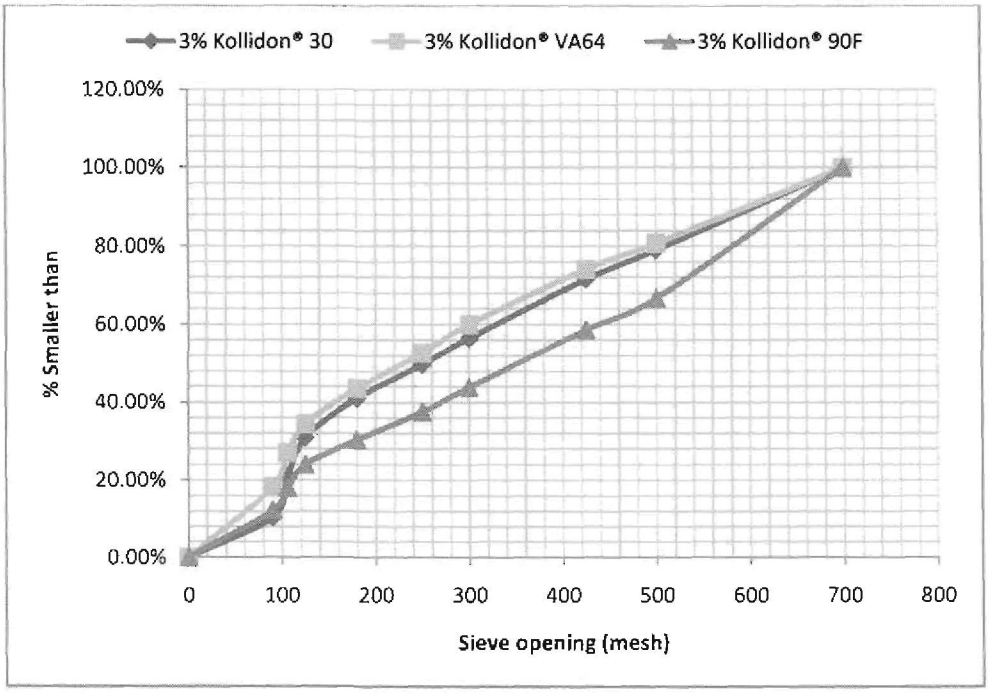


Fig. 3.2: Cumulative distribution frequency diagram of powder mixtures containing 3% w/w binder.

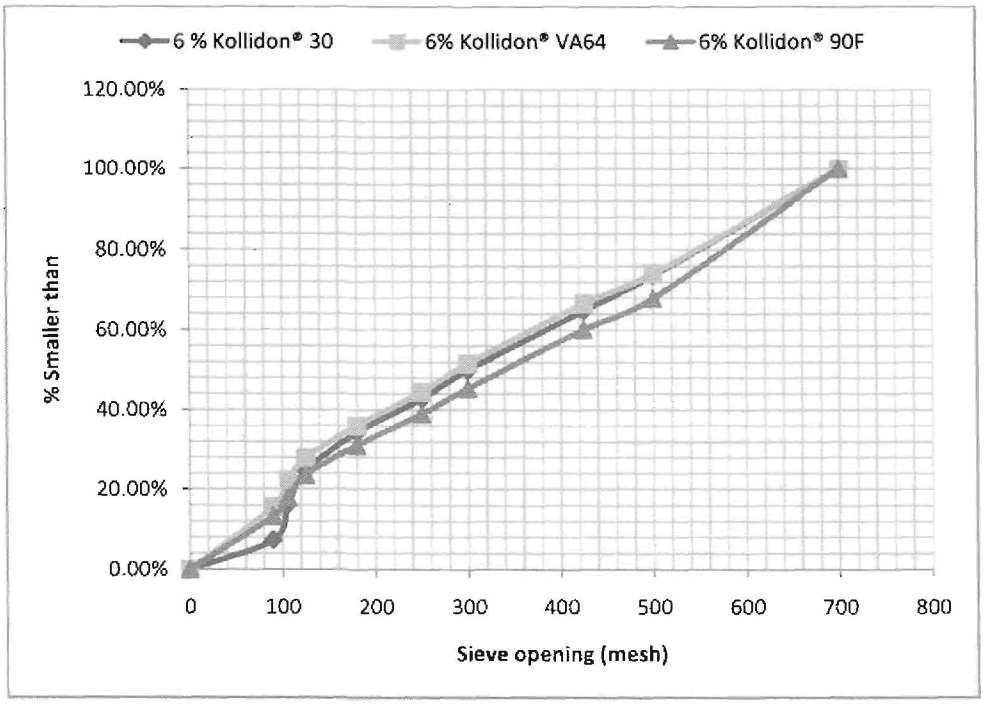


Fig. 3.3: Cumulative distribution frequency diagram of powder mixtures containing 6% w/w binder.

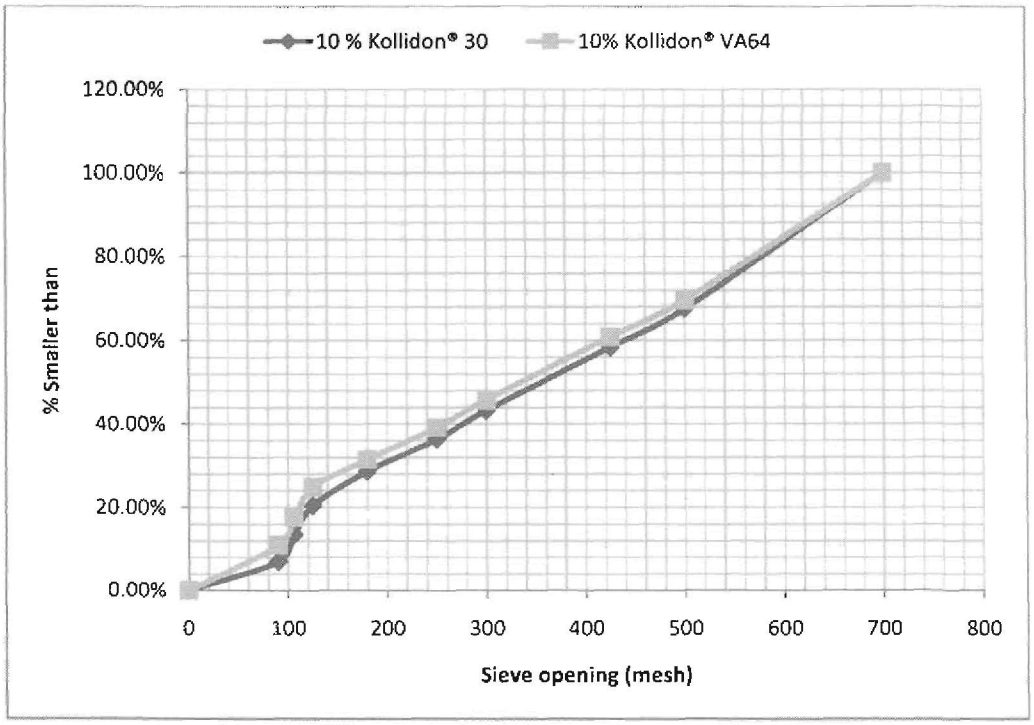


Fig. 3.4: Cumulative distribution frequency diagram of powder mixtures containing 10% w/w binder. (The powder mixture containing 10% w/w Kollidon® 90F could not be prepared due to difficulty during granulation).

3.2.3 Flow rate

The flow rate of each powder was determined as discussed in section 2.4.4. The flow rate as a function of binder concentration (% w/w) is graphically depicted in fig. 3.5. Kollidon® VA64 formulations exhibited a similar flow rate over the concentration range (3, 6 and 10% w/w) employed. The average flow rate values for the different Kollidon® VA64 formulations revealed no statistically significant differences amongst each other (ANOVA, Tukey test, $p > 0.05$). The highest flow rate (0.753 ± 0.088 g.s^{-1}) was obtained with the 6% w/w Kollidon® 90F formulation. This difference proved statistically significant (ANOVA, Tukey test, $p < 0.05$). The higher flow rate of the Kollidon® 90F formulation can possibly be linked to the bigger particle size of the granules in this mixture. This is in agreement with Staniforth (2000:604) who reported that larger powder particles and particles with uniform particle shape exhibited better flow properties. The Kollidon® 90F formulations consisted out of much more coarse particles and less fine particles (see fig. 3.2-3.4) in comparison to the other formulations, resulting in better flow properties. However, despite this difference exhibited by the 6% w/w Kollidon® 90F formulation it is hypothesized that it would have a

negligible effect on the final product (e.g. tablets), as all the formulations exhibited acceptable flow behavior as characterized by flow rate, as well as angle of repose.

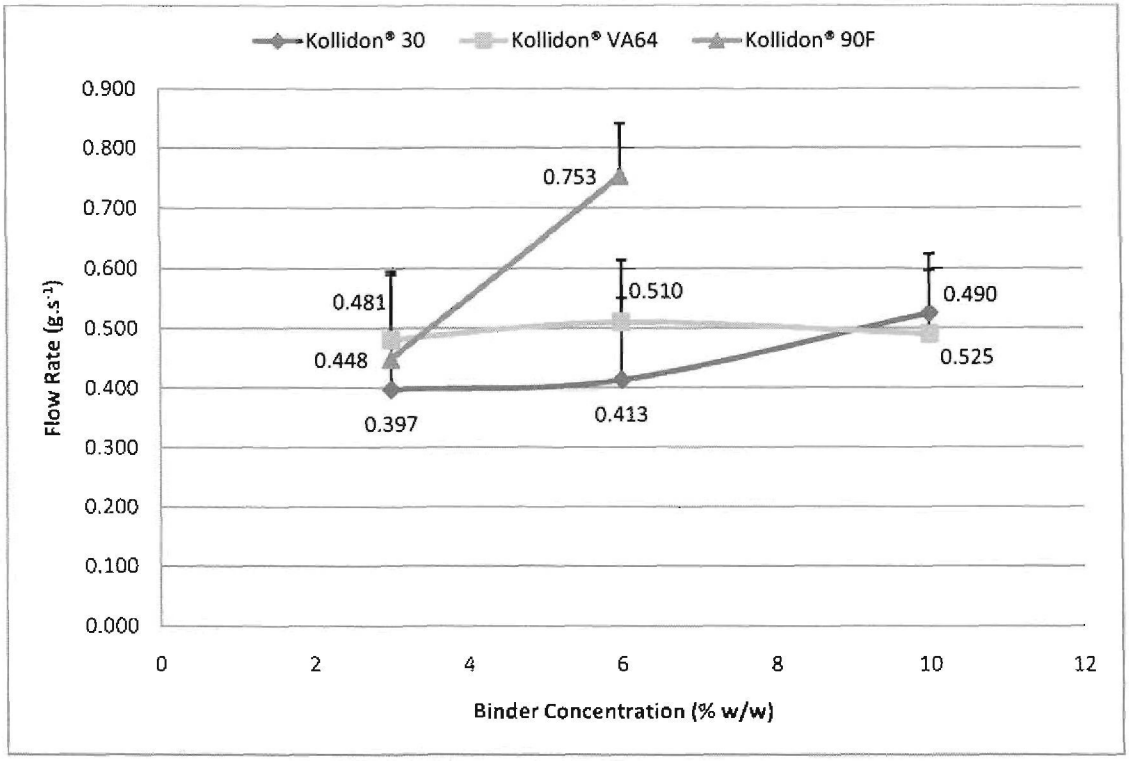


Fig. 3.5: The flow rate ($g.s^{-1}$) of the powders prepared from different concentrations (3, 6 and 10% w/w) of the Kollidon® range. (The powder mixture containing 10% w/w Kollidon® 90F could not be prepared due to difficulty during granulation).

3.2.4 Compressibility index and angle of repose

The compressibility index (Carr's Index) is an important parameter when determining powder flow properties. The compressibility index was determined as discussed in section 2.4.2.3.

Fig. 3.6 presents the realtionship between angle of repose and the compressibility index (Carr's Index). Wells (2002:135) found that a powder mixture will exhibit better flow when the angle of repose and compressibilty index is closer to the zero region.

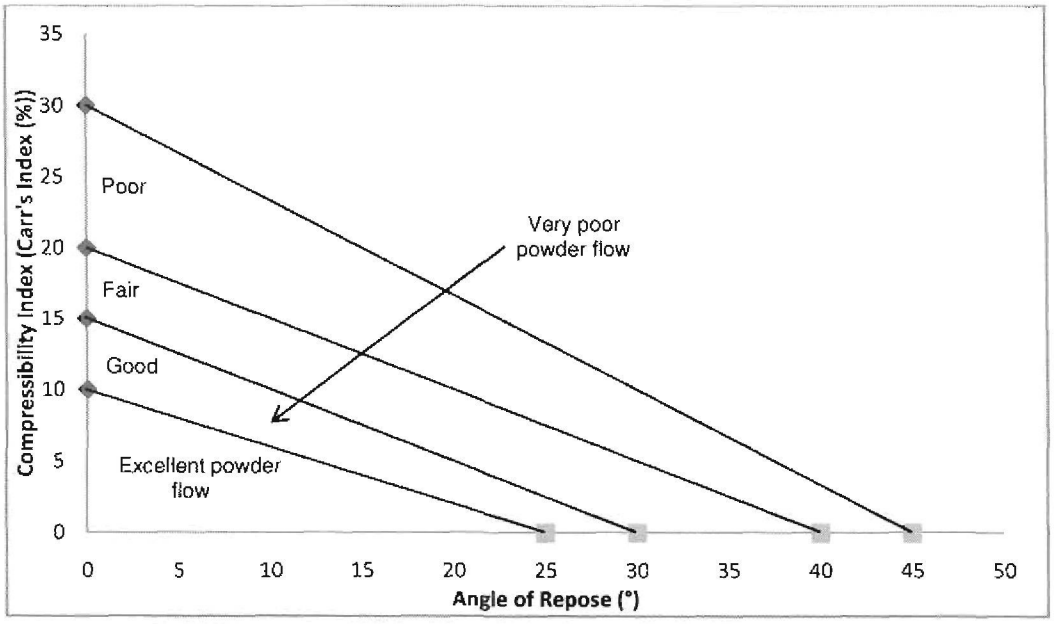


Fig. 3.6: The relationship between angle of repose (°) and compressibility index (%) (Wells, 2002:135).

Fig. 3.7 illustrates the relationship between the angle of repose and compressibility index for the different Kollidon® formulations at different concentration levels (% w/w). The compressibility index is an important factor determining weight variation of compressed tablets and how a specific powder will settle during handling.

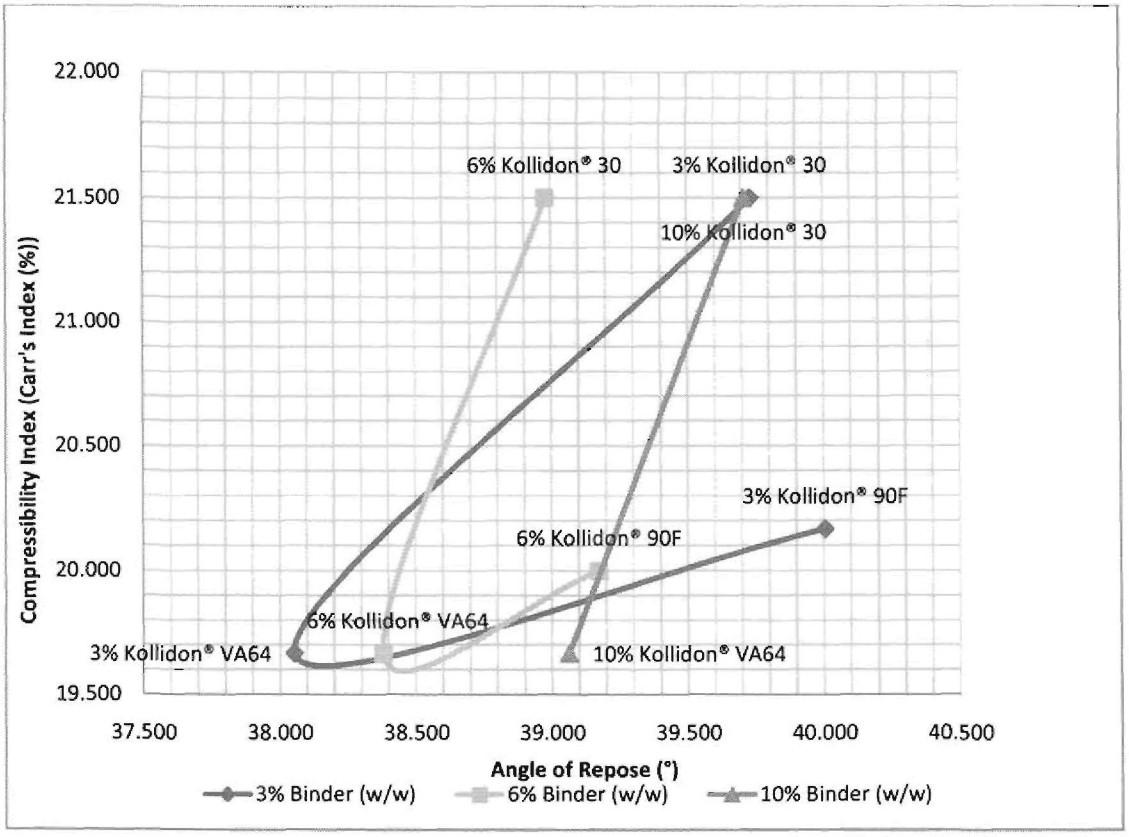


Fig. 3.7: The relationship between angle of repose (°) and the compressibility index (%). (The powder mixture containing 10% w/w Kollidon® 90F could not be prepared due to difficulty during granulation).

Considering fig. 3.7, it is evident that Kollidon® VA64 exhibited more favorable results at every concentration level (nearer to the zero region) in comparison to the other formulations. Compared to Kollidon® 30 and 90F; Kollidon® VA64 differed statistically significant (ANOVA, Tukey test, $p < 0.05$) at every concentration employed. The better compressibility index of the Kollidon® VA64 formualtions can possibly be attributed to the more fine particles (see fig. 3.2-3.4 in the 0-45 sieve region), filling voids between adjacent bigger particles, resulting in a less porous powder (Martin *et al.*, 1983:664).

3.2.5 Tablet weight variation (%RSD)

Low tablet weight variation (%RSD) is necessary to produce homogeneous tablets, i.e. each tablet must contain the same amount of active ingredient. Kollidon® VA64 produced, throughout the formulation range, more fine particles and this explaines why Kollidon® VA64 exhibited a beter compressibility index compared to Kollidon® 30 and 90F.

The weight variation (%RSD) of tablets are included, because it is an acceptable indirect method to characterize powder flow properties. A large %RSD-value represents poor powder flow and a small value, good flow.

Weight variation of twenty tablets was determined and the relative standard deviation (%RSD) was calculated (see section 2.5.2).

From table 3.1 it is evident that all the %RSD-values are below 5%. This can be considered satisfactory in terms of tablet weight variation. The fact that all the %RSD-values are below 5% indicate that all the formulations exhibited acceptable flow. It can, therefore, be concluded that despite the better flow rate (0.753 ± 0.088 $g.s^{-1}$) exhibited by the 6% Kollidon® 90F formulation, this had no significant effect on tablet weight variation and, therefore, flow behavior during tableting. Furthermore, the finer particles of the Kollidon® VA64 formulations also had no significant effect on flow behavior during tableting, as this would be evidenced by a significant variation in tablet weight (> 5%).

3.3 Summary and conclusion

Formulations with different Kollidon® polymers as binders were successfully prepared except the formulation containing 10% w/w Kollidon® 90F. This formulation could not be prepared because of difficulty experienced during the granulation process. All the formulations exhibited acceptable flow as characterized by angle of repose, flow rate and compressibility index.

Despite the fact that all the Kollidon® VA64 formulations exhibited a finer particle composition in comparison to the other formulations, this proved to have no significant effect on flow properties as all formulations exhibited %RSD-values of less than 5% with respect to tablet weight variation. Tablet weight variation was included because powder flow problems will be reflected in an increase in tablet weight variation and, therefore, a corresponding variation in drug content. As all the formulations exhibited %RSD-values below 5% it can, therefore, be concluded that all the formulations exhibited acceptable flow, and in terms of flow behavior no binder proved to be superior.

Chapter 4

THE EVALUATION OF TABLETS PREPARED FROM POWDERS CONTAINING DIFFERENT GRADES OF KOLLIDON®

4.1 Introduction

The results from chapter 3 (Powder properties) did not reveal differences with practical implication in terms of powder flow between powders prepared from the different grades of Kollidon®. All the powders produced, incorporating the different binders, rendered similar results upon evaluation with respect to angle of repose, flow rate and compressibility index. All the powders exhibited acceptable flow rates as well as angle of repose values and compressibility indexes. This chapter deals with the evaluation of tablets produced from the powders that incorporated the different grades of Kollidon®, compressed at two different compression settings (stroke length 1 and 4). Tablets were evaluated (see section 2.5.2-2.5.5) with respect to:

- tablet weight variation,
- crushing strength,
- friability, and
- disintegration time.

The bulk volume of a powder and the air spaces between adjacent particles are reduced when external pressure is applied on the powder mass. During the process of compaction, particles are moved into closer proximity to each other and bonds may be established between particles. The term compression is often used to describe the process of volume reduction and the term compaction is used to describe the whole process, including the subsequent establishment of bonds between particles (Olsson & Nyström, 2001:203).

Powders containing Kollidon® (30, VA64 and 90F) at different concentration levels (3, 6 and 10% w/w) were prepared and used to manufacture tablets at two different compression settings (stroke length 1 and 4). The same concentration levels of Explotab® (1% w/w) and magnesium stearate (0.5% w/w) were used in all powder formulations. Explotab® was incorporated in a 50 : 50 ratio (intra-granular : extra-granular). The die volume of the tablet press was kept constant and different compression settings (upper punch setting 1 and 4) were employed to manufacture tablets with different hardness profiles. The punches used to compress the tablets were 8 mm in diameter and flat faced (see section 2.5.1).

4.2 Average tablet weight and percentage relative standard deviation (%RSD)

The average tablet weight and the accompanying %RSD-value (see section 2.5.2 for calculations) is an important parameter when comparing and evaluating tablet properties. Weight variation test results are important because it gives an indication of the variation in active ingredient content among tablets. The tablets compressed from powder mixtures of Kollidon® 30, VA64 and 90F were evaluated and compared. The volume of the die of the single station tablet press was kept constant throughout the study for all powder formulations (see section 2.5.1). Two different compression settings (stroke length 1 and 4) were used to determine how the different grades of Kollidon® reacted under different pressures as this can influence properties such as disintegration and crushing strength of tablets. Table 4.1 displays the average weight and %RSD-values from tablets produced from the different formulations at two different compression settings. Kollidon® VA64 possesses lower bulk density values (0.24-0.28 $g.cm^{-3}$) (Bühler, 2003:207) than Kollidon® 30 and 90F (0.4-0.5 $g.cm^{-3}$) (Bühler, 2003:32) and, therefore, rendered lighter tablets in comparison to Kollidon® 30 and 90F at increased binder concentration levels (6 and 10% w/w). A greater amount of Kollidon® VA64 is present in the 6 and 10% formulations and had a greater effect on powder density compared to the 3% Kollidon® VA64 formulations.

Table 4.1: The average weight and accompanying %RSD-values of tablets compressed at two compression settings (stroke length 1 and 4). The values in brackets represent standard deviation (SD).

Binder Concentration (% w/w)	Binder	Compression Setting 1		Compression Setting 4	
		Average tablet weight (mg)	%RSD	Average tablet weight (mg)	%RSD
3	Kollidon® 30	258.9 (9.54)	3.68	259.2 (7.15)	2.76
	Kollidon® VA64	273.0 (2.74)	1.00	273.7 (1.26)	0.46
	Kollidon® 90F	283.3 (9.58)	3.38	298.5 (1.7)	0.57
6	Kollidon® 30	268.3 (1.98)	0.74	257.8 (8.21)	3.19
	Kollidon® VA64	252.5 (10.69)	4.23	258.1 (7.06)	2.73
	Kollidon® 90F	281.3 (2.22)	0.79	266.5 (4.02)	1.51
10	Kollidon® 30	273.5 (12.67)	4.63	284.6 (2.26)	0.79
	Kollidon® VA64	254.5 (9.05)	3.55	245.3 (8.58)	3.50
	Kollidon® 90F *	0	0	0	0

* The powder mixture containing 10% w/w Kollidon® 90F could not be prepared due to difficulty during the granulation process. (The wet powder mass could not be screened through the 30 mesh sieve to produce granules).

From table 4.1 it is evident that all formulations exhibited %RSD-values below 5%. This indicates that tablet weight variation is within acceptable limits and it can, therefore, be concluded that all formulations exhibited acceptable flow properties. This implies that the variation in drug content (if the formulations would have contained an active ingredient) would be within acceptable limits given that the active ingredient does not have a significant effect on the flow behavior of the powder mixtures.

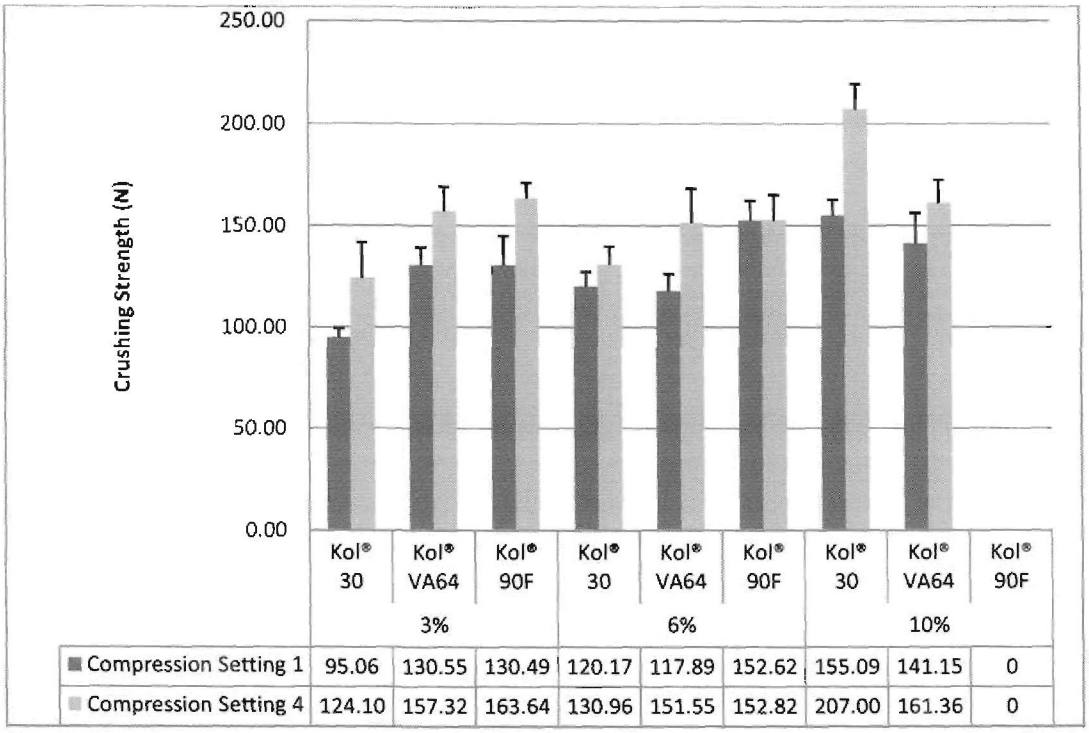
4.3 Crushing strength and friability

The mechanical strength (crushing strength and friability) of tablets prepared from the different powder formulations were determined as described in sections 2.5.3 and 2.5.4 respectively. In table 4.2 the results obtained for friability, crushing strength and disintegration time are presented. The results obtained for the crushing strength experiments are graphically presented in fig. 4.1.

Table 4.2: The crushing strength, %-friability and disintegration results of tablets prepared from the different powder mixtures, compressed at two different compression settings. The values in brackets represent standard deviation (SD).

Binder Concentration (% w/w)	Binder	Compression Setting 1			Compression Setting 4		
		%-Friability	Average Crushing Strength (N)	Average Disintegration Time (min:sec)	%-Friability	Average Crushing Strength (N)	Average Disintegration Time (min:sec)
3	Kollidon® 30	0.53%	95.06 (4.39)	6:42 (0.11)	0.39%	124.10 (17.73)	13:45 (0.04)
	Kollidon® VA64	0.66%	130.55 (8.85)	3:24 (0.01)	0.66%	157.32 (11.94)	5:24 (0.02)
	Kollidon® 90F	0.39%	130.49 (14.51)	>20	0.30%	163.64 (7.58)	>20
6	Kollidon® 30	0.36%	120.17 (7.14)	15:58 (0.01)	0.36%	130.96 (8.89)	16:32 (0.03)
	Kollidon® VA64	0.52%	117.89 (8.39)	5:06 (0.02)	0.42%	151.55 (16.89)	8:22 (0.02)
	Kollidon® 90F	0.25%	152.62 (9.88)	>20	0.26%	152.82 (12.45)	>20
10	Kollidon® 30	0.27%	155.09 (7.78)	19:34 (0.01)	0.20%	207.00 (12.56)	20:00 (0.00)
	Kollidon® VA64	0.35%	141.15 (15.36)	9:26 (0.02)	0.34%	161.36 (11.33)	9:37 (0.05)
	Kollidon® 90F *	0	0	0	0	0	0

* The disintegration times of the tablets produced from powder mixtures of 3 and 6% w/w Kollidon® 90F exceeded twenty minutes (disintegration time limit) and are therefore not noted. (The powder mixture containing 10% w/w Kollidon® 90F could not be prepared due to difficulty during granulation).



	Kol® 30	Kol® VA64	Kol® 90F	Kol® 30	Kol® VA64	Kol® 90F	Kol® 30	Kol® VA64	Kol® 90F
	3%			6%			10%		
Compression Setting 1	95.06	130.55	130.49	120.17	117.89	152.62	155.09	141.15	0
Compression Setting 4	124.10	157.32	163.64	130.96	151.55	152.82	207.00	161.36	0

Fig. 4.1: Illustration of average crushing strength of tablets prepared from the different powder mixtures at different compression settings (stroke length 1 and 4). (Tablets for 10% w/w Kollidon® 90F could not be prepared due to difficulty during granulation).

From fig. 4.1 it is evident that an increase in compression setting resulted in an increase in crushing strength. This was expected, as an increase in compression setting implied an increase in compression force. With an increase in compression force, particles are being compressed within closer proximity, therefore, enlarging surface contact area between adjacent particles. This phenomenon enables enhanced binding between adjacent particles, rendering tablets with greater mechanical strength (crushing strength and friability) (Parrot, 1981:158-160).

When considering the effect of binder concentration (% w/w), it is evident that an increase in binder concentration for Kollidon® 30 resulted in an increase in crushing strength and, therefore, an increase in the mechanical strength of the tablets. This effect was observed at both compression settings and the increase proved to be statistically significant at all three concentration levels employed (ANOVA, Tukey test, $p < 0.05$). However, Kollidon® 90F did not exhibit the same phenomenon, as tablets produced from the 6% w/w formulation rendered similar crushing strength results at compression setting 1 and 4 (152.62 ± 9.88 N and 152 ± 12.45 N respectively). When comparing these two binders at the same concentration level, it is evident that Kollidon® 90F rendered tablets with a higher average

crushing strength compared to that of Kollidon® 30 (Note: the formulation containing 10% w/w Kollidon® 90F could not be prepared due to granulation difficulty). This was observed at both compression settings employed. These results indicate that Kollidon® 90F possessed better binding properties than Kollidon® 30 at the same concentration level (% w/w). A possible explanation for this phenomenon can be the difference in K-values between Kollidon® 30 and 90F (28-32 and 85-95 respectively) (Bühler, 2003:22). This value is calculated from the relative viscosity in water (Bühler, 2003:24). Kollidon® 90F possesses the highest viscosity (300-700 mPa s vs 5.5-8.5 mPa s respectively) and, therefore, the highest K-value (85-95), possibly explaining Kollidon® 90F's better binding properties and harder tablets as a result of its higher viscosity. It should also be noted that Kollidon® 90F was wetted with distilled water in comparison to ethanol as granulation liquid for Kollidon® 30 and VA64. Furthermore, Kollidon® 90F was dried at 50 ± 1 °C in comparison to 37 ± 1 °C of Kollidon® 30 and VA64. However, whether these differences were influential on the binding properties of Kollidon® 90F must be investigated in future studies.

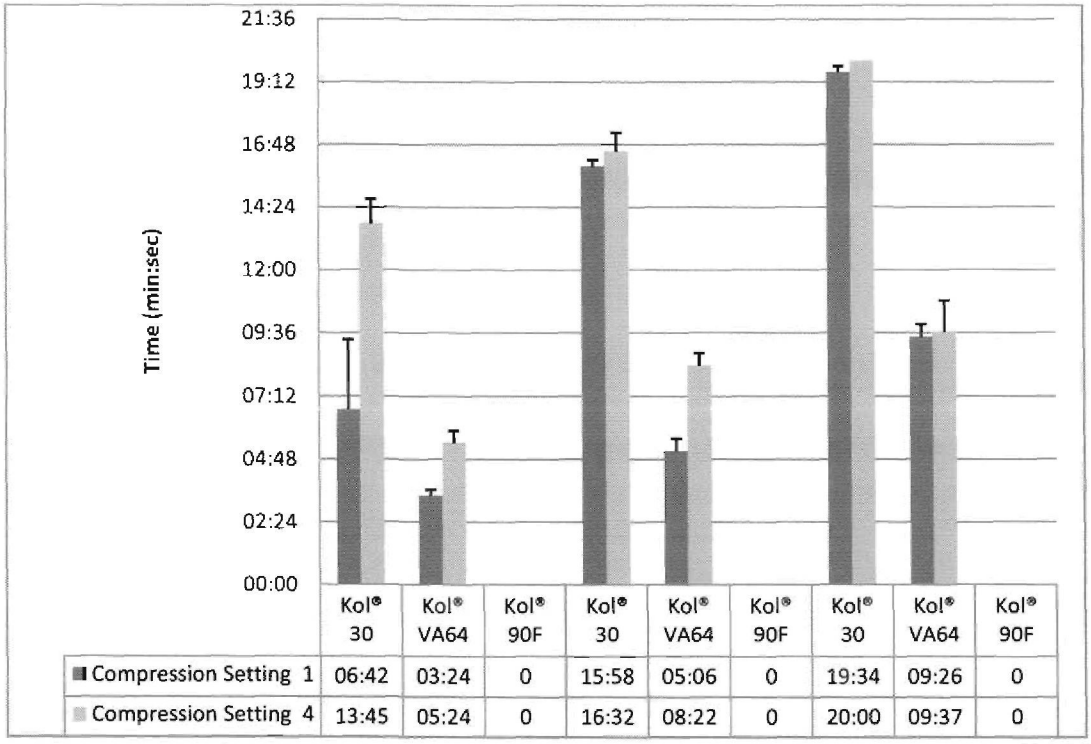
With respect to Kollidon® VA64, an increase in concentration from 3 to 10% w/w did not result in a statistically significant difference (ANOVA, Tukey test, $p > 0.05$) in crushing strength (130.55 ± 8.85 N vs 141.15 ± 15.36 N) and, therefore, the mechanical strength of the tablets produced at compression setting 1. This tendency was also observed at compression setting 4. These results thus indicate no significant benefit in terms of the mechanical strength of tablets by increasing Kollidon® VA64's concentration. However, an increase in compression force resulted in a statistically significant increase (ANOVA, Tukey test, $p < 0.05$) in crushing strength at all three concentration levels employed. This therefore indicates better mechanical strength of tablets with an increase in compression force at the same concentration level (% w/w) as was seen for both Kollidon® 30 and 90F.

From the friability results (see table 4.2) it is evident that all the formulations exhibited average %-friability values below 1%, indicating acceptable resistance to friability for all the formulations (British Pharmacopoeia, 2007:A396). Although a tendency towards lower %-friability with an increase in binder concentration (% w/w) can be seen, no statistically significant differences with respect to the %-friability results of the different formulations were found (ANOVA, Tukey test, $p > 0.05$). As all the formulations exhibited %-friability values below 1%, it therefore appears that with respect to the mechanical strength of the tablets prepared from the different formulations, it renders no significant benefit to increase binder concentration levels for any of the three binders employed. It is important to note that all the formulations evaluated contained no active ingredient (placebo formulations). As an active ingredient can influence tablet properties, the influence of an active ingredient on properties

such as crushing strength and friability most probably needs to be investigated on an individual basis.

4.4 Disintegration time

The disintegration results are displayed in fig. 4.2.

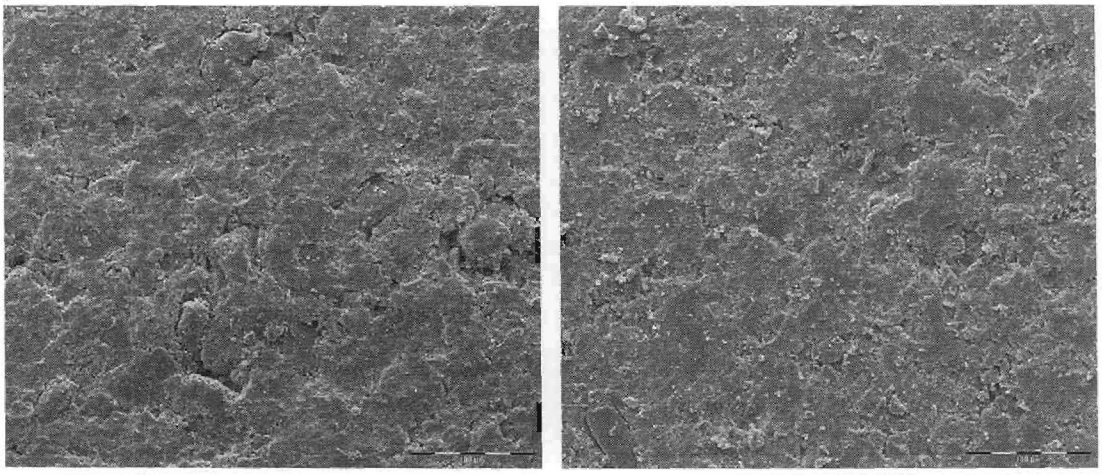


	Kol® 30	Kol® VA64	Kol® 90F	Kol® 30	Kol® VA64	Kol® 90F	Kol® 30	Kol® VA64	Kol® 90F
Compression Setting 1	06:42	03:24	0	15:58	05:06	0	19:34	09:26	0
Compression Setting 4	13:45	05:24	0	16:32	08:22	0	20:00	09:37	0

Fig. 4.2: Illustration of average disintegration times of tablets prepared from the different powder mixtures at two compression settings (stroke length 1 and 4). (Tablets for 10% w/w Kollidon® 90F could not be prepared due to difficulty during granulation). The tablets prepared from powder mixtures of 3 and 6% w/w Kollidon® 90F exceeded the disintegration time limit of twenty minutes and, therefore, could not be noted.

Upon inspection of fig. 4.2, a tendency towards an increase in disintegration time with an increase in compression force is observed. This increase in disintegration time is exhibited by all three binders at all three concentration levels (% w/w) employed. However, an increase in compression force did not affect the different binders at the different concentration levels to the same extent. This increase in disintegration time with an increase in compression force is in agreement with results reported by Fox *et al.* (1963:260) and Parrott (1981:161). These researchers attributed the increase in disintegration time to a decrease in capillary porosity due to an increase in compression force. To investigate this possibility, scanning electron microscope (SEM) images of the different formulations were

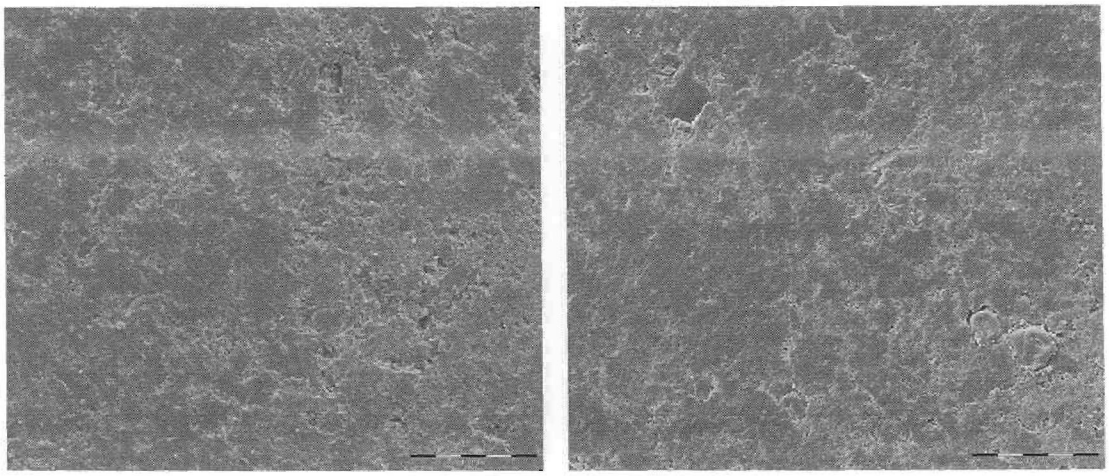
captured. All SEM-images (for the different formulations) appeared similar. In fig. 4.3, as an example, SEM-images of the 3% w/w Kollidon® VA64 containing formulation is displayed. This formulation exhibited average disintegration times of 3:24 ± 0.01 and 5:24 ± 0.02 min:sec for compression setting 1 and 4 respectively. This corresponds to a 58.8% increase in disintegration time for this formulation. From these two images it is evident that the tablets compressed at a higher compression setting (stroke length 4) possessed lower porosity compared to the tablets prepared at compression setting 1. This observation, therefore, confirms that capillary porosity had an influence on disintegration time. A decrease in capillary porosity at a higher compression setting can thus explain longer disintegration times, because water cannot enter freely into the tablet matrix.



(a) (b)

Fig. 4.3: The surface of a tablet prepared with 3% w/w Kollidon® VA64 at compression setting 1 (a) and the surface of a tablet compressed at compression setting 4 of the same formulation (b).

It is evident from fig. 4.2 that none of the Kollidon® 90F formulations disintegrated within the set time limit of twenty minutes. A possible explanation for this phenomenon may be that the tablets produced from Kollidon® 90F formulations possessed low porosity and, therefore, little capillary pores in comparison to the tablets manufactured from Kollidon® VA64 formulations (see fig. 4.3), therefore minimizing water uptake into the tablet matrix. The low porosity and few capillary pores can be seen in the SEM-images (see fig. 4.4). Low porosity and little capillary pores contribute to longer disintegration times, because water cannot enter the tablet matrix, consequently rupturing the tablet matrix (Fox *et al.*, 1963:260).



(a) (b)

Fig. 4.4: Surface of a tablet prepared with 3% w/w Kollidon® 90F at compression setting 1 (a) and 4 (b).

When comparing the disintegration results of the Kollidon® 30 formulations with the disintegration results of the Kollidon® VA64 formulations, it is clear that the Kollidon® VA64 formulations consistently exhibited shorter disintegration times compared to the Kollidon® 30 formulations at all three concentration levels (3, 6 and 10% w/w) and both compression settings (stroke length 1 and 4). This difference in disintegration time was statistically significant (ANOVA, Tukey test, $p < 0.05$) at all three concentration levels and both compression settings employed. Furthermore, all three Kollidon® VA64 formulations at both compression settings exhibited average disintegration times below ten minutes, with the shortest disintegration time (3:24 ± 0.01 min:sec) exhibited by the 3% w/w formulation compressed at stroke length 1 and the longest average disintegration time (9:37 ± 0.05 min:sec) exhibited by the tablets produced from the 10% w/w formulation compressed at stroke length 4. All the formulations containing Kollidon® 90F as binder exhibited disintegration times in excess of twenty minutes (disintegration time limit), despite the fact that lactose is water soluble. Besides the low porosity level of the tablets prepared from the Kollidon® 90F formulations, the high viscosity of Kollidon® 90F also might have contributed to the longer disintegration times of these tablets. It is postulated that as a result of the high viscosity of Kollidon® 90F, the quantity of water that did enter the tablet matrix ended up hydrating the Kollidon® 90F rather than the Explotab® and in effect prevented tablet disintegration within twenty minutes. The fact that the tablets prepared from the Kollidon® 30 formulations exhibited disintegration within twenty minutes indicates that the viscosity of the polymers might play a role in tablet disintegration, as the viscosity of Kollidon® 30 is lower compared to that of Kollidon® 90F. It was, therefore, hypothesized that the formulations

containing Kollidon® 90F could exhibit unfavorable dissolution profiles as poor disintegration could have a detrimental effect on dissolution behavior, especially in the case of a poor water soluble and water wettable drug such as furosemide.

In order to evaluate the effect of tablet hardness on the disintegration time of the tablets prepared from the different formulations, which disintegrated below the set time limit of twenty minutes, a hardness-disintegration index (HD-index) was calculated by dividing average disintegration time by the average crushing strength for each disintegrating tablet formulation. This index was utilized by Hüttenrauch *et al.* (1970:630) to correlate the mechanical binding properties of a formulation with the observed disintegration time. Results obtained for the different Kollidon® containing formulations are graphically presented in fig. 4.5.

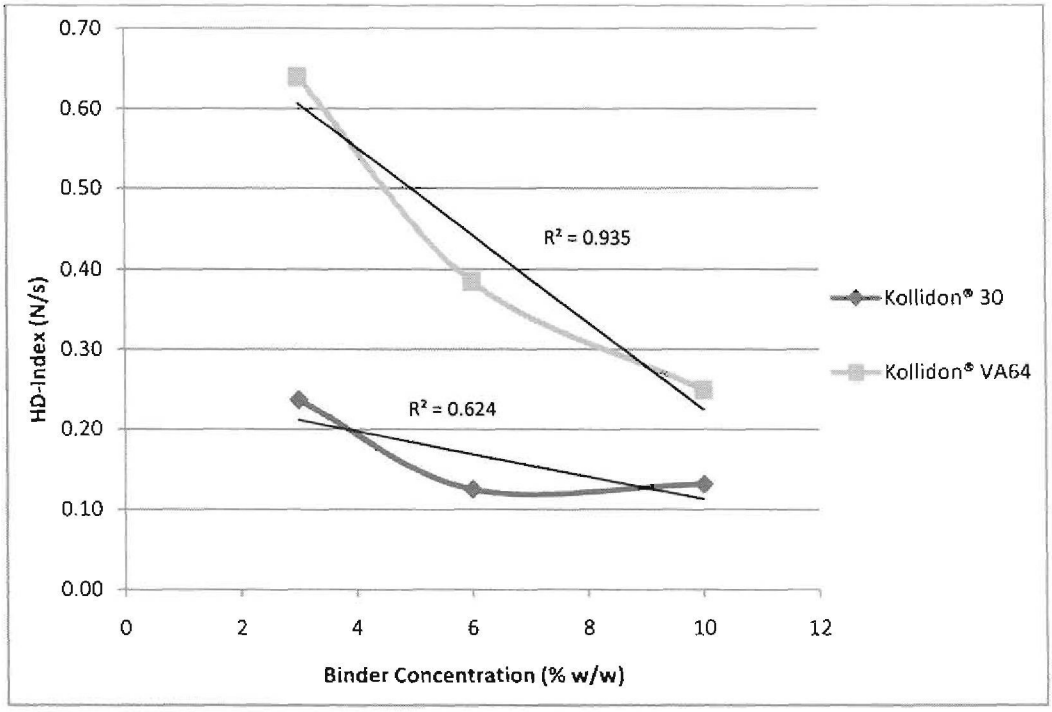


Fig. 4.5: The effect of crushing strength on disintegration time of tablets prepared from Kollidon® 30 and VA64 powder mixtures at compression setting 1. (Tablets for 10% w/w Kollidon® 90F could not be prepared due to difficulty during granulation). The tablets prepared from powder mixtures of 3 and 6% w/w Kollidon® 90F exceeded the disintegration time limit of twenty minutes and therefore could not be noted.

Fig. 4.5 indicates that an increase in binder concentration for Kollidon® VA64 did not render any benefit with regard to the crushing strength of the tablets, but had a negative effect on the disintegration time of the tablets. This is confirmed by the negative slope of the line.

This means that when binder concentration increased, the tablet strength did not necessarily increase, but disintegration time did. With regard to Kollidon® 30 it is clear from fig. 4.5 that an increase in binder concentration resulted in a tendency towards an increase in both crushing strength as well as disintegration time. This behavior of both polymers was, however, only observed at the lower compression setting (stroke length 1). The reason for the difference in behavior of the two polymers is unclear.

4.6 Summary and conclusion

Tablets from powder mixtures containing different concentrations of Kollidon® 30, VA64 and 90F at three concentration levels (3, 6 and 10% w/w) were successfully prepared and evaluated with respect to weight variation, crushing strength, friability and disintegration.

All the formulations exhibited %RSD-values below 5% with respect to tablet weight variation. This indicates acceptable flow behavior for all the formulations and confirms the results of chapter 3. This implies that the variation in drug content (if the formulations would have contained an active ingredient) would be within acceptable limits, provided that the active ingredient does not have a significant effect on the flow behavior of the powder mixture.

Increased compression force resulted in an increase in the average crushing strength of tablets prepared from the different powder formulations. For both Kollidon® 30 and 90F, an increase in binder concentration (% w/w) resulted in a significant increase in the average tablet crushing strength. In comparison to Kollidon® 30, Kollidon® 90F rendered tablets with a higher average crushing strength. This can possibly be attributed to the higher K-value and, therefore, higher viscosity of Kollidon® 90F in comparison to Kollidon® 30. In terms of mechanical strength (crushing strength and friability), Kollidon® VA64 containing formulations revealed no statistically significant benefit with regard to an increase in binder concentration from 3 to 10% w/w. All the formulations exhibited %-friability values below 1%, indicating acceptable resistance to friability. As all the formulations exhibited acceptable friability, it can, therefore, be concluded that all formulations exhibited sufficient mechanical strength for all three binders at a 3% w/w concentration level, indicating no additional benefit by increasing binder concentration.

A tendency towards an increase in disintegration time with an increase in compression force was observed for all formulations. This could possibly be attributed by a decrease in capillary porosity with an increase in compression force. This was confirmed with SEM-images. With respect to the different binders, Kollidon® VA64 containing formulations were the only formulations to exhibit average disintegration times below ten minutes for all three concentration levels at both compression settings. Furthermore, increased binder

concentrations of Kollidon® VA64 influenced disintegration of tablets negatively. The reason for this phenomenon is unclear.

In conclusion it can be stated that Kollidon® VA64 was a more efficient binder and rendered satisfactory disintegration results over the concentration range employed in comparison to Kollidon® 30 and 90F.

Chapter 5

EVALUATION OF TABLETS PREPARED WITH KOLLIDON® VA64, CONTAINING FUROSEMIDE AS ACTIVE INGREDIENT

5.1 Introduction

The success of a formulation can be evaluated in terms of its pharmaceutical availability, i.e. the process of dissolution.

Dissolution is defined as the process by which a solid substance enters into the solvent to yield a solution. Simply stated, dissolution is the process by which a solid substance dissolves. Fundamentally, it is controlled by the affinity between the solid substance and the solvent (Banakar, 1991:1). The dissolution rate is determined by the amount of active ingredient that passes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. The most common theory for dissolution, the film theory (or diffusion layer model) espouses the assumption that dissolution belongs to the type of heterogeneous reactions where the rate is determined by the transport process (Abdou, 1989:11).

Factors influencing dissolution rate from solid dosage forms include the following:

- factors related to the physicochemical properties of the drug,
- factors related to drug product formulation,
- factors related to the dosage form,
- factors related to the dissolution testing apparatus,
- factors related to dissolution test parameters, and
- miscellaneous factors (Banakar, 1991:134).

According to the general dissolution equation, the rate of dissolution depends primarily upon the surface area in contact with the surrounding medium (the effective surface area of the drug). It could, therefore, be assumed that any factor, which affects the establishment of rapid contact between the drug particles and the surrounding medium, could influence both the rate and extent of drug dissolution. Therefore, the aim during tablet formulation is to optimize drug release and dissolution through manipulation of formulation variables such as the choice of the excipients and their concentration, and through manipulation of process variables.

Results from the previous chapter revealed the influence of binder type, concentration and compression force on formulations, especially in terms of disintegration. Since tablet properties have a significant influence on drug dissolution, it could be expected that drug dissolution profiles from tablets containing different binders at different concentrations, would differ as well.

From the results in chapter 4, it was apparent that Kollidon® VA64 exhibited better disintegration results in comparison to the other Kollidon® polymers (Kollidon® 30 and 90F). Disintegration has an important influence on dissolution and, therefore, Kollidon® VA64 was selected to prepare tablets incorporating a sparingly water soluble drug, i.e. furosemide. The formulations containing furosemide, was produced using wet granulation and the same binder concentration levels (3, 6 and 10% w/w). Tablets were compressed at two compression settings (stroke length 1 and 4). The weight variation, hardness profiles, %-friability and disintegration time of the furosemide containing formulations were determined and compared to the results of the Kollidon® VA64 formulations not containing furosemide (placebo formulations). Additionally, dissolution testing was performed on the formulations containing furosemide. Finally, the results obtained from dissolution testing were compared to investigate release behavior of furosemide from the tablets.

5.2.1 Average tablet weight and percentage relative standard deviation (%RSD)

Tablets were compressed (see section 2.5.1) at two compression settings (stroke length 1 and 4) from powder mixtures of Kollidon® VA64 at different concentration levels (3, 6 and 10% w/w). Tablets that contained furosemide were produced by the same methods used to produce the placebo tablets incorporating Kollidon® VA64 (see section 2.5.1). The average weight was determined for each formulation and %RSD calculated with equation 2.5. Table 5.1 presents the results obtained from evaluation tests and fig. 5.1 depicts a graphical comparison of the %RSD-values of the formulations.

Table 5.1: The average weight and %RSD of tablets prepared from the different powder mixtures of Kollidon® VA64. Values in brackets represent standard deviation (SD).

Binder Concentration (% w/w)	Compression Setting	Average Weight (mg)		%RSD	
		Furosemide	Placebo	Furosemide	Placebo
3	1	260.9 (5.24)	273.0 (2.74)	2.01	1.00
	4	268.1 (3.16)	273.7 (1.26)	1.18	0.46
6	1	257.6 (2.06)	252.5 (10.69)	0.80	4.23
	4	286.6 (1.70)	258.1 (7.06)	0.59	2.73
10	1	277.7 (8.62)	254.5 (9.05)	3.10	3.55
	4	264.3 (1.78)	245.3 (8.58)	0.67	3.50

Upon inspection of fig. 5.1, it is evident that %RSD-values for the placebo formulations (as discussed in section 4.2) and furosemide containing formulations are below 5%. As weight variation can be used as an indirect indication of powder flow properties, it can be concluded that all formulations exhibited acceptable powder flow behavior, and as a consequence thereof, acceptable tablet weight variation. The low %RSD-values of the tablets implies that the weight variation of the active ingredient (furosemide) is within acceptable limits and that the active ingredient did not have a significant influence on the flow properties of the powder mixtures.

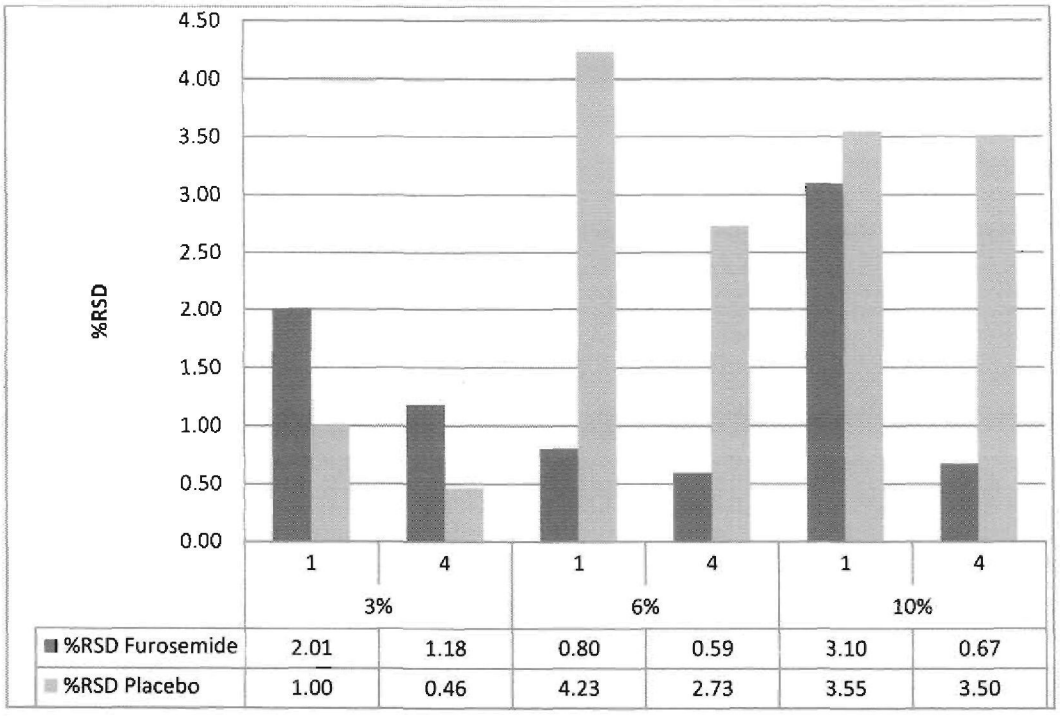


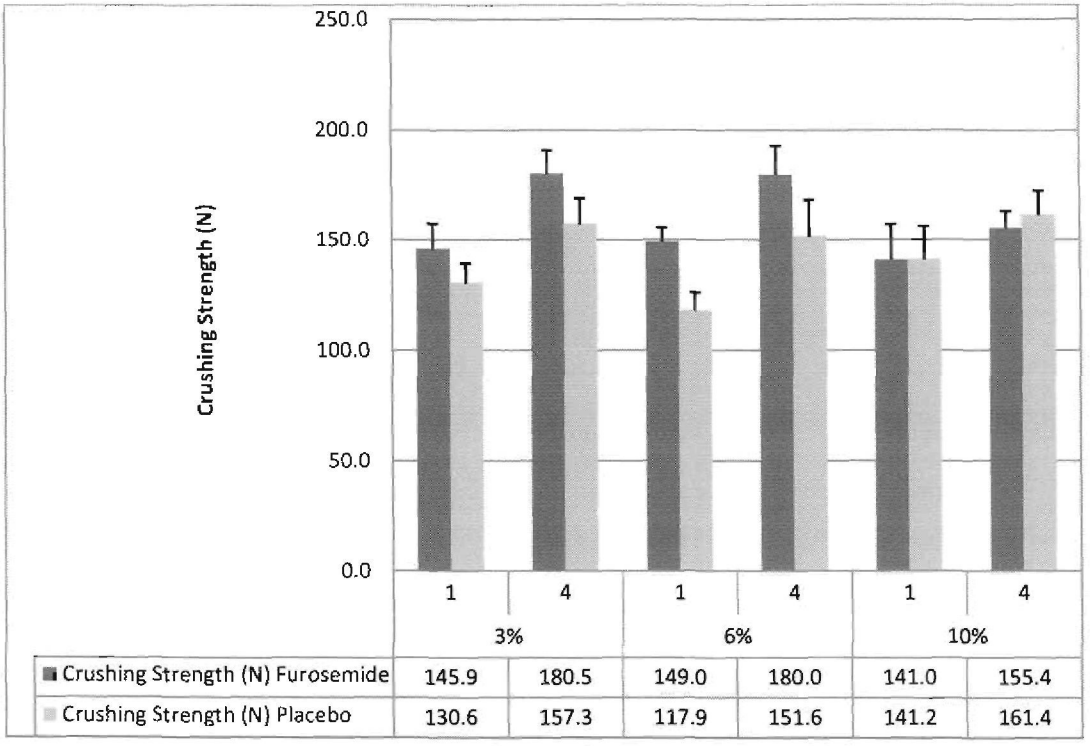
Fig. 5.1: Illustration of weight variation (%RSD) of tablets prepared from the different powder mixtures of Kollidon® VA64.

5.2.2 Crushing strength and friability

The results of the placebo formulations of chapter 4 were compared to the results obtained from tablets produced from Kollidon® VA64 formulation containing furosemide (see table 5.2). The crushing strength results are graphically depicted in fig. 5.2.

Table 5.2: The crushing strength and %-friability of tablets prepared from the different powder mixtures of Kollidon® VA64. Values in brackets represent standard deviation (SD).

Binder Concentration (% w/w)	Compression Setting	Crushing Strength (N)		%-Friability	
		Furosemide	Placebo	Furosemide	Placebo
3	1	145.9 (11.72)	130.6 (8.85)	0.57%	0.66%
	4	180.5 (10.56)	157.3 (11.94)	0.59%	0.66%
6	1	149.0 (6.76)	117.9 (8.39)	0.39%	0.52%
	4	180.0 (12.81)	151.6 (16.89)	0.28%	0.42%
10	1	141.0 (16.31)	141.2 (15.36)	0.44%	0.35%
	4	155.4 (8.05)	161.4 (11.328)	0.42%	0.34%



Crushing Strength (N) Furosemide	145.9	180.5	149.0	180.0	141.0	155.4
Crushing Strength (N) Placebo	130.6	157.3	117.9	151.6	141.2	161.4

Fig. 5.2: Illustration of the crushing strength of tablets prepared from the different powder mixtures of Kollidon® VA64 containing furosemide.

Upon inspection of fig. 5.2, it is evident that as with the placebo formulations, an increase in binder concentration from 3 to 10% w/w did not result in a statistically significant difference (ANOVA, Tukey test, $p > 0.05$) in crushing strength (145.9 ± 11.72 N vs 141.0 ± 16.31 N respectively), and therefore, the mechanical strength of the tablets produced at compression setting 1. This tendency was also observed at compression setting 4 for the 3 and 6% w/w formulation but not for the 10% w/w formulation. As with the placebo formulations, an increase in compression force for the furosemide containing formulations also resulted in a statistically significant difference (ANOVA, Tukey test, $p < 0.05$) in crushing strength at all three concentration levels employed. This, therefore, indicates better mechanical strength of tablets with an increase in compression force at the same concentration level.

With regard to the friability results (see table 5.2), it is evident that all the formulations (placebo and furosemide containing) exhibited %-friability values below 1%, indicating acceptable mechanical strength and resistance to friability. It can, therefore, be concluded that no significant benefits are acquired in terms of mechanical strength (crushing strength and friability) of tablets by increasing Kollidon® VA64's concentration. Furthermore, from the crushing strength and friability results it can be concluded that furosemide did not have a detrimental effect on the mechanical strength of the tablets.

5.2.3 Disintegration time

The disintegration times of placebo tablets from the previous chapter (chapter 4) were compared to the results obtained from tablets produced from different Kollidon® VA64 powder mixtures containing furosemide (see table 5.3).

Table 5.3: The disintegration results of tablets prepared from the different powder mixtures of Kollidon® VA64. The values between brackets represent standard deviation (SD).

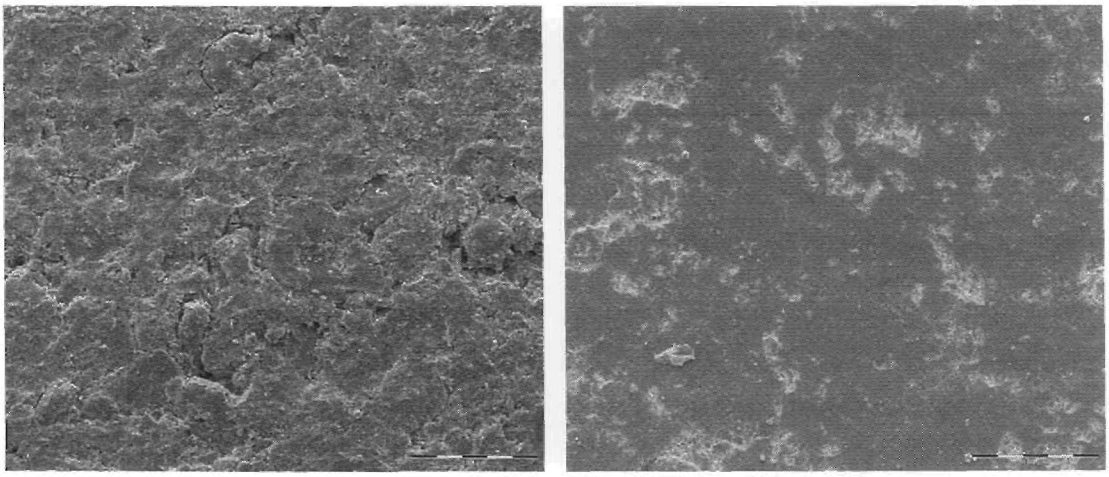
Binder Concentration (% w/w)	Compression Setting	Disintegration Time (min:sec)	
		Furosemide	Placebo
3	1	11:23 (0.04)	3:24 (0.01)
	4	18:59 (0.03)	5:24 (0.02)
6	1	>20 (0.00)	5:06 (0.02)
	4	>20 (0.00)	8:22 (0.02)
10	1	>20 (0.00)	9:26 (0.02)
	4	>20 (0.00)	9:37 (0.05)

The placebo tablets prepared from the different powder mixtures (3, 6 and 10% w/w) of Kollidon® VA64 exhibited acceptable disintegration, with average disintegration times being below ten minutes. However, only the furosemide containing tablets prepared from the 3% w/w powder mixture exhibited average disintegration times below twenty minutes (11:23 ± 0.04 and 18:59 ± 0.03 (min:sec) for the tablets compressed at compression setting 1 and 4 respectively). The tablets prepared from the 6 and 10% w/w formulations containing furosemide exceeded the disintegration time limit of twenty minutes. This illustrates that the active ingredient (furosemide) had a considerable influence on the disintegration behavior of the formulations. Furosemide possesses low water solubility and wettability (Boles Ponto & Schoenwald, 1990:305), and therefore, could have a significant influence on disintegration. Furthermore, when comparing tablet surfaces (see fig. 5.3), it is evident why tablets containing furosemide exhibited longer disintegration times. The tablets containing furosemide possessed lower porosity in comparison to that of the placebo tablets. Water could easily penetrate the placebo tablet matrix and rupture it, resulting in quick disintegration. The low porosity of the furosemide containing tablets impairs water penetration into the tablets' matrix, and as a consequence prolongs disintegration. Therefore, the disintegration of the tablets produced from the 3% w/w formulations, containing furosemide, is slow and disintegration is unsuccessful at higher binder concentration levels (6 and 10% w/w). The lower porosity level as well as the hydrophobic

character of furosemide (poor solubility and wettability) was probably instrumental in the detrimental effect on the disintegration time of the furosemide containing tablets.

From fig. 5.3 it is also evident that the tablet surface of the furosemide containing formulation has a smoother appearance in comparison to the placebo formulation. This smoother surface can only be attributed to the active ingredient as this was the only difference between the two formulations (placebo and furosemide containing). It appears almost as if the furosemide formed a coating on the tablet surface as well as closing of the surface pores. It can, therefore, be concluded that the slow disintegration time of the 3% w/w Kollidon® VA64 formulation and the unsuccessful disintegration behavior of the 6 and 10% w/w formulations can be attributed to the active ingredient, i.e. furosemide. These results, thus, confirm that a low dosage drug (e.g. furosemide) could have an influence on disintegration and, therefore, dissolution. However, the effect of disintegration on dissolution needs to be verified by dissolution testing.

The fact that the tablets produced from the 3% w/w Kollidon® VA64 formulation disintegrated, but the 6 and 10% w/w formulations did not, might also indicate a combination effect of binder concentration and drug type on dissolution that requires investigation.



(a) (b)

Fig. 5.3: The illustration of a tablet's surface prepared with the 3% w/w Kollidon® VA64 powder mixture at compression setting 1 not containing furosemide (a) and the surface of a furosemide containing tablet produced from 3% w/w Kollidon® VA64 powder mixture at compression setting 1 (b).

5.3 Dissolution studies

The dissolution profiles of tablets produced from Kollidon® VA64 powder mixtures, containing furosemide, at two compression settings (stroke length 1 and 4) were determined

as described in section 2.6. From the dissolution data obtained, two dissolution parameters were calculated, namely DR_i, (indicating the initial rate of drug dissolution) and AUC (representing the extent of drug dissolution) (see section 2.6.7). The calculated DR_i and AUC-values for the different formulations are reported in table 5.4.

Table 5.4: The initial rate (DR_i) and extent of dissolution (AUC) of furosemide from tablets prepared by the different Kollidon® VA64 powder mixtures at two compression settings (stroke length 1 and 4). Values between brackets represent standard deviation (SD).

Parameter	Compression Setting	Binder Concentration (% w/w Kollidon® VA64)		
		3	6	10
DR_i ($mg.cm^{-3}.min^{-1}$)	1	0.0007994 (0.0000969)	0.0000654 (0.0000415)	0.000125 (0.0000077)
	4	0.0006992 (0.0004514)	0.0000006 (0.0000004)	0.0000027 (0.0000022)
AUC ($mg.cm^{-3}.min^{-1}$)	1	1.1983904 (0.017291)	1.0504298 (0.038920)	1.1138264 (0.042592)
	4	1.1747947 (0.056725)	0.0902284 (0.020278)	0.0905819 (0.009232)

The dissolution profiles of furosemide from the tablets produced from the different powder mixtures of Kollidon® VA64 (3, 6 and 10% w/w) at two compression settings (stroke length 1 and 4) in 0.1 M HCl at 75 rpm are presented in fig. 5.4 and 5.5 respectively.

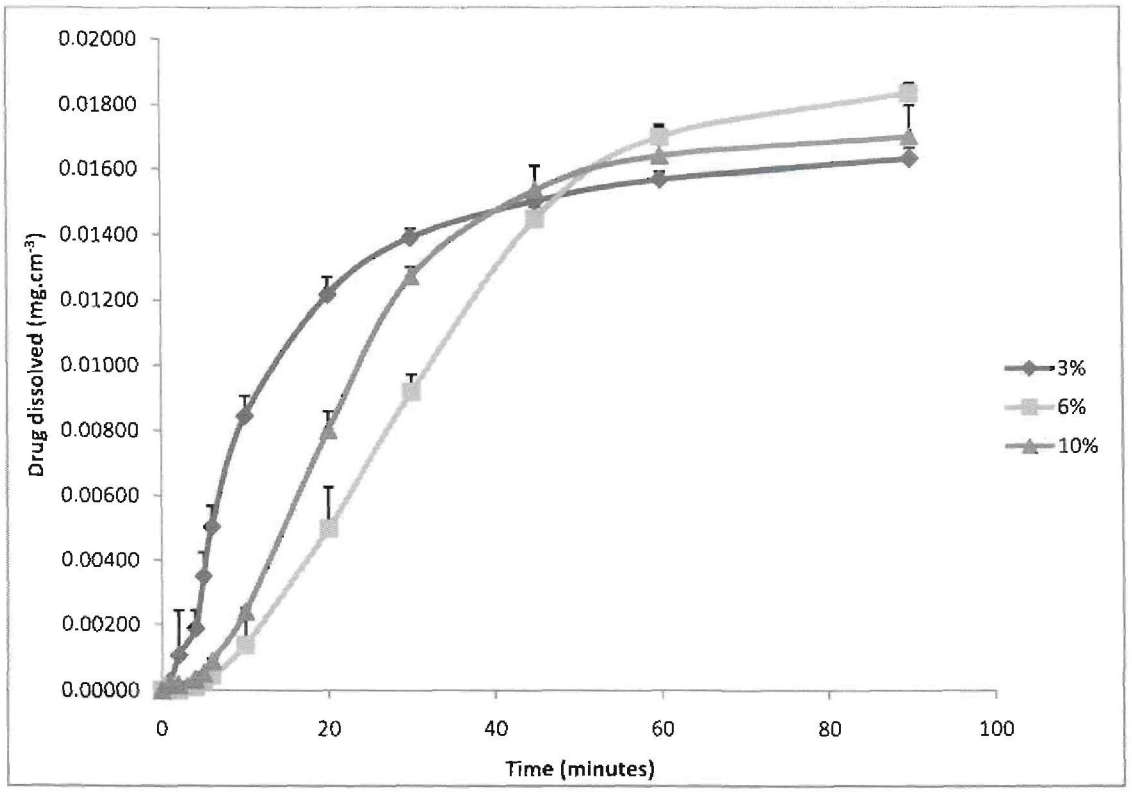


Fig. 5.4: The dissolution profiles of furosemide in 0.1 M HCl at 75 rpm from tablets prepared from different powder mixtures of Kollidon® VA64 (3, 6 and 10% w/w) at compression setting 1.

The dissolution profiles of furosemide from tablets of the three binder concentrations (3, 6 and 10% w/w), compressed at compression setting 1, exhibited profiles associated with disintegrating tablets. However, disintegration results (see section 5.2.3) showed that only the tablets produced at a 3% w/w binder concentration level exhibited disintegration. Tablets produced with higher Kollidon® VA64 content did not disintegrate in less than twenty minutes (disintegration time limit). Despite this, the tablets produced at concentration levels of 6 and 10% w/w Kollidon® VA64 exhibited dissolution profiles similar to that of the 3% w/w Kollidon® VA64 formulation and the DR_t of the tablets produced from the powder mixture of 10% w/w Kollidon® VA64 was higher in comparison to that of the tablets produced from the 6% w/w Kollidon® VA64 formulation (0.000125 ± 0.0000077 and 0.0000654 ± 0.0000415 $mg.cm^{-3}.min^{-1}$, respectively). A possible explanation for this phenomenon could be that Kollidon® VA64 increased the solubility of furosemide. In support of this explanation, Bühler (2003:121-123) found that Kollidon® VA64 increases the solubility of furosemide. The amount of Kollidon® VA64 present in the 10% w/w formulation (± 25 mg in a tablet weighing 250 mg) is higher than in the 6% w/w formulation (± 15 mg in a tablet weighing 250 mg). This signifies that more Kollidon® VA64 is present in the 10% w/w formulation to increase

furosemide's solubility in comparison to the 6% w/w formulation, and this could have contributed to the higher DR_i-value of the 10% w/w formulation. However, the difference in DR_i and AUC-values between the 6 and 10% w/w Kollidon® VA64 formulations was not statistically significant (ANOVA, Tukey test, $p > 0.05$), but the DR_i-value of the 3% w/w formulation differed statistically significant (ANOVA, Tukey test, $p < 0.05$) from the 6 and 10% w/w formulations. This difference can be related to the fact that the disintegration times of the 6 and 10% w/w formulation exceeded twenty minutes and this signifies that the surface area available for dissolution was smaller for these two formulations in comparison to the 3% w/w formulation. The smaller surface area available for dissolution therefore led to a slower DR_i.

The average AUC-values of the 6 and 10% w/w formulations were smaller than that of the 3% w/w formulation. This difference was statistically significant (ANOVA, Tukey test, $p < 0.05$). This implies that the extent (AUC) of furosemide dissolution exhibited by the tablets of the 6 and 10% w/w formulations were significantly smaller than that exhibited by the 3% w/w formulation. Thus, although the tablets of the 6 and 10% w/w formulations did exhibit dissolution profiles similar to that of the 3% w/w formulation, it could be concluded that because of the non-disintegrating behavior, it exhibited DR_i and AUC-values respectively slower and smaller in comparison to the disintegrating formulation (3% w/w). Whether this would have a significant therapeutic effect can only be evaluated *in vivo*.

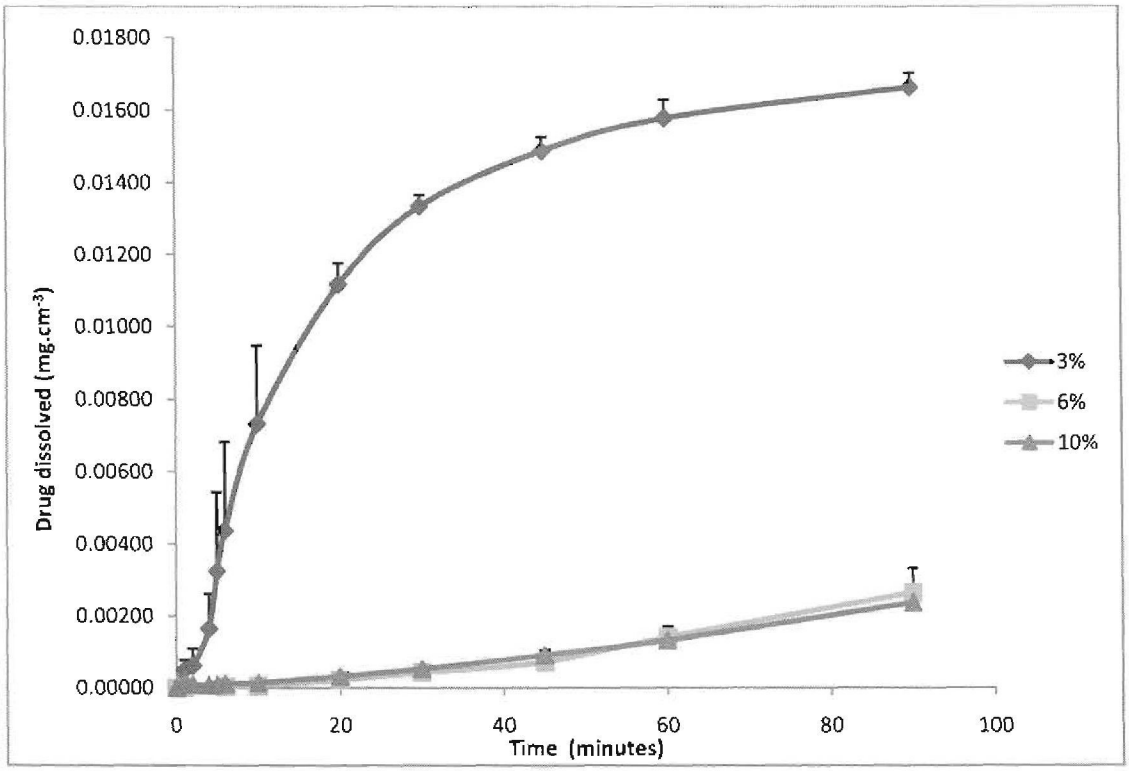


Fig. 5.5: The dissolution profiles of furosemide in 0.1 M HCl at 75 rpm from tablets prepared from different powder mixtures of Kollidon® VA64 (3, 6 and 10% w/w) at compression setting 4.

The tablets produced from 3% w/w Kollidon® VA64 at compression setting 4 exhibited dissolution profiles typical of disintegrating tablets. As expected, the DR_i and AUC-values was lower for the tablets produced at compression setting 4 in comparison to that of the tablets produced at compression setting 1 at the same concentration level (3% w/w). This was expected as the tablets compressed at compression setting 4 was harder, indicating a higher degree of compaction. The higher mechanical strength is confirmed by average crushing strength values of 145.9 ± 11.72 N and 180.5 ± 10.56 N for the tablets compressed at compression setting 1 and 4 respectively. However, the higher mechanical strength did not result in a statistically significant difference with respect to DR_i and AUC respectively (ANOVA, Tukey test, $p > 0.05$). Although the average disintegration time of the tablets compressed at compression setting 4 was longer in comparison to that of the tablets prepared at compression setting 1 (see table 5.3), it can be concluded that as long as the tablets disintegrate it does not have a significant influence on the rate (DR_i) and extent (AUC) of dissolution at a low binder concentration (3% w/w).

From fig. 5.5, it is evident that the tablets prepared from the 6 and 10% w/w formulations at compression setting 4 exhibited poor dissolution profiles. This behavior can be related to

two factors, namely furosemide content and compression force. These two formulations exhibited higher average crushing strength values compared to the same formulations compressed at compression setting 1 (see fig 5.2). As these formulations (6 and 10% w/w) were exactly the same compared to that in fig. 5.4 (6 and 10% w/w), with the only difference being the compression setting at which the respective formulations were compressed, it can therefore be concluded that the dissolution profiles of these two formulations were negatively influenced by the compression force of these tablets. This can be confirmed by the fact that the tablets prepared from the same formulations (both 6 and 10% w/w) and compressed at compression setting 1 also did not disintegrate, but still exhibited dissolution profiles similar to disintegrating tablets. As shown in chapter 4, section 4.4, a higher compression force resulted in a prolonged disintegration time. The higher compression force caused a decrease in tablet porosity and as a result the disintegration time was prolonged. Water penetrated the tablet matrix to a lesser extent and disintegration was negatively influenced. This, in combination with the hydrophobic nature of furosemide, is the likely cause for the poor dissolution behavior of the tablets prepared from the 6 and 10% w/w Kollidon® VA64 formulation at compression setting 4.

From the DR_i and AUC-results reported in table 5.4, it is evident that both the 6 and 10% w/w formulations exhibited average DR_i and AUC-values respectively slower and smaller in comparison to the 3% w/w formulation compressed at compression setting 1. This was statistically significant (ANOVA, Tukey test, $p < 0.05$) for both parameters and both the 6 and 10% w/w concentration. These formulations will most probably render therapeutic problems as the rate and extent of dissolution were poor.

5.4 Summary and conclusion

Incorporation of furosemide had no detrimental effect on the weight variation as well as the mechanical strength (crushing strength and friability) of the tablets produced from the different formulations. However, disintegration behavior was negatively affected by the incorporation of the active ingredient. Only the tablets prepared from the 3% w/w Kollidon® VA64 formulation and compressed at compression setting 1 and 4 exhibited average disintegration times below twenty minutes. The average disintegration times of the tablets compressed at both compression settings for both the 6 and 10% w/w formulations were above twenty minutes. The negative effect on disintegration time could be attributed to the hydrophobic nature of furosemide as well as a decrease in surface porosity of the tablets, resulting in less water penetration of the tablet matrix and, therefore, longer disintegration times.

At compression setting 1, all three formulations (3, 6 and 10% w/w) exhibited similar dissolution profiles. However, dissolution results revealed significant differences in the rate (DR_i) and extent (AUC) of furosemide dissolution between the 3% w/w and both the 6 and 10% w/w formulations. Whether this would have a significant therapeutic effect can only be evaluated *in vivo*. At compression setting 4, only the 3% w/w Kollidon® VA64 formulation exhibited a dissolution profile similar to the dissolution profile at compression setting 1. Both the 6 and 10% w/w Kollidon® VA64 formulations at compression setting 4 exhibited poor dissolution profiles, resulting in both average DR_i and AUC-values significantly slower and smaller in comparison to the 3% w/w formulation.

From the dissolution results it can, therefore, be concluded that the active ingredient (even low doses), binder concentration and compression force have a significant influence on drug dissolution. Despite that tablet properties such as crushing strength and disintegration proved to be acceptable with placebo formulations (formulations without the active), the inclusion of a low-dose drug proved to have a significant influence on dosage form properties such as disintegration and as a consequence drug dissolution.

Results showed that the disintegration process plays a significant role in the dissolution process of a sparingly water soluble drug like furosemide in terms of establishment of rapid contact between drug particles and the surrounding medium. Although disintegration does not assure drug dissolution, a prolongation of this process can result in slow dissolution rates resulting in a low rate and extent of drug dissolution.

Finally, it was concluded that low-dosage drugs (e.g. furosemide) can alter tablet properties and plays a major role in wet granulation when using Kollidon® VA64. Furthermore, it was concluded that an increase in binder concentration level (from 3 to10% w/w) does not necessarily render significant advantages, as elevated binder concentration levels affected disintegration and dissolution negatively.

Chapter 6

SUMMARY AND FUTURE PROSPECTS

6.1 Summary

Tablets account for about 80% of pharmaceutical preparations and are very popular for its numerous advantages. Wet granulation is the oldest technique used to produce solid pharmaceutical dosage forms, but it is still widely used and is a very popular technique. Drawbacks, however, for this technique are cost, energy and labor intensity. Despite this, it is a commonly used process by many pharmaceutical industries worldwide, especially when certain dosage forms contain a large amount of active ingredient. Direct compression is ineffective when the concentration of active ingredient incorporated in the tablet is high, because binding properties in the tablet becomes a major concern.

Lactose was used as filler in this study and three different binders (Kollidon® 30, VA64 and 90F) at three different concentration levels (3, 6 and 10% w/w) were employed to manufacture granules by using wet granulation as manufacturing process. The wet granulate was dried and mixed with Explotab® as disintegrant and magnesium stearate as lubricant. Powder characteristics were evaluated in terms of flow rate, angle of repose, compressibility and particle size distribution. Tablets were compressed on a single station tablet press at two different compression settings (stroke length 1 and 4) using 8 mm flat faced punches at a constant die volume. The tablets were evaluated in terms of weight variation, mechanical strength (crushing strength and friability) and disintegration. Tablets containing furosemide as model drug was compressed, dissolution studies were conducted and the DR_i and AUC-values were calculated.

Granules were successfully prepared with the different binders, with the exception of the 10% w/w Kollidon® 90F powder mixture, which could not be prepared due to difficulty during the granulation process. All the powder mixtures exhibited acceptable flow as characterized by angle of repose, flow rate and compressibility index (Carr's Index).

The tablets (placebo) produced from the different powder mixtures exhibited acceptable weight variation (%RSD), values being below 5%. This implies that the variation in drug content (if the formulations would have contained an active ingredient) would be within acceptable limits given that the active ingredient does not have a significant effect on the flow behavior of the powder mixtures. %RSD-values can also be indicative of powder flow behavior, as bigger values would indicate impaired flow properties.

An increase in compression force resulted in a significant increase in average crushing strength of the placebo tablets prepared from all the powder mixtures. With regard to binder concentration, both Kollidon® 30 and 90F rendered tablets with a significant higher average crushing strength at increased binder concentrations. However, Kollidon® VA64 containing formulations revealed no statistically significant (ANOVA, Tukey test, $p > 0.05$) benefit with regard to an increase in binder concentration. All the formulations exhibited acceptable resistance to friability, values being below 1%. From the crushing strength results as well as the friability results it is evident that all the placebo formulations rendered tablets with acceptable mechanical strength.

A tendency towards increased disintegration time was observed with an increase in compression force for all the formulations. This could possibly be attributed to harder tablets and lower tablet porosity with an increase in compression force. All the Kollidon® VA64 formulations exhibited average disintegration times below ten minutes. It can, therefore, be concluded that Kollidon® VA64 was an efficient binder and rendered satisfactory disintegration results over the concentration range employed in comparison to Kollidon® 30 and 90F.

In view of the results obtained with the different placebo formulations, Kollidon® VA64 was selected to prepare formulations containing a sparingly water soluble and poorly water wettable drug (i.e. furosemide) to determine the effects of a low-dose drug on tablet properties. Only the tablets, containing furosemide, prepared with 3% w/w Kollidon® VA64 disintegrated within twenty minutes (disintegration time limit). However, tablets produced from the 6 and 10% w/w Kollidon® VA64 powder mixtures at compression setting 1, exhibited dissolution profiles similar to that of the 3% w/w formulation, indicating that disintegration is not an absolute prerequisite for dissolution at this compression setting. The fact that the tablets produced from the 3% w/w Kollidon® VA64 formulation disintegrated, but the 6 and 10% w/w formulations did not, might also indicate a combination effect of binder concentration and drug type on dissolution that requires investigation on a case by case basis (with regard to active ingredient). Kollidon® VA64 proved to be more efficient at lower concentrations (below 6% w/w). At lower concentrations, the produced tablets disintegrated and exhibited acceptable dissolution profiles while the weight variation (%RSD) and mechanical strength (crushing strength and friability) proved to be acceptable.

In general, it can be concluded that with regard to Kollidon®, an increase in binder concentration does not necessarily render improved mechanical tablet strength as all the formulations exhibited acceptable crushing strength and %-friability values, although binder concentration could affect disintegration. It can also be concluded that compression force

plays a major role in terms of disintegration and dissolution and also that disintegration is not an absolute prerequisite for dissolution depending on compression force. With respect to the mechanical strength (crushing strength and friability) of tablets, it can be concluded that all the binders performed equally.

6.2 Future prospects

Throughout the present study, a water soluble filler, i.e. lactose and three different binders (Kollidon 30®, VA64 and 90F) were employed to produce granules by means of wet granulation. Alongside this, a low-dose sparingly water soluble drug (i.e. furosemide) was employed to evaluate the effect of an active ingredient of this nature on the binder properties. These two particulars certainly raise several possibilities that can be investigated in future studies. The following variables or factors can be investigated in future studies:

- Insoluble fillers such as dicalcium phosphate and microcrystalline cellulose to investigate the influence of these fillers on binder properties and tablet properties such as disintegration.
- Water soluble and wettable drugs to investigate whether the same tendency with regard to disintegration and dissolution is observed.
- Other drugs exhibiting low water solubility to investigate whether their influence on binder and tablet properties are similar.
- Lower concentration levels of Kollidon® to determine whether tablets (containing a poorly water soluble and wettable drug) with acceptable mechanical strength and enhanced disintegration behavior can be prepared.
- Drugs with high doses such as paracetamol to investigate whether Kollidon® VA64 is still the binder of choice.

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