THE EFFECT OF SOLUBLE AND INSOLUBLE FILLERS/BINDERS ON THE DISINTEGRATION AND DISSOLUTION OF DRUGS FROM DIRECTLY COMPRESSED TABLET FORMULATIONS

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INTRODUCTION, HYPOTHESIS AND AIM

The properties of directly compressed tablet formulations depend mainly on the physicochemical characteristics of the filler, since they often comprise more than 80% of the total tablet weight. These additives, however, do not only affect and determine the physical properties of the tablets, but also significantly affect (positively or negatively) the release and dissolution of the drug from the tablet formulation. It could therefore be assumed that significant differences between the physical properties of different fillers would result in varying physical tablet properties which could result in differences in drug release and drug dissolution patterns from these formulations.

Microcrystalline cellulose (marketed as Avicel® PH 200) and lactose (marketed as Tablettose®) are two compounds which are currently used as directly compressible fillers. These two fillers differ significantly in terms of their physicochemical properties. Avicel® PH 200 is an insoluble filler with excellent disintegrating properties (Fox *et al.,* 1963:260), whilst Tablettose® is classified as a soluble filler without any disintegrating characteristics (Schmidt & Rubensdörfer, 1994:2907). Johnson *et al.* (1991:469) found that soluble tablet formulations did not need a disintegrant, and stated that the efficiency of swelling disintegrants may actually be impeded in these formulations. The hypothesis however, is that these findings may not be applicable to slowly dissolving systems, such as would be the case with Tablettose® formulations, and that these type of fillers would exhibit the same properties suggested for insoluble fillers without disintegrating properties.

Although disintegration is not always a prerequisite for drug dissolution, this process plays a significant role in the rate and extent of dissolution, especially in the case of sparingly water-soluble drugs (like furosemide). The contribution of the disintegration process to drug dissolution can be attributed to an increase in the effective surface-area of the drug (i.e. the surface-area exposed to or in direct contact with the surrounding aqueous medium). Disintegrants facilitate break-up of tablets, resulting in the rapid release of primary drug particles with a large surface area, which according to the general dissolution equation, is one of the main contributing factors to optimal drug dissolution (Kanig & Rudnic, 1984:51).

Most of the disintegrants employed in directly compressible tablet formulations, i.e. the so-called superdisintegrants like croscarmellose sodium (Ac-Di-Sol®), sodium starch glycolate and povidone (Kollidon® CL) swell upon contact with liquid molecules, resulting in the development of a disintegrating force inside the tablet structure, which breaks interparticulate bonds and leads to subsequent drug release. It could therefore be expected that any factor which prevent contact between the disintegrant and the surrounding medium, could reduce disintegrant efficiency and ultimately decrease drug dissolution. These factors include hydrophobic constituents (drug and excipients), insoluble formulation components (especially the filler/binder) and compression force (which increases tablet density or decreases tablet porosity, thereby slowing down liquid penetration into tablets).

The aim of this study was therefore to test the following hypothesis:

1. The differences in the solubility and disintegrating properties of directly compressible fillers have a significant effect on the dissolution of drugs for which dissolution is the rate-limiting step, i.e. sparingly water-soluble drugs like furosemide.
2. Formulation variables affecting contact between disintegrant particles and the surrounding medium can have a significant effect on drug dissolution.

To achieve the aim of the study the following will be undertaken:

- Characterisation and comparison of the physical powder properties of Avicel® PH 200 and Tablettose® (chosen as typical examples of insoluble, disintegrating and soluble non-disintegrating directly compressible fillers respectively).
- Changes to Tablettose® formulations to improve certain shortcomings in the properties of tablets through the incorporation of specific excipients, like a dry binder and a disintegrant.
- Comparison of the dissolution profiles of a sparingly water-soluble drug (furosemide) from basic Avicel® PH 200, basic Tablettose® and altered Tablettose® formulations.
- Evaluation of the success of the addition of excipients to Tablettose® formulations in terms of its effect on drug dissolution.

ABSTRACT

THE EFFECT OF SOLUBLE AND INSOLUBLE FILLERS/BINDERS ON THE DISINTEGRATION AND DISSOLUTION OF SPARINGLY SOLUBLE DRUGS FROM DIRECTLY COMPRESSED TABLET FORMULATIONS

Although disintegration is not always a prerequisite for drug dissolution, this process plays a significant role in the rate and extent of dissolution, especially in the case of sparingly water-soluble drugs (like furosemide). Any factor that influences tablet disintegration, therefore, will influence drug dissolution. Since the filler often comprises more than 80% of the total tablet weight, it will affect tablet properties and therefore disintegration. The solubility of the filler is expected to play a major role in determining tablet disintegration.

During the initial stage of the study the physical powder properties (density, particle size, flow properties and compressibility) of Tablettose® (soluble) and Avicel® PH 200 (insoluble) as tablet fillers were determined and compared in order to establish their inherent powder properties.

Tablets from mixtures containing each filler and 0.5% w/w magnesium stearate (as lubricant) were prepared at a constant die fill volume at different compression pressures. Since Tablettose® could not be tableted without a lubricant due to high friction during ejection, magnesium stearate was included in all formulations. Tablets were evaluated in terms of weight variation, crushing strength, friability and disintegration times. Tablettose® produced tablets with extremely low crushing strengths and high friability compared to Avicel® PH 200, which produced tablets with acceptable physical properties. The most significant difference between the two formulations was observed in the disintegration times, with the Avicel® tablets producing rapid disintegration whilst Tablettose® produced slowly dissolving rather than disintegrating tablets. These results indicated shortcomings in the properties of Tablettose® as directly compressible filler and suggested possible problems in terms of drug release.

Following the results from the previous experiments, the effect of addition of 3.5, 5 and 7% w/w Kollidon® 30 and Kollidon® VA 64 as dry binder (to increase mechanical strength) and 0.5, 1 and 2% w/w Ac-Di-Sol®, Kollidon® CL and sodium starch

glycolate as disintegrant (to induce tablet disintegration) on the physical properties of Tablettose® formulations was evaluated in order to eliminate the observed poor physical tablet properties. Although the presence of a dry binder had little effect on the crushing strength of the tablets it did increase the compression range during tableting, thereby increasing the compression force before capping occurred. Kollidon® VA 64 (3.5%) proved to be the most efficient. The incorporation of a disintegrant, irrespective of the type or concentration of the disintegrant, resulted in a significant decrease in disintegration time (1% of each disintegrant provided efficient disintegration). This was ascribed to a change from slowly dissolving tablets (with disintegration exceeding 15 minutes) to rapidly disintegrating tablets (with disintegration times less than 3 minutes).

In the final stage the dissolution of furosemide (chosen as model drug representing sparingly water-soluble drugs for which dissolution is the rate-limiting step) from Avicel®, Tablettose® and Tablettose®/Kollidon® VA 64 and Ac-Di-Sol®, Kollidon® CL or sodium starch glycolate formulations was determined in 0.1M HCl. Dissolution results were compared using calculated dissolution parameters, namely the initial dissolution rate (DRi) and the extent of dissolution (AUC). Dissolution from the slowly dissolving Tablettose® tablets was significantly slower compared to the rapid disintegrating Avicel® tablets, confirming the hypothesis that slowly dissolving (but non-disintegrating) formulations impede drug dissolution due to the small surface-area of the drug exposed to the surrounding medium. The incorporation of Kollidon® VA 64 (as dry binder) in Tablettose® formulations resulted in unexpectedly high drug dissolution comparable with profiles obtained from the Avicel® tablets, despite the fact that the tablets did not disintegrate. The literature provided an answer, indicating that Kollidon® VA 64 increased the solubility of furosemide (Bühler, 1993:114), possibly due to the formation of a drug/excipient complex. Addition of a disintegrant to this formulation further increased drug dissolution due to rapid tablet disintegration. Once again no significant difference in drug dissolution was observed between the three disintegrants used. The dissolution results also indicate a dependency of the extent of drug dissolution (AUC) on the initial dissolution rate (DRi), indicating the importance (although not an absolute prerequisite) of establishment of rapid contact between drug particles and the surrounding medium through the incorporation of a disintegrant.

UITTREKSEL

DIE EFFEK VAN OPLOSBARE EN ONOPLOSBARE VULSTOWWE OP DIE DISINTEGRASIE EN DISSOLUSIE VAN SWAK WATEROPLOSBARE GENEESMIDDELS VANUIT DIREK SAAMGEPERSDE TABLETTE

Alhoewel disintegrasie nie altyd 'n voorvereiste vir dissolusie is nie, speel dit tog 'n baie belangrike rol in die tempo en mate van dissolusie, veral in die geval van swak wateroplosbare geneesmiddels (bv. furosemied). Dissolusie sal dus beïnvloed word deur enige faktor wat disintegrasie beïnvloed. Aangesien meer as 80% van 'n tablet gewoonlik uit die vulstof bestaan, sal die vulstof die tableteienskappe en uiteindelik ook die disintegrasie beïnvloed. Dit word verwag dat die oplosbaarheid van die vulstof 'n groot invloed sal hê op disintegrasie.

Aan die begin van die studie is die fisiese poeier-eienskappe (digtheid, deeltjiegrootte, vloei-eienskappe en saampersbaarheid) van Tablettose® (oplosbaar) en Avicel® PH 200 (onoplosbaar) as vulstowwe, bepaal. Hierdie eienskappe is met mekaar vergelyk om die vulstowwe se inherente poeier-eienskappe te bepaal.

Tablette is berei vanaf mengsels van elke vulstof met 0.5% m/m magnesiumstearaat as smeermiddel. Die tablette is by 'n konstante matrysvolume en by verskillende samepersingsdrukke getabletteer. Magnesiumstearaat is by alle tabletformules gevoeg omdat Tablettose® nie getabletteer kon word sonder 'n smeermiddel nie, a.g.v. hoë wrywing tydens uitstoting van die tablette. Tablette is geëvalueer ten opsigte van massavariasie, breeksterkte, afsplyting en disintegrasietyd. Tablettose® het tablette gelewer met baie lae breeksterktes en hoë afsplyting in vergelyking met Avicel® PH 200. Avicel® PH 200 het tablette gelewer met aanvaarbare fisiese eienskappe. Die belangrikste verskil tussen die twee vulstowwe was hulle disintegrasietye. Die Avicel® tablette het vinnige disintegrasie getoon, maar die Tablettose® tablette het eerder stadig opgelos as om te disintegreer. Hierdie resultate het gedui op tekortkominge in Tablettose® as direksaampersbare vulstof en moontlike probleme met geneesmiddelvrystelling vanuit hierdie tablette.

Na aanleiding van die laasgenoemde resultate is die effek van die byvoeging van sekere hulpstowwe op die fisiese eienskappe van Tablettose® tablette ondersoek in 'n poging om die waargenome tekortkominge uit te skakel. Hierdie hulpstowwe het ingesluit Kollidon® 30 en Kollidon® VA 64 as droë bindmiddel (3.5, 5 en 7% m/m), en Ac-Di-Sol®, Kollidon® CL en natriumstyselglikolaat as disintegreermiddel (0.5, 1 en

2% m/m). Die byvoeging van die droë bindmiddel het min effek op die breeksterkte van die tablette gehad, alhoewel dit die samepersingsdruk verhoog het waarby tablette getabletteer kon word voor dekselvorming 'n probleem geword het. Kollidon® VA 64 (3.5% m/m) was die doeltreffendste bindmiddel. Die byvoeging van 'n disintegreermiddel (ongeag die tipe of konsentrasie) het betekenisvolle vinniger disintegrasie tot gevolg gehad. 'n Konsentrasie van 1% van enige disintegreermiddel het bevredigende disintegrasie gelewer. Hierdie afname in disintegrasietyd kon toegeskryf word aan die verandering van stadig oplosbare tablette (met disintegrasietye langer as 15 minute) na vinnig disintegrerende tablette (met disintegrasietye van minder as 3 minute).

Laastens is die dissolusie van furosemied (in 0.1 M HCl), as modelgeneesmiddel vir swak wateroplosbare geneesmiddels waar dissolusie die snelheidsbepalende stap is, bepaal. Dissolusieprofiele is bepaal vir tablette van Avicel®, Tablettose® en Tablettose®/Kollidon® VA 64 met Ac-Di-Sol®, Kollidon® CL of natriumstyselglikolaat. Dissolusieresultate is vergelyk in terme van twee berekende dissolusieparameters, naamlik die aanvanklike dissolusiesnelheid (DRi) en die mate van dissolusie (AUC). Dissolusie was aansienlik stadiger vanuit die stadig-oplosbare Tablettose® tablette in vergelyking met die vinnig disintegrerende Avicel® tablette. Hierdie stadige dissolusie vanuit Tablettose® tablette bevestig die hipotese dat stadig oplosbare tablette wat nie disintegreer nie, dissolusie van geneesmiddels vertraag, as gevolg van die klein oppervlakarea van die geneesmiddel wat aan die omringende medium blootgestel is. Die byvoeging van Kollidon® VA 64 (as droë bindmiddel) by Tablettose® formules het gelei tot 'n onverwagse hoë dissolusie van die geneesmiddel wat vergelykbaar is met dissolusieprofiele wat vanaf Avicel® tablette verkry is, ondanks die feit dat die tablette nie gedisintegreer het nie. Die rede vir hierdie verbeterde dissolusie is dat Kollidon® VA 64 die oplosbaarheid van furosemied verbeter het (Bühler, 1993:114). Dit mag moontlik wees a.g.v. die vorming van 'n geneesmiddel-hulpstof kompleks. Deur die byvoeging van 'n disintegreermiddel by hierdie Kollidon®-formule, is die dissolusie verder verhoog, wat toegeskryf kan word aan die vinnige disintegrasie van hierdie tablette. Weereens was daar nie 'n betekenisvolle verskil tussen die drie verskillende disintegreermiddels nie. Die dissolusieresultate het ook aangedui dat die mate van dissolusie (AUC) van die aanvanklike dissolusiesnelheid (DRi) afhanklik is. Dit is dus baie belangrik dat daar genoegsame kontak tussen die geneesmiddeldeeltjies en die omringende medium is, wat bewerkstellig word deur die teenwoordigheid van 'n effektiewe disintegreermiddel.

1. CHAPTER 1

DIRECT COMPRESSION AND FORMULATION EXCIPIENTS: EFFECT ON TABLET PROPERTIES AND DRUG RELEASE- A LITERATURE REVIEW

1.1 INTRODUCTION

Since the active ingredient usually constitutes such a small percentage of the total tablet weight, the disintegration and dissolution of the tablet and thus bioavailability of the drug, depend largely on the characteristics of the excipients used in the tablet formulation.

1.2 DRUG RELEASE AND DISSOLUTION FROM COMPRESSED SYSTEMS

Orally administered drugs must dissolve in the gastrointestinal fluids to assure rapid and optimum absorption into the systemic circulation. The dissolution of sparingly water-soluble and poorly water-wettable drugs in the GI-fluids is, amongst other factors, dependant on the effective surface-area of the drug, i.e. the surface area of the drug in contact with the surrounding aqueous medium in the GI-tract. These drugs exhibit extremely slow dissolution rates and incomplete dissolution due to their inherent low solubilities. The latter is further aggravated during tableting (compression) because of a significant reduction in the effective surface-area of the drug. In order to facilitate rapid and complete release of drug particles from the tablet matrix, the bonds between tablet components formed during compression must be broken. This process of tablet break-up, or better known as disintegration, is facilitated by excipients known as disintegrants (discussed in section 1.4.1.3).

Therefore, it seems valid to assume that tablet disintegration may be an important factor (play a significant role) during the absorption of drugs for which dissolution is the rate-controlling step, and that it may well influence the eventual rate and extent of the therapeutic onset and efficiency of these drugs. The interdependency of tablet disintegration, drug dissolution and drug absorption is depicted in figure 1.1 as proposed by Wagner (1970:33).

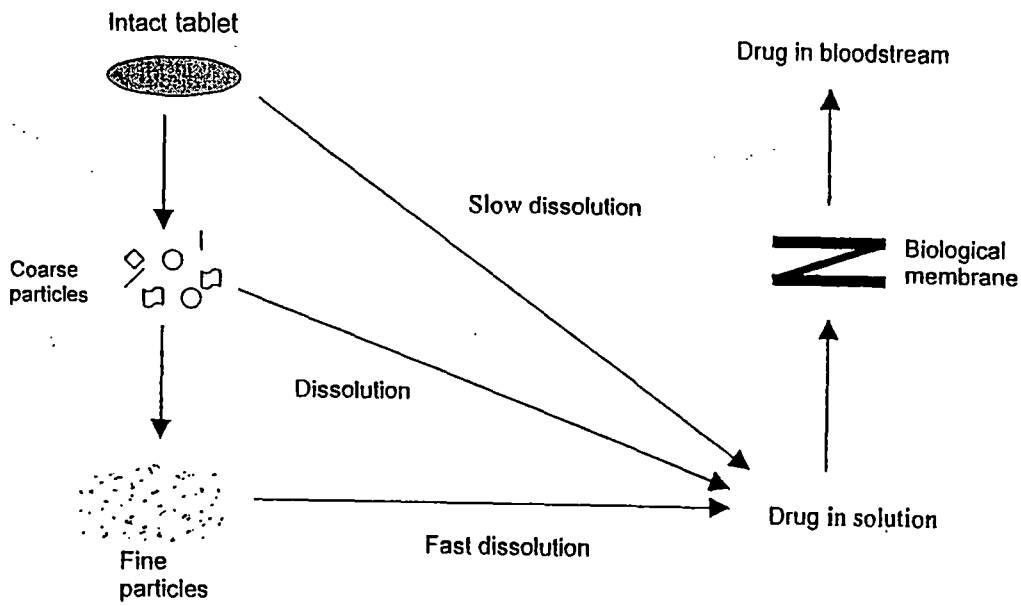

Figure 1.1: *A schematic representation of the processes preceding the appearance of a drug in the blood after oral administration of a tablet or capsule (Wagner, 1970:33).*

The first documented study of the dissolution process dated back more than a century (Noyes & Whitney, 1897:932). The major findings of their study can be summarised as follows: "the rate of solution of solids is mainly governed by the difference in the concentration of the solid at the solid interface and its concentration in the surrounding medium" and can be quantified by equation 1.1.

$$\frac{dC}{dt} = k(Cs - Ct) \qquad [1.1]$$

Various researchers have studied, criticised and extended their work, which resulted in the general dissolution equation depicted in equation 1.2.

$$\frac{dC}{dt} = k.A(Cs - Ct) \qquad [1.2]$$

where dC/dt = dissolution rate, k = a dissolution rate constant, A = the effective surface area of the solid, Cs = the saturation concentration of the solid and Ct = the concentration at any given time t.

The dissolution of solids in liquids can be seen as two consecutive stages. During the first stage, solid molecules are removed from the surface of the solid through an interface reaction (a reaction between the solid and liquid molecules in contact with each other at the solid-liquid interface). During the second stage these "loosened" molecules are transported from the surface of the solid to the surrounding medium under the influence of diffusion or convection (Abdou, 1989:11).

Factors influencing the dissolution rate of orally administered drugs can be deduced from the dissolution equation. The most important factor for the purpose of this study is the effective drug surface area, which in turn depends on the particle size, disintegration and deaggregation, and the effect of manufacturing procedures. Another factor is the solubility of the drug in the diffusion layer, which depends on pH effects and salt formation.

While tablet disintegration is frequently a necessary prerequisite for drug dissolution, it in no manner assures that a drug will dissolve. However, dissolution cannot effectively take place without prior disintegration (Kanig & Rudnic, 1984:51). Therefore, disintegration can to some extent govern drug efficiency, especially in the case of poorly water-soluble drugs.

Formulation and processing factors influencing drug release from tablets include manufacturing procedures, type of filler/binder used, type of disintegrant used, lubricant, hygroscopicity, solubility, compression force and mixing conditions.

1.3 DIRECT COMPRESSION: A SIGNIFICANT ADVANCE IN TABLET MANUFACTURING

Wet granulation is the oldest and best documented method of tablet manufacture and involves the manufacturing of granules in order to provide mixtures with tabletable properties. These properties include binding forces, uniform particle size and good flow properties to ensure effective compaction. The term direct compression is used to define the process by which tablets are compressed directly from powder blends of the

active ingredient and suitable excipients (including fillers, disintegrants and lubricants), that will flow uniformly into a die cavity and form into a firm compact. The advent of direct compression was made possible by the commercial availability of directly compressible vehicles that possess both fluidity and compressibility. The simplicity of the direct-compression process is obvious. It requires, however, a new and critical approach to the selection of raw materials, flow properties of powder blends, and effects of formulation variables on compressibility. 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, and there are few drugs that cannot be directly compressed (Shangraw, 1989:196).

The most obvious advantage of direct compression is economy. Savings can occur in a number of areas, including reduced processing time and thus reduced labour costs, fewer manufacturing steps and pieces of equipment, less process validation, and a lower consumption of power. The most significant advantage in terms of tablet quality is that of processing without the need for moisture and heat which is inherent in most wet granulation procedures, and the avoidance of high compaction pressures involved in producing tablets by slugging or roll compaction. The unnecessary exposure of a drug to moisture and heat can never be justified; it cannot be beneficial and may certainly be detrimental. Probably one of the least recognised advantages is the optimisation 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 drug particles with a large surface area are "glued" into larger agglomerates, is in direct opposition to the principle of increased surface area for rapid drug dissolution. Disintegrating agents, such as starch, added prior to wet granulation are known to be less effective than those added just prior to compression. In direct compression all of the disintegrant is able to perform optimally, and when properly formulated, tablets made by direct compression should disintegrate rapidly to the primary state. However, it is important that sufficient disintegrant be used to separate each drug particle if ideal dissolution is to occur (Shangraw, 1989:198).

Although there are many advantages to direct compression, there are also some restrictions. Many active ingredients are not compressible in either their crystalline or their amorphous forms. Thus, in choosing a vehicle it is necessary to consider the dilution potential of the major filler (i.e. the proportion of active ingredient that can be compressed into an acceptable compact utilising that filler). Fillers range from highly compressible materials such as microcrystalline cellulose to substances that have very low dilution capacity such as spray-dried lactose. It is not possible to give specific values for each filler because the dilution capacity depends on the properties of the drug itself. Another concern in direct compression is content uniformity. The granulation process locks active ingredients into place and, provided the powders are intimately dispersed before granulation and no drying-initiated unblending occurs after wetting, this can be advantageous. Direct compression blends are subject to unblending in postblending handling steps. The lack of moisture in the blends may give rise to static charges that can lead to unblending. Differences in particle size or density between drug and excipient particles may also lead to unblending in the tablet press (Shangraw, 1989:200). To prevent particle segregation due to size differences in the mixture component, the filler must have a fairly uniform particle size and particle shape. Thus, wet granulation ensures uniform mixture content, but with direct compression the uniformity of the mixture depends largely on the mixing process. Since the filler constitutes the largest percentage of the mixture, the tableting properties are largely determined by the properties of the filler. With wet granulation a binding agent is always added, but it is often not necessary to add a binding agent to directly compressible mixtures. Some directly compressible fillers possess binding properties such as cohesive forces or hydrogen bonding (Battista & Smith, 1962:21; Fox *et al.,* 1963:260). In turn, these bindings affect the crushing strength, friability and disintegration of the tablets. A binding agent has to be added to formulations where the filler does not possess adequate binding properties. The solubility and hygroscopicity of the filler will determine the necessity for the incorporation of other excipients such as disintegrants.

The aim of formulation must be to produce tablets with fast and effective drug release and dissolution. It is important to note that with direct compression, higher compression pressures are used than with wet granulation. These higher compression pressures are necessary to form 'strong' tablets, in other words, to produce and enhance bonds

between individual particles. This can lead to capping, long disintegration times and slow dissolution. Therefore the choice of excipients (especially the filler) is very important in direct compression.

1.4 EFFECT OF FORMULATION VARIABLES AND PROCESSING FACTORS ON PROPERTIES OF AND DRUG RELEASE FROM DIRECTLY COMPRESSED TABLETS

The factors influencing tablet properties and drug release and dissolution profiles from directly compressed tablets can be classified into two groups, namely:

- formulation variables and
- processing variables.

The following section contains a brief discussion of the various factors, emphasising the interdependency of these factors and the importance of each in order to assure a quality product (in terms of physical properties) and effective drug release and dissolution (both in terms of rate and extent) necessary for optimum drug efficiency. The discussion also focuses (with motivation) on the excipients and processes employed in this particular study. In figure 1.2 the factors affecting drug release and dissolution are shown.

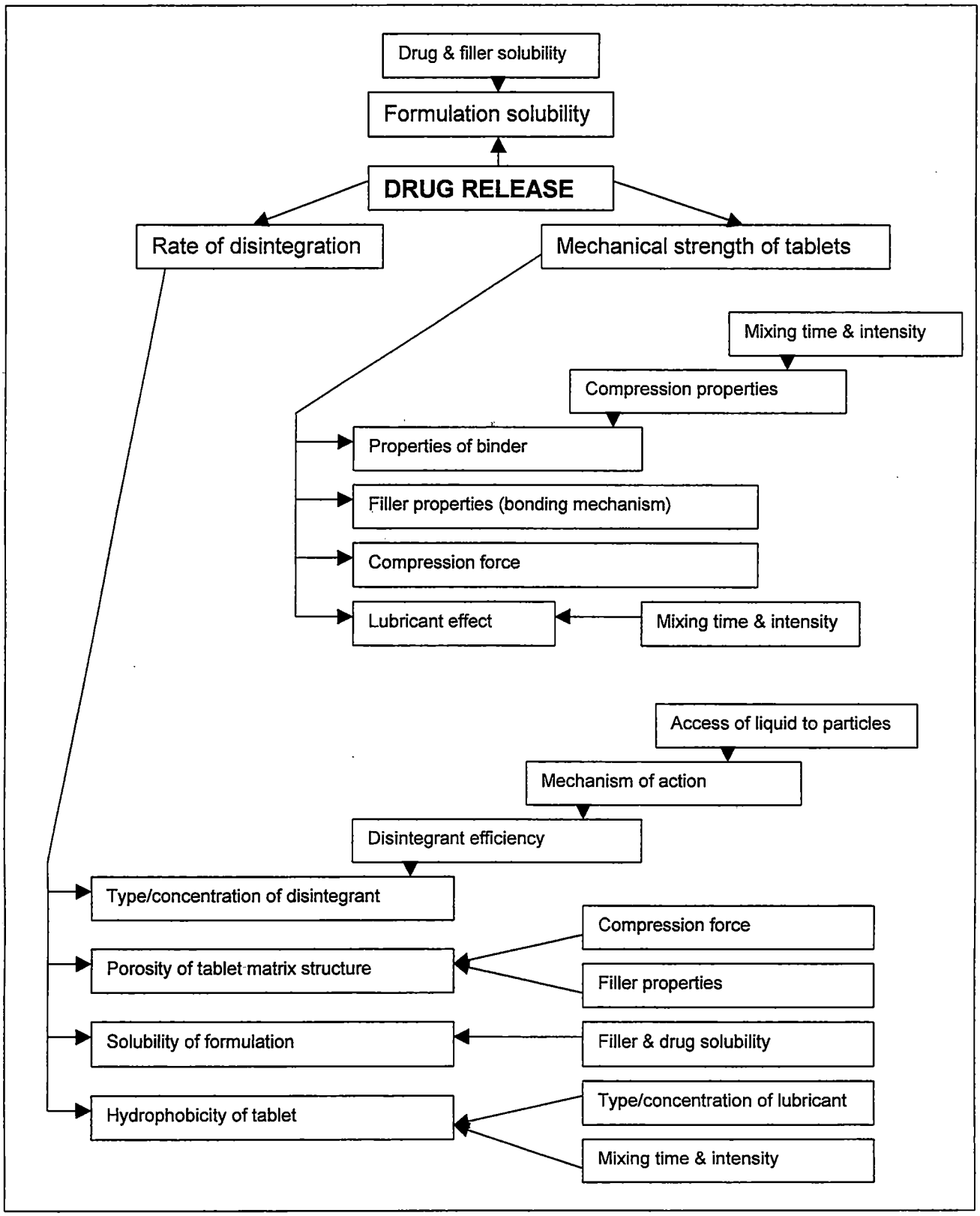

Figure 1.2: *Factors influencing drug release and dissolution from an intact tablet*

1.4.1 PROPERTIES OF SOME POPULAR EXCIPIENTS USED IN DIRECT COMPRESSION FORMULATIONS AND THEIR EFFECT ON TABLET CHARACTERISTICS AND DRUG RELEASE

The filler is the most important excipient in direct compression, since it is the filler that determines the tableting properties of the mixture, and it is not possible to directly compress only the active ingredient. The filler is the only excipient without which direct compression is not possible. Other excipients sometimes used in direct compression, depending on the properties of the filler, are binders, disintegrants and lubricants. The binder provides binding properties to the tablets. Binders can increase the mechanical strength of a tablet, and therefore retard disintegration and dissolution. Then it becomes important to add the right disintegrant in the right concentration to the formulation to ensure that the tablet can overcome the bonding forces between individual particles. Lubricants are added to minimise adhesion forces that develop between the tablet and the die wall. Some fillers possess adequate bonding, disintegrating or lubrication properties, and it is not necessary to include any of these excipients to the formulation.

Some of the traditional excipients used in tablet formulations, like the starches, gave way to new and better excipients with better flow properties and better compressibility. The ideal excipient for direct compression tableting should be free-flowing, inert with respect to chemical, physical and physiological reactivity, relatively inexpensive, and compressible into tablets which exhibit excellent hardness, friability, disintegration time and dissolution rate of the active ingredient (Bolhuis & Lerk, 1973:471). Its particle size distribution must match with a wide range of drugs, it must have a good pressure-hardness profile and capable of handling without a decrease in compressibility or fluidity (Shangraw, 1989:203). It is therefore important to give careful consideration to the choice of the excipients used in a formulation.

1.4.1.1 Fillers

Since the active ingredient usually constitutes such a small percentage of the total tablet weight, it is impossible to compress tablets containing only the active ingredient. Therefore inert substances, namely fillers, are added to reach a tabletable weight. Other reasons for including fillers in tablet formulations are to:

1. provide tablets with certain physical characteristics,
2. improve powder flow,
3. make direct compression possible,
4. improve tablet disintegration and
5. provide binding properties.

There are many types of fillers/binders available for direct compression as shown in table 1.1.

Table 1.1: *Fillers for direct compression* (Bolhuis & Lerk, 1973:469-471).

Filler	**Trade name**
α-lactose monohydrate	Tablettose®
α-lactose monohydrate/PVP	Ludipress®
Microcrystalline cellulose	Avicel® PH
Microfine cellulose	Elcema®
Dicalcium phosphate dihydrate	Emcompress®
Directly compressible starch	STA-Rx 1500®, Emdex®. Celutab®
Sucrose	Sugartab®, Di-Pac®, Nu-Tab®

The most frequently used fillers include the lactose-types, microcrystalline cellulose and dicalcium phosphate dihydrate. Lactose is probably the oldest filler/binder in tableting. It has no disintegrant properties and because lactose lacks essential fluidity and compressibility in its regular form, common lactose cannot be used in direct compression of tablets without modification. Riepma *et al.* (1992:123) showed differences in consolidation and compaction between the granular lactose types, i.e. roller-dried β-lactose and anhydrous α-lactose, and the non-granular lactose types, namely, crystalline β-lactose and α-lactose monohydrate.

α-lactose monohydrate

Ludipress® contains α-lactose-monohydrate as filler/binder. The other components, povidone (Kollidon® 30) and crospovidone (Kollidon® CL), increase compactibility and provide a certain swelling activity (Schmidt & Rubensdörfer, 1994:2901). Due to its

composition, Ludipress® as a single adjuvant can substitute various tablet ingredients and acts as a multipurpose excipient for direct compression (Schmidt & Rubensdörfer 1994:2925).

Ludipress® granules have a spherical shape, which explains the good flowability of this excipient. The single crystals are held together by amorphous components. These are mainly povidone, crospovidone and amorphous lactose ("lactose glass", which is generated during the production process). As lactose glass undergoes plastic deformation during compaction, it increases the binding capacity of lactose. Therefore, in order to achieve a high dilution potential, a lactose based tableting excipient should contain a high amount of lactose glass (Schmidt & Rubensdörfer, 1994:2905).

A disintegration or dissolution optimum at a certain compaction load of a lactose based granule containing povidone and crospovidone has been reported earlier by Khan and Rooke (1976:633). Disintegration efficiency increases progressively with increasing pressure, until an optimum pressure is reached. This phenomenon can be explained by the packing density of the tablet.

At 75.1 MPa, packing of the tablet is loose. Intact lactose crystals and amorphous constituents can be detected clearly. During water uptake the swelling of the crospovidone (a cross-linked insoluble polymer) will lead to tablet disintegration. Due to the loose packing of the tablet, a certain amount of swelling volume will vanish into the numerous voids of the compact causing prolonged disintegration. By increasing the compaction load up to 100 MPa, plastic deformation of the amorphous constituents occurs, providing optimal tablet properties. The single crystals are "glued" together, leading to a significant reduction in friability. Due to the augmented packed density, the interparticulate volume decreases, thus enabling the crospovidone in Ludipress® to establish its swelling activity properly. A further increase of the compaction pressure causes a more brittle fracture of the lactose crystals and a strong decrease in tablet porosity. Consequently water uptake is impeded and disintegration time increases (Schmidt & Rubensdörfer, 1994:2913).

Tablettose® is soluble in water and consists of a free-flowing α-lactose-monohydrate granule instead of the fine lactose used in the production of Ludipress®. Ludipress® also contains an additional binder (povidone) and disintegrant (crospovidone), and is therefore more efficient than Tablettose®. Ludipress® produces harder tablets compared to tablets prepared from Tablettose® (Schmidt & Rubensdörfer, 1994:2907).

Anhydrous lactose

Anhydrous lactose possesses excellent flow and compression properties. It produced highly elegant tablets on a high-speed rotary tablet machine. Both placebo and active tablets were excellent as shown by the elegance, small tablet weight variation, uniform distribution of the active ingredient, fast disintegration and dissolution rates, good hardness, low friability, and lack of binding, sticking, and capping (Batuyios, 1966:728).

Lerk *et al.* (1974:951) found that lactose could not be tableted without lubricant because of high ejection forces, resulting in crushing of the tablets during ejection, and because of sticking to the punches and die. Direct compression was consequently in all cases performed with 0.5% magnesium stearate. Lactose anhydrous exhibits a flowability which was just sufficient for direct compression and produced strong compacts. Combination of anhydrous lactose with extra fine crystalline (EFK) lactose or Avicel® PH-101, produced products with good flowability and compacts with good strength, and a somewhat increased disintegration time. The lactose anhydrous-Avicel® compacts showed no significant change in crushing strength with an increase in the amount of Avicel®.

Combination of extra fine crystalline lactose with Avicel®, however, produced a sharp decrease in disintegration time and an increase in crushing strength with an increase in percentage of Avicel®. The remarkable difference in effect of Avicel® on the disintegration behaviour of Avicel®-lactose anhydrous compacts compared with Avicel®-lactose EFK compacts can most probably be attributed to the pronounced difference in dissolution time between lactose anhydrous and lactose EFK (Lerk *et al.,* 1974:955).

Both crushing strength and disintegration time are strongly dependent on the type of the lactose used. The incorporation of 0.5% magnesium stearate caused a decrease in crushing strength and an increase in disintegration time for all lactose tablets. The largest increase in disintegration time was found for tablets containing α-lactose monohydrate (Van Kamp *et al.,* 1986:221).

Van Kamp *et al.* (1986:221) studied the effect of the nature of the lactose and the presence of the lubricant on the dissolution rate of caffeine from tablets. For unlubricated tablets, the dissolution rate of caffeine strongly depends on the type of lactose used and was, in comparison with the other types, lowest for anhydrous α-lactose. The presence of magnesium stearate decreased the dissolution rate of caffeine for all the tablets investigated, but the magnitude of the effect was dependent on the lactose used.

Dicalcium phosphate dihydrate

Emcompress® is a free-flowing form of dicalcium phosphate dihydrate and is insoluble in water. It offers a fairly good pressure-hardness profile, possesses satisfactory flowability and has a capacity potential for the incorporation of non-compressible material to the extent of about 40%. The non-hygroscopicity of dicalcium phosphate dihydrate is outstanding. It should be noted that dicalcium phosphate dihydrate is on the alkaline side, with a pH of 7.0 to 7.3, which precludes its use with active ingredients that are extremely sensitive to even minimal amounts of alkalinity (Mendell,1972:43).

Although Emcompress® has a good compressibility, it has no disintegrating action. It is therefore necessary to include an excipient with disintegrating properties, like Avicel® PH-102, in the formulation (Lerk *et al.,* 1974:946).

Microcrystalline cellulose

Along with the characteristic inertness and absorbent properties exhibited by most cellulose compounds, Avicel®, which consists of microcrystalline cellulose, is nonfibrous, free-flowing and possesses an extremely high surface area. Battista and Smith (1962:21) found that this microcrystalline "flour" could be compressed into very hard tablets with normal tableting equipment. Such tablets disintegrated immediately when placed in water as a result of the destruction of the cohesive bonding forces holding the microcrystalline particles together. Thus, microcrystalline cellulose has the ability to form extremely hard tablets that are not friable and yet possess unusually short disintegration times.

Avicel® can be used as a filler, binder, disintegrating agent and lubricant in tablet formulations (Fox *et al.,* 1963:161). Preliminary investigation showed that microcrystalline cellulose had good flow properties in spite of its extremely small particle size, and that in high concentrations it acted as its own lubricant. Although in high concentrations it appears to be nonadherent in respect to the punches and die, it cannot be classified as a lubricant. The reason for this, is that when the concentration is reduced below the point where other constituents have significant wall contact, the addition of a true lubricant is necessary (Fox *et al.,* 1963:260).

Fox *et al.* (1963:258) predicted that as long as the concentration of microcrystalline cellulose is kept above 60 to 70%, direct compression of many formulations without the inclusion of any additives would be possible. The concentration of microcrystalline cellulose might even be reduced further if crystalline active ingredients or diluents are used. Another major advantage of microcrystalline cellulose appears to be its ability to act as a dry binder. Many chemical substances that are impossible to compress alone

or in reasonable dilution with other fillers may be tableted with microcrystalline cellulose (Fox *et al.*, 1963:260).

Disintegration action of microcrystalline cellulose

The disintegration of microcrystalline cellulose tablets has been attributed to the entrance of water into the tablet matrix by means of capillary pores and the subsequent breaking of the hydrogen bonding between adjacent bundles of cellulose microcrystals (Fox *et al.*, 1963:260). When compression pressure is increased, capillary porosity becomes smaller and disintegration time increases. Upon pressure the matchstick-like bundles of microcrystals (figure1.3) appear to line themselves up into layers. This arrangement decreases the bond distance between particles and further increases the inter-particulate forces, and thus reduces the entrance of water into the tablet matrix with an increase in disintegration time. Avicel® might prove useful in specific formulations solely on the basis of its disintegrating ability. When it is employed as a filler/binder in concentrations above 20 per cent, microcrystalline cellulose gives extraordinary disintegration results.

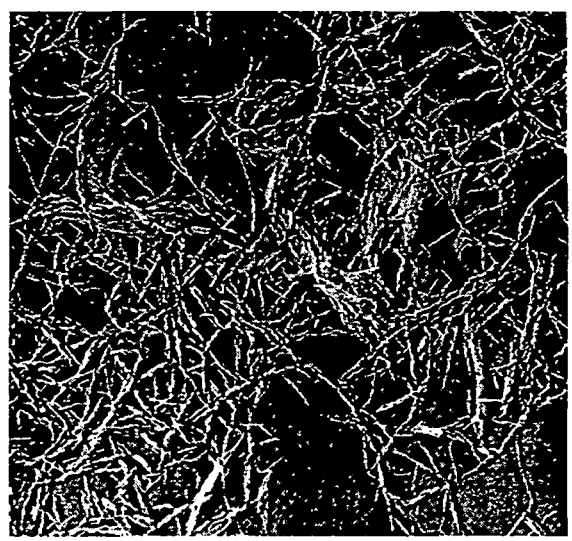

Figure 1.3: *Matchstick-like bundles of microcrystalline cellulose microcrystals (Fox et al., 1963:163).*

In high concentrations, disintegration is so rapid that difficulty in swallowing tablets results from break-up in the mouth. Another striking effect is a sticking of the tablets to

the tongue or oral mucosa. The saliva is apparently absorbed into the capillary spaces, dehydrating the moist surface, and causing adhesion (Fox *et al.*, 1963:260).

Characteristics of different Avicel® grades

PH means the excipient is suitable for dry applications like direct compression. Avicel® PH grades differ from each other by their particle size, particle shape and moisture content. Doelker *et al.* (1995:643-661) studied the characteristics of different Avicel® PH grades (Table 1.2). This evaluation should not be put in parallel with other published evaluations where the operating conditions were generally different.

Table 1.2: *Evaluation of the basic and tableting properties of the Avicel® PH grades relatively to Avicel® PH-101 (Doelker et al., 1995:659).*

(+,++ better; = not significantly different; -, -- worse)

Material	Hausner ratio[1]	Compac-tibility[2]	Sensitivity to lubricant[3]	Regularity of weight	Disintegra-tion[4]
Avicel® PH-105	-	+	+	--	--
Avicel® PH-103	=	=	-	=	=
Avicel® PH-102	=	=	-	+	=
Avicel® PH-112	+	=	--	+	=
Avicel® PH-200	++	=	--	++	=

[1]Compressibility on tapping; [2]Based on the compact crushing strength; [3]Strength reduction ratio on adding 0.5% magnesium stearate; [4]Both with or without disks.

The large-particle-size-grade PH-200 display a compactibility close to that of almost all the other Avicel® PH grades, but the highest susceptibility to magnesium stearate. The larger the particles in the powder mixture, the larger are the shearing forces during mixing. Shearing forces form a magnesium stearate film on the particles, producing weaker tablets when compressed (Doelker *et al.*, 1995:659).

Tablets made of Avicel® PH-200 exhibit the lowest weight variability because of its good flowability. The disintegration properties of the tablets are similar to those made of other PH grades, however, the higher the amounts of PH-200 in the mixture, the faster the tablets disintegrate. The shortest disintegration time of tablets is achieved when only Avicel® PH-200 is used.

Avicel® PH-200 showed certain advantages when compared to the other PH grades and were therefore chosen to evaluate in this study:

- It is the only free-flowing material in the group with the highest flow rate at 13.3 $g.sec^{-1}$;
- It has the highest true and bulk density (1.54 and 0.375 $g.cm^{-3}$ respectively);
- It produces tablets with the best tablet weight reproducibility, lowest weight variation and lowest variation in tablet thickness;
- Relatively fast disintegration times (Doelker *et al.,* 1995:652-657).

When compressed, the weakest tablets are formed of Avicel® PH-200, but they still have a crushing strength of over 135N at moderate compression forces.

1.4.1.2 Binders

Binders supply or increase binding forces between particles, to ensure that particles stay together. Many fillers also possess binding properties and will therefore be referred to as fillers/binders. Where the filler does not possess binding properties, a binding agent has to be added to the formulation in order to compress tablets from the mixture.

Kollidon® 30 (povidone, polyvidone)

The soluble grades of Kollidon® possess a number of very useful properties for which they are widely used in pharmaceuticals. Because of these properties, the products can perform different functions in different dosage forms. General properties of the soluble Kollidon® grades are:

- solubility in all conventional solvents,

- adhesive and binding power,
- film formation,
- affinity to hydrophilic and hydrophobic surfaces,
- ability to form complexes,
- availability in different molecular weights and
- thickening properties (Bühler, 1993:70).

Their adhesive and binding power is particularly important in tableting. Kollidon® is available in grades of different average molecular weight (indicated by the K-value in the trade name). With increasing molecular weight, the dissolution rate of the soluble Kollidon® grades decreases, while the adhesive power, the viscosity and often also the ability to form complexes increase. This dependence of the properties on the molecular weight makes it possible to provide the optimum grade for each dosage form or formulation and to achieve the optimum effect (Bühler, 1993:72).

The main area of application of Kollidon® 25, 30 and 90 is as binder for tablets. Kollidon® 90 is a stronger binder than Kollidon® 25 or 30. Kollidon® 30 was chosen for the purpose of this study, as it has intermediate properties.

Kollidon® VA 64 (copolyvidone)

In contrast to the soluble grades of Kollidon® described above, the number, 64 in the trade name, Kollidon® VA 64, is not a K-value but the mass ratio of the two monomers, vinylpyrrolidone and vinyl acetate. Kollidon® VA 64 is however, also water-soluble. The K-value of Kollidon® VA 64 is of the same order of magnitude as that of Kollidon® 30 and is also used as a measure of the molecular weight (Bühler, 1993:191).

The main area of application of Kollidon® VA 64 is as a binder in tablets and granules, regardless if they are manufactured by wet granulation or direct compression, as it is equally as effective in all three cases. The advantage of Kollidon® VA 64 over Kollidon® 25 and Kollidon® 30 in solid dosage forms lies mainly in its lower hygroscopicity. An important property of Kollidon® VA 64, in its use as a binder for tablets, is its plasticity, a

property that Kollidon® 30 does not possess. This property gives granules and mixtures that are less susceptible to capping during compression, and tablets that are less brittle. The tablets also have less tendency to stick to the punches when tableting machines are operated under humid conditions (Bühler, 1993:214). Both Kollidon® 30 and Kollidon® VA 64 are used in concentrations of 2-5%.

1.4.1.3 Disintegrants

For tablets containing sparingly water-soluble drugs, it is often desirable that the start of dissolution is not delayed by a prolonged lag time due to slow or poor wetting of the tablet surface and slow or poor liquid penetration into the tablet matrix, resulting in slow disintegration of the tablets. Hence, disintegrants with a fast action are most useful in tablet formulations of sparingly water-soluble drugs (Gissinger & Stamm, 1980:189).

A wide range of materials has been used as disintegrants in tablet formulations (Lowenthal, 1972:1696). Of these, the starches are the most well-known and widely used, but they have certain shortcomings in direct compression, including:

- relatively high concentrations needed for optimum disintegrant efficiency,
- poor disintegration in insoluble formulations,
- suspect to high compression forces which decrease their efficiency,
- decreased disintegration efficiency in the presence of hydrophobic lubricants, and
- poor compression properties (Marais, 2000:64).

The use of the traditional starches in directly compressed formulations presented problems in terms of the high concentrations needed for optimum disintegration. These materials cause significant weight variations in directly compressed formulations. This led to the search for new, more effective disintegrants. The result of this research was the marketing of a group of materials, called the superdisintegrants, which included sodium starch glycolate (Explotab® and Primojel®), croscarmellose sodium (Ac-Di-Sol®) and crospovidone (Kollidon® CL).

These disintegrants were chosen to be evaluated in this study because they proved to be superior to the traditional disintegrants in wet granulated and directly compressed tablets and in both soluble and insoluble formulations. They are highly effective in relatively low concentrations (compared to that of the starches) and do not affect negatively the process of direct compression or impart negative properties in tablets (Marais, 2000:64).

Mechanisms of disintegrant action

Disintegrants exert their disintegrating action when they come in contact with water. They can act through swelling in the presence of water to burst open the tablet. Starch is the most common disintegrant in tablet formulation and is believed to act by swelling. However, other effective disintegrants do not swell in contact with water and the mechanisms by which disintegrants act are the subject of some controversy (Lowenthal, 1973:589-609). It is believed that disintegrants that do not swell exert their disintegrating action by capillary action. Liquid is drawn up through capillary pathways within the tablet and ruptures the interparticulate bonds. This action serves to break the tablet apart. There is no problem in seeing the mechanism of action of disintegrants that generate a gas, such as CO_2 or oxygen, when moistened. The pressure of the gas formed disrupts the tablet. Another obvious mechanism of tablet disintegration is dissolution. Tablets mainly composed of a water-soluble filler and/or drug will readily fall apart due to the dissolution of the ingredient(s). Lowenthal (1973:589-609) has discussed in detail the various mechanisms of disintegration. Although the mechanisms of disintegrant action has been strongly debated in the literature, it seems as if water uptake (or water penetration), swelling upon contact with an aqueous medium, and the development of a disintegrating force (Caramella *et al.,* 1988:2167-2177) are the three most widely accepted mechanisms of action of disintegration.

In this study only swelling disintegrants will be evaluated. A comparison of the swelling properties of the most commonly used disintegrants is given in table 1.3 (Caramella *et al.,* 1984:137). Water contact is essential for the effectiveness of these disintegrants, because they swell when in contact with water, exert pressure on the tablet structure and cause disintegration to occur. Any factor that retards water penetration into the

tablet structure will retard the swelling activity and force development, and ultimately disintegration and dissolution. Magnesium stearate, a hydrophobic lubricant, can have this influence on tablet disintegration as it repels water from the surface of the tablet. The force exerted due to swelling is dependent on the solubility and the porosity of the tablet structure. In a porous structure, a certain amount of swelling volume will vanish into the numerous voids of the compact causing prolonged disintegration (Schmidt & Rubensdörfer, 1994:2913). A soluble filler will start to dissolve when placed in water and form a porous structure within the tablet, again causing prolonged disintegration. An insoluble filler will allow the swelling disintegrant to exert pressure within the tablet structure, causing fast disintegration.

Table 1.3: *Particle swelling (%) of disintegrants in 0.1 M HCl.*

Disintegrant	Volume increase (%)
Maize starch	42
Explotab®	73
Avicel® PH 101	69
Ac-Di-Sol®	104
Kollidon® CL	120
Amberlite® IRP 88	59

The extent of water uptake as well as the rate of water uptake is of critical importance for a number of tablet disintegrants (Bolhuis *et al.*, 1981:1328). Rudnic *et al.* (1983:303) confirmed this by observing that, as the molecular structure of sodium starch glycolate was altered to improve water uptake, disintegrant efficiency also improved. Thus, there is a positive correlation between the rate of swelling and disintegrant action. List and Muazzam (1978:161) concluded that disintegrants capable of producing a significant force of swelling generally are more effective disintegrants.

Bolhuis *et al.* (1982:111) found that rapidly swelling particles, such as sodium starch glycolate and croscarmellose sodium type A, are capable of overcoming the negative effects of hydrophobic tablet components that normally would block the passage of aqueous fluids through the porous network within the tablet matrix.

As particles swell, there must be little or no accommodation by the tablet matrix of that swelling; if the matrix yields elastically to the swelling, little or no force will be expended on the system and disintegration will not take place. If the matrix is rigid and does not accommodate swelling, however, deaggregation or disintegration will occur.

Croscarmellose sodium

Ferrero *et al.* (1997:11-21) conducted a study to assess the performance of the superdisintegrant, Ac-Di-Sol® (croscarmellose sodium), in a direct compression formulation containing a poorly water-soluble drug at high dosage. The drug used was albumin tanate, and given that it is poorly water soluble, its bioavailability is more likely due to the disintegration process. They found that, at certain concentrations of Ac-Di-Sol®, the disintegration time increased when the applied pressure increased. The disintegration time decreased when Ac-Di-Sol® concentration increased, just to a certain concentration of Ac-Di-Sol®, where after the disintegration time increased again.

On the basis of this data, it is possible to establish a correlation between particles deformation, tablet porosity and the disintegration process according to the two disintegration mechanisms involved with Ac-Di-Sol® namely porosity and strong swelling, the last one being the most important (Bolhuis *et al.*, 1981:1328). When the concentration of superdisintegrant is low, the total porosity and pore mean diameter decrease when applied pressure increases and, consequently, the disintegration time increases.

At higher concentrations of superdisintegrant (above 8%), there might only be a small decrease in disintegration time, and there can even be an increase in disintegration time. This may be explained by the relatively coarse pore structure noticed at these percentages of disintegrant. Rapid penetration of the largest capillaries isolates other areas of finer pore structure from which air cannot escape. These areas then make no contribution to the overall uptake of liquid (Selkirk & Ganderton, 1970:86).

According to yield pressure values, the higher the disintegration, the less prone it is to plastic deformation. During the compression process, particle deformation strongly enhanced porosity reduction, especially porosity due to the different rearrangement of particles. Differences in water content, as well as differences in surface properties, also might have an effect on densification behaviour at high levels of disintegrant (Nystrom *et al.*, 1993:2143).

Sodium starch glycolate

Sodium starch glycolate is the sodium salt of a relatively low substituted carboxymethylether of potato starch and is prepared by both crosslinking and substitution of potato starch. It is a widely used superdisintegrant in tablets prepared by both direct compression and wet granulation. The superdisintegrant is currently marketed by two companies under the names Explotab® and Primojel®. Several studies have shown that these two products behave differently, which was attributed to differences in the degree of molecular substitution arising from different manufacturing procedures (Patel & Hopponen, 1966:1065; Lowenthal & Burrus, 1971:1325).

Muñoz *et al.* (1998:785) conducted a study to investigate the efficiency of Explotab® in a direct-compression formulation. They used an experimental design with two variables, applied pressure and concentration of Explotab®, to determine its effect on the tableting and mechanical properties of the final tablets. They found that an increase in the concentration of Explotab® had a positive effect on flow properties. Also, the effect of applied pressure and disintegrant concentration was found to be significant on all compression parameters. The response surface of the tablets showed a certain level of Explotab®, around 7%, at which the disintegration time was the shortest. At this level, the surface response was independent of the applied pressure.

Crospovidone

Cross-linked **poly**vin**yl**pyrroli**done** (crospovidone) is a white, free flowing, high molecular weight, cross-linked polymer of vinylpyrrolidone formed under the influence of a special catalytic environment. Cross-linked polyvinylpyrrolidone is highly insoluble in water,

strong mineral acids and alkali, so consequently there is a lack of information relating to its molecular weight (Kornblum & Stoopak, 1973:44). Kollidon® CL is the commercially available form of crospovidone.

Kornblum and Stoopak (1973:46) believe that the mechanism of action of cross-linked polyvinylpyrrolidone depends greatly upon capillary effect in the presence of water with a secondary swelling effect. It is therefore difficult to provide a conclusive statement as to the overall mechanism of action. The interesting properties of cross-linked polyvinylpyrrolidone stem from its ability at low concentrations (2-5%) to bring about acceptable tablet disintegration as well as its inherent ability to function as a tablet binder. Cross-linked polyvinylpyrrolidone has been proven to be directly compressible in pure form, and this phenomenon relates to the low percent friability exhibited with its tablet formulations (Kornblum & Stoopak, 1973:47).

When compared to starch and alginic acid, cross-linked polyvinylpyrrolidone enhances the dissolution rate for isoquinazolinone tablets (Kornblum & Stoopak, 1973:48). Increasing proportions of the cross-linked polymer (1-10%) does not influence crushing force or friability of acetaminophen tablets, but significantly decreases disintegration and dissolution time (Salem *et al.*, 1995:1807).

1.4.1.4 Lubricant

During compression, strong adhesion forces may develop between the tablet and the die wall. These forces may lead to friction, which is minimised by adding a lubricant. Lubricants act by forming an intermediate layer between the tablet surface and the die wall (Shah & Mlodozeniec, 1977:1377).

Properties of the compact critical to its performance include the ejection force, tablet hardness, disintegration and dissolution. A lubricant, such as magnesium stearate, modifies these properties. The duration of mixing in the lubricant component may not only affect the properties of the compact, but also the properties of the blended mixture by altering the apparent bulk volume, the compression force required to make a

prescribed compact, and the hydrophobic character of the mixture (Shah & Mlodozeniec, 1977:1377).

The occasional nonpredicted increased disintegration time of a compressed tablet associated with a decreased hardness or crushing- force requirement, prompted Shah and Mlodozeniec (1977:1377) to launch an investigation into the effects of lubricants (e.g. stearates) and mixing duration on the physical properties of a blended mixture and compact. They found that lubricancy in mixtures improves the fluidity and packing characteristics of a blended mix and permits a homogeneous mix to be transferred compositionally intact to a target volume such as a compressing die. Agents that reduce such interparticulate friction also alter the particle packing characteristics by modifying the particle size and shape factors and have been termed glidants. The degree and extent of surface coverage of a substrate particle by such agents can be described theoretically for pharmaceutical mixtures by invoking at least three different mechanisms:

a) adsorption or surface contact adhesions,
b) diffusion or solids penetration, which includes mechanical interlocking and
c) delamination or deagglomeration of the lubricating agent to form a film coating (usually discontinuous) on the substrate particles.

Whichever mechanisms may be involved, the effect of mixing time should modify both glidant and lubricant roles of the agent.

The true lubricant role of these antifriction agents in pharmaceutical mixes occurs during and after the primary compaction process in tablet manufacturing. While facilitating consolidation of particles in the die cavity, these agents prevent adhesion of the tablet surface to the dies and punches during compression. During ejection, the agents act as boundary lubricants by reducing the frictional force needed to overcome the shear strength at the die wall (Shah & Mlodozeniec, 1977:1378).

Effect of mixing time on lubricancy and lubricant efficiency

The duration of mixing should be related to the clustering around specific sites on the solid surface, which will affect the polarity of the localised surface and create sufficient

large or small areas of hydrophilic character; these areas can affect glidancy, consolidation, ejection, dissolution and other tablet processing variables (Shah & Mlodozeniec, 1977:1381).

Shah and Mlodozeniec (1977:1381) found that, when using magnesium stearate as lubricant, the duration of mixing had major effects upon tablet disintegration. The mixtures blended for a longer time, yielded tablets with prolonged disintegration. The observed effect upon tablet disintegration may be attributed to the formation of a hydrophobic surface by the lubricant upon mixing. A correlation of disintegration time with tablet hardness represents a unique case, where disintegration time is inversely proportional to tablet hardness (i.e., the harder the tablet, the faster it disintegrates). This result is due to the decline in tablet hardness and prolongation of disintegration time as a result of the lubricant covering over the surface of lactose particles upon mixing.

According to the mechanisms of boundary lubrication put forward by Strickland *et al.* (1956:51), solid lubricants such as magnesium stearate are adsorbed on the granule surface. These lubricants form a uniform surface-adsorbed film in a manner similar to a Langmuir-type adsorption. If it is assumed that during the mixing process lubricant particles first adsorb on the surface and then, upon continued mixing, distribute uniformly upon the granule surface, the breaking of these lubricant particles by delamination or deagglomeration may take place. Such processes would result in greater coverage of the granule surface by the lubricant, thereby producing a greater interfacial surface between the lubricant and the excipient granule, i.e., surface of separation.

Bolhuis *et al.* (1975:317) conducted a study to evaluate the effect of mixing time on amylose V and powdered sodium chloride tablets when compressed from blends containing magnesium stearate. The results show increased flowability with an increase in mixing time. Also a dramatic decrease in crushing strength with an increase in mixing time. When the concentration of magnesium stearate or mixing time is increased, the dissolution rate is reduced. Furthermore, the effect of degree of mixing is greater the lower the concentration of magnesium stearate. The results confirm the hypothesis that magnesium stearate forms a film around a particulate solid during mixing.

Hydrophobicity

Hydrophobic surfaces are those granule or tablet surfaces on which water will not spread. Ganderton (1969:16S) described the effect of lubricant distribution on the penetration of a tablet by water. The degree of mixing, both in duration and shearing energy, may affect the porosity, air permeability and liquid penetration rate of the tablet. Magnesium stearate is a widely used lubricant and is strongly hydrophobic. In general, it is not desirable to render a dosage form hydrophobic inasmuch as the poor wetting of a tablet or other solid dosage form can retard drug release and dissolution.

Thus, the hydrophobicity or water repellence of a surface, when measured by contact angle affects the capillary action involved in pore penetration (Ganderton, 1969:16S). Even if the pores of a surface are hydrophobic, water vapour can pass through them if a sufficient hydrostatic pressure is imposed. The pressure of hydrophilic sites, which are almost always present even on hydrophobic solids, also facilitates the interaction of water on a granule or tablet. Thus, it can be assumed that the nature of a hydrophobic surface coverage on a tablet or other solid dosage form enhances or retards the interaction rate but does not inhibit the primary intermolecular attractions at work during disintegration and dissolution.

1.4.1.5 Hygroscopicity

From studies conducted by Kornblum and Stoopak (1973:43), it is evident that the hygroscopicity and the swelling are two completely different test criteria. The hygroscopicity is of more importance in regard to the stability on storage.

Hygroscopic ingredients decrease the effectiveness of superdisintegrants in promoting *in vitro* dissolution. The greater the hygroscopicity, the larger the decrease in disintegrant efficiency. This may be because the hygroscopic components compete for the locally available water. The water is then unavailable for disintegrant uptake and swelling (Gordan & Chowhan, 1987:907).

1.4.1.6 Solubility

Hygroscopicity and solubility are closely related factors. Highly soluble and/or hygroscopic ingredients decrease the effectiveness of superdisintegrants in promoting *in vitro* dissolution. The greater the overall hygroscopicity and solubility of the tablet formulation, the larger the decrease in the efficiency of the superdisintegrant (Johnson *et al.*, 1991:469).

The solubility of the major component in a tablet formulation affects both the rate and the mechanism of tablet disintegration. Since the dissolution of a soluble system takes place by erosion at the outer surfaces, swelling of disintegrant particles is not expected to play a major role. Thus, water-soluble materials tend to dissolve rather than disintegrate, while insoluble materials will produce a rapidly disintegrating tablet if an appropriate amount of disintegrant is included in the formulation. Therefore, tablets prepared from lactose (soluble) would be expected to show a different behaviour from that shown by microcrystalline cellulose (insoluble). Bhatia *et al.* (1978:38) showed that superdisintegrants had a much greater effect on disintegration time in an insoluble system than in a soluble or partially soluble system; the systems were direct compression formulations. Sakr *et al.* (1975:283) examined the rate of water absorption of disintegrants and found that it generally correlated positively with the speed of

disintegration, but Wan and Prasad (1989:147) found that water uptake alone does not determine the disintegration process.

Johnson *et al.* (1991:469) conducted a study to investigate the effect of tablet formulation solubility and hygroscopicity on the dissolution efficiency of three superdisintegrants (sodium starch glycolate, crospovidone and croscarmellose sodium) in tablets prepared by wet granulation. The overall tablet solubility was varied by changing the main component from lactose, which is very soluble, to calcium phosphate dibasic, which is insoluble. The hygroscopicity was varied by using naproxen sodium, sorbitol, or a 50:50 mixture of sorbitol and calcium phosphate dibasic. Lactose and calcium phosphate dibasic are nonhygroscopic. The results of this study seem to confirm the suggestion that higher overall tablet hygroscopicity may have a negative influence on the efficiency of the superdisintegrants. The superdisintegrants were found to be effective in both the soluble lactose system and the insoluble calcium phosphate dibasic system.

Although the superdisintegrants significantly improved dissolution in both of these systems when compared with control formulations, the calcium phosphate dibasic formulations exhibited a slightly faster dissolution rate than their lactose counterparts. Since lactose is water-soluble, it dissolves and forms a diffusion barrier layer of saturated lactose solution around the tablet. This diffusion layer may impede the availability of water to the superdisintegrant, slowing the rate of water entry. Calcium phosphate dibasic is insoluble in water. Therefore, with the addition of a disintegrant, the matrix can be quickly broken up with no soluble diffusion layer present, allowing the superdisintegrant to more readily pick up water and thus speed up dissolution (Johnson *et al.,* 1991:469).

The hygroscopicity and/or high solubility of both sorbitol and naproxen sodium have a deleterious effect on superdisintegrant efficiency in wet granulated tablets. It appears that these compounds may compete with the superdisintegrants for locally available water, thus inhibiting disintegrant action. The extent of the decrease in efficiency of the disintegrants depends on the composite hygroscopicity and/or solubility of the tablet

formulation and can be altered by the choice of the excipients (Johnson *et al.*, 1991:471).

1.4.2 EFFECT OF PROCESSING FACTORS ON TABLET CHARACTERISTICS AND DRUG RELEASE

The mixing time and intensity play an important role in lubricant efficiency, as discussed in section 1.4.1.4. As shown in figure 1.2, mixing play an indirect role in disintegration. The lubricant forms a hydrophobic surface upon mixing, and can retard water penetration and drug release. Figure 1.2 shows that compression plays a more pronounced role in promoting drug release, as it has an effect on the mechanical strength as well as the porosity of the tablet.

1.4.2.1 Mixing

As discussed in section 1.3, the mixing process is of utmost importance in direct compression. Furthermore, to ensure that a patient will take in the correct dose of a drug when taking in a certain dosage unit (a tablet), it is important that all tablet ingredients must be homogeneously mixed during production. The composition of each unit (tablet) must be representative of the total mixture. Mixing is also important to optimise the effects of the excipients in the formula, to ensure that the final product will be physically and chemically stable, effective, pharmaceutically acceptable and has a good and acceptable appearance.

Thwaites (1992:2009) demonstrated the significance of mixer intensity on the compression properties of Tablettose®. Low intensity processes such as roller mixing appeared to have little or no effect on the compression properties of this material even at mixing times of 30 minutes, whilst a high intensity process such as the high speed mixer altered the physical and mechanical properties of the powder after only 2 minutes. Clearly mixing processes of intermediate intensity might be expected to have proportionate effects.

It is important to establish and validate a balance between the required efficiency of the mixing process and an acceptable level of damage to the excipients. By optimising the

former and limiting the latter, the chances of obtaining the production goal of a reproducible process with limited inter-batch variation are increased. While the work by Thwaites (1992:2009) has been directed towards characterising the effects of mixer intensity on Tablettose®, the principle is equally applicable to all such excipients that might be used in direct compression formulations

Mixing conditions were not included in this study as a variable, and were kept constant so as to evaluate the effect of other variables.

1.4.2.2 Compression force

Usually the disintegration time increases as the compression force is increased. Frequently, there is an exponential relationship between disintegration time and compression force (Lowenthal, 1972:1695).

For starch-containing tablets compressed under relatively small forces, there is a large void, and the contact of starch grains in the interparticular space is discontinuous. Thus, there is a lag period before the starch grains, which swell due to water uptake, contact and exert a force on the surrounding tablet structure. For tablets compressed at a certain (intermediate) force, the contact of the starch grains immediately exerts pressure, causing the most rapid disintegration. For tablets compressed at forces greater than that producing the minimum disintegration time, the porosity is such that more time is required for the penetration of water into the tablet, with a resulting increase in disintegration time (Parrott, 1981:161). This relationship is shown in figure 1.4.

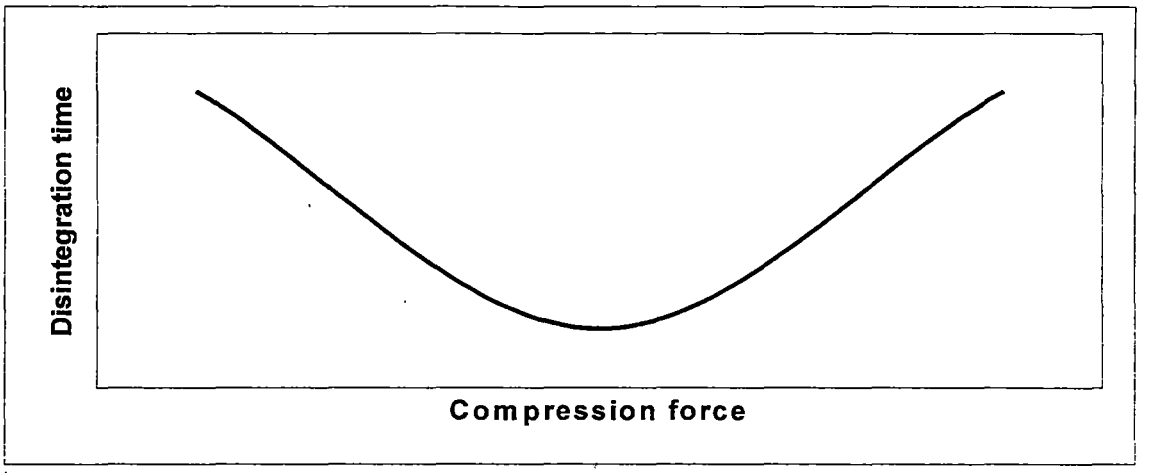

Figure 1.4: *Effect of compression force on disintegration time.*

The concentration of a disintegrant influences the relationship between compression force and disintegration time. However, Khan and Rooke (1976:634) found that the well-known supposition, "harder tablets take longer to disintegrate", is not applicable to the dicalcium phosphate dihydrate system they studied. In fact, the converse was shown. In this system, for tablets containing disintegrants for which swelling is the most dominant mechanism, an increase in pressure caused an increase in dissolution efficiency. This increase was more pronounced for the tablets containing cross-linked polyvinylpyrrolidone, where the dissolution efficiency increased progressively with increasing pressure (figure 1.5). In the lactose system studied, the disintegration time generally increased with pressure except for tablets containing cross-linked polyvinylpirrolidone and cation exchange resin for which there was an initial decrease (figure 1.6).

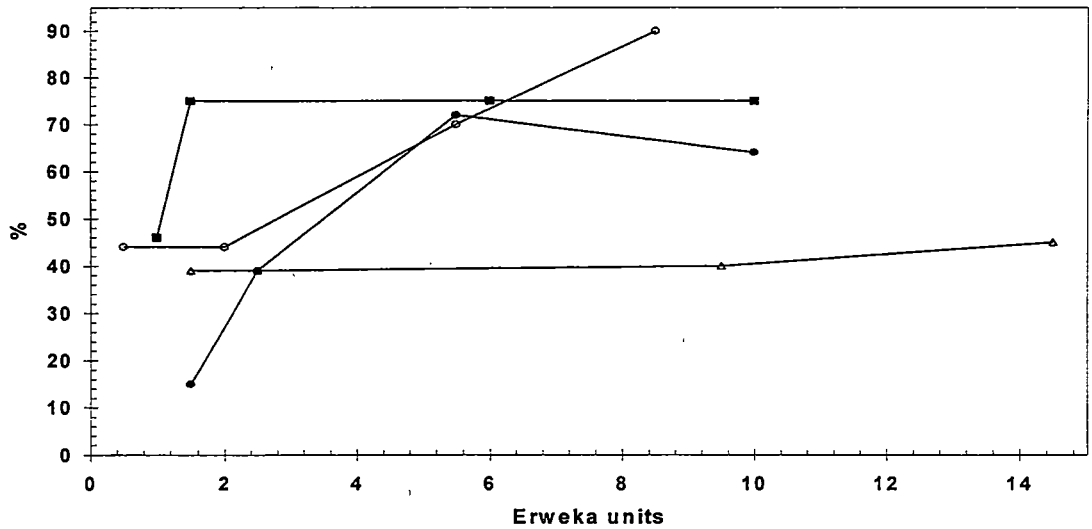

Figure 1.5: *The effect of hardness (Erweka) on the dissolution efficiencies (%) of tablets prepared from unmilled dicalcium phosphate dihydrate (1% w/w Amaranth) containing several disintegrants (5% w/w). o Cross-linked polyvilylpyrrolidone. ▮ Relatively insoluble sodium carboxymethyl cellulose. • Calcium carboxymethyl cellulose. ▲ Casein formaldehyde (Khan & Rooke, 1976:634).*

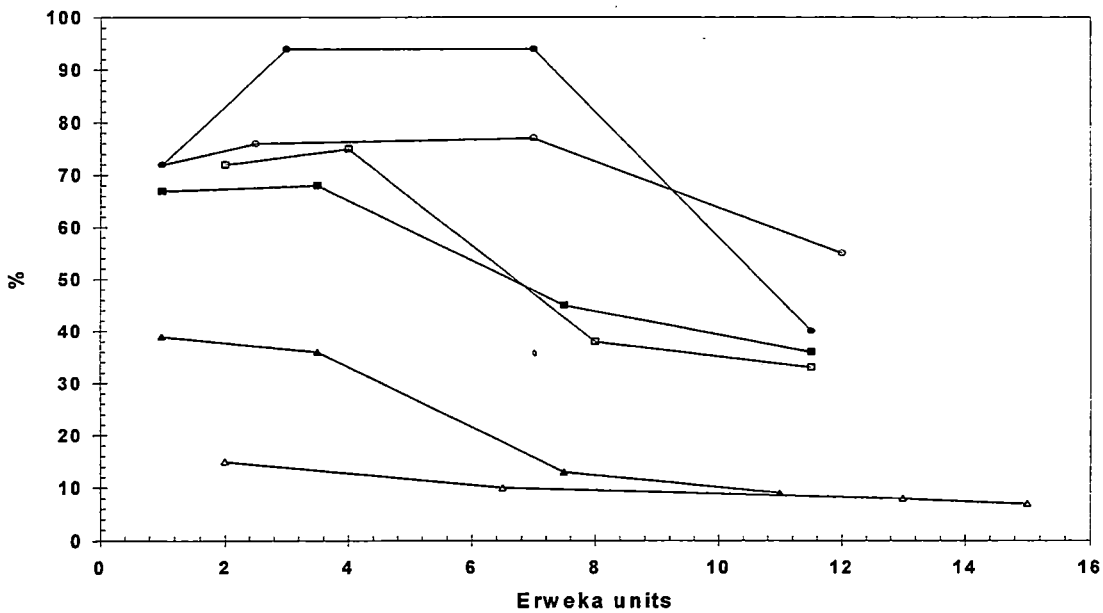

Figure 1.6: *The effect of hardness (Erweka) on the dissolution efficiencies (%) of tablets prepared from lactose system (1% w/w amaranth and 2% w/w polyvinylpyrrolidone) containing several disintegrants (5% w/w) • cross-linked polyvinylpyrrolidone. o Cation exchange resin. ▮ Relatively insoluble sodium carboxymethyl cellulose. □ Sodium starch glycolate. ▲ Sodium carboxymethyl cellulose. Δ Without disintegrant. (Khan & Rooke, 1976:634).*

Increasing the compression force while compressing Avicel® PH 200 tablets resulted in stronger and more slowly disintegrating tablets. Capillary porosity decreased, and this resulted in slower disintegration (Fox *et al.*, 1963:260). Also, when Ac-Di-Sol® was used in a tablet formulation, the breaking force increased when the applied pressure was increased. The effect of applied pressure is important at low proportions of disintegrant (the disintegration time increased when the applied pressure was increased), but this effect diminished at concentrations near to 10% (Ferrero *et al.*, 1997:16).

Thus, it is evident that the type of excipients in a tablet formulation determines the effect that compression force will have on the tablet formulation. There is no fixed relationship between compression force and dissolution properties of a tablet formulation.

1.5 CONCLUSION

A review of the literature indicated (revealed) the ongoing interest in direct compression as a method for tablet manufacture during the past decade or two. Much of the research was aimed at evaluation (and comparison) of traditionally used excipients employed in wet granulation in terms of their applicability and efficiency in directly compressed tablet formulations or evaluation of new compounds to be introduced (as excipients) in these formulations.

The two most important characteristics required from excipients to be deemed suitable for inclusion in directly compressible formulations are good flow and compression properties. These are prerequisites to produce tablets with low weight variation and acceptable mechanical strength to ensure low friability. Some of the most well known fillers/binders currently used in directly compressible tablet formulations are microcrystalline cellulose (Avicel®), dicalcium phosphate dihydrate (Emcompress®) and two lactose-based compounds, namely Ludipress® and Tablettose®. Amongst these fillers/binders only Ludipress® and Avicel® (to a lesser extent), can be classified as truly multipurpose excipients (MPE's), i.e. an excipient which could perform multiple functions in a tablet formulation. All the others need additional excipients to provide tablet disintegration, particle binding and lubrication.

In most directly compressible tablet formulations the physical properties of the filler play a significant role in the tablet properties due to the fact that this excipient comprises 80% or more of the final tablet composition. However, even more than its contribution to the physical properties of tablets, the filler also significantly contributes towards and often governs drug release (disintegration) and drug dissolution. The general thought is that tablets containing insoluble, non-disintegrating fillers need a disintegrant to facilitate tablet break-up and enhance drug release, whilst this excipient would be unnecessary in soluble tablets (containing highly soluble fillers) due to drug release as a result of solution of the tablet.

Some questions that remain are, however:

- What is the actual contribution of the filler towards drug release and dissolution, especially in the case of sparingly water-soluble drugs for which dissolution is the rate-limiting step in absorption?
- How do the characteristics of the filler reflect in the physical properties of the tablets?
- How do differences in drug release and dissolution profiles of the drug relate to differences in the physical properties of the fillers?
- What would the case be in slowly soluble tablet formulations in terms of its effect on the rate of drug release, the rate and extent of drug dissolution and the need and efficiency of a disintegrant in these formulations?

2. CHAPTER 2

EXPERIMENTAL METHODS

This chapter deals with the experimental methods and apparatus used repeatedly throughout the study.

2.1 MATERIALS

The materials, lot numbers and manufacturers are presented in table 2.1.

Table 2.1: *Materials used in the study.*

Material	Lot number	Manufacturer
Furosemide	14859	Adcock Ingram Ltd, Wadeville, South Africa
Magnesium stearate	ART 5876	Merck, Darmstadt, Germany
Avicel® PH 200	M926C	FMC International, Wallingstown, Little Island, Cork., Ireland
Tablettose®	L0116	Meggle GmbH, Wasserberg, Germany
Ac-Di-Sol®	T124	FMC Corporation, Philadelphia, Pennsylvania, USA
Sodium starch glycolate	SSGP0601	Mirren Pty Ltd, Johannesburg, South Africa
Kollidon® CL	30-1411	BASF Aktiengesellschaft, Ludwigshafen, Germany
Kollidon® 30	175 3826	BASF Aktiengesellschaft, Ludwigshafen, Germany
Kollidon® VA 64	62-8826	BASF Aktiengesellschaft, Ludwigshafen, Germany

Furosemide was chosen to represent sparingly water-soluble and poorly water-wettable drugs. For these drugs dissolution is often the rate-determining step during absorption, and tablet disintegration may be expected to significantly affect the rate and extent of dissolution through its contribution towards optimising drug contact with the surrounding aqueous environment.

2.2 *METHODS AND APPARATUS*

2.2.1 MIXTURE COMPOSITION AND PREPARATION

The composition of the various mixtures prepared and evaluated during this study is presented in table 2.2. Of each formulation mixtures of 200 g were prepared in 1000 cm^3 glass fruit jars, closed with Parafilm®, and mixed in a Turbula®-mixer (model T2C, W.A. Bachhofen, Bastle, Switzerland) for 10 minutes at 69 rpm.

Table 2.2: *Mixture composition.*

Component	Function	Percentage w/w
Furosemide	Drug	8.7 or 5.8%
Avicel® PH 200 or Tablettose®	Filler/binder	qs to 100%
Ac-Di-Sol® or Sodium starch glycolate or Kollidon® CL	Disintegrant	0, 0.5, 1, or 2%
Kollidon® 30 or Kollidon® VA 64	Binder	0, 3.5, 5 or 7%
Magnesium stearate	Lubricant	0 or 0.5%

2.2.2 COMPRESSION OF TABLETS

Tablets were compressed on a Cadmach® single station (eccentric) press, using slightly concave punches with a 9 mm diameter. For both the Avicel® PH 200 and Tablettose® formulations, the die volume was kept constant.

Various compression pressures were used to evaluate filler compressibility (mechanical strength and friability) and to determine the effect of differences in the crushing strength on tablet properties (tablet disintegration and drug dissolution). Since an instrumented tablet press was not available, compression force was manipulated by changing the depth of movement of the upper punch into the die during compression (using the scale, ranging between 0 and 35, provided on the machine). Since the fill volume (die volume) was kept constant during compression of different mixtures, a higher compression setting would represent a higher compression force resulting in an increase in tablet crushing strength (see section 3.3). Therefore, data presented in this study does not indicate compression force, but only a compression setting, which could be related to a determined crushing strength.

The first 10 tablets compressed of each mixture were disposed of. The tablets were transferred to glass bottles, which were sealed with Parafilm® before closure with screw caps, and stored in a dark cabinet at room temperature for at least 24 hours prior to testing.

2.3 POWDER CHARACTERISTICS AND PHYSICAL PROPERTIES OF POWDER COMPACTS

The following powder characteristics and physical properties of the compacted powder were determined from each formulation compressed at the various compression settings:

- particle size,
- powder density,
- weight variation,
- crushing strength,
- friability and
- disintegration times.

2.3.1 PARTICLE SIZE ANALYSIS

A particle size analysis on Avicel® PH 200 and Tablettose® was done, using a Malvern® Mastersizer X (Malvern Instruments Ltd., Worcestershire, UK) with a MSX14 sample suspension unit. The sample pump rate, cell stir rate, ultrasonic stir rate and sample suspension stir rate were all set to velocity setting 5 throughout the analysis. A 300 mm lens was used. Samples were prepared by suspending 1 g of Avicel® PH 200 in 10 cm^3 of distilled water, and 2 g of Tablettose® in 10 cm^3 95% ethanol. The values given are the means of 4 determinations. A total volume of 300 cm^3 dispersing medium was used for each analysis.

2.3.2 POWDER DENSITY

The true density of Avicel® PH 200 and Tablettose® was determined, using a Quantachrome® stereopycnometer (model no SPY-4, Quantachrome Corporation, Boynton Beach). Helium gas was used to displace the air.

The weight of 20 cm^3 of each filler was determined and the following equation was used to calculate the bulk density:

$$density = \frac{mass(g)}{volume(cm^3)} \qquad [2.1]$$

2.3.3 CRUSHING STRENGTH

The crushing strength of 10 tablets from each formulation was determined using a Pharma Test tablet test unit (model PTB-311, Pharma Test, Switzerland).

2.3.4 FRIABILITY

The percentage friability of ten tablets was determined by weighing the tablets before and after placing them in a Roche® friabilator for ten minutes at 53 rpm, and then using the following equation:

$$\%friability = \frac{WEIGHT\ before - WEIGHT\ after}{WEIGHT\ before} * 100 \qquad [2.2]$$

2.3.5 DISINTEGRATION TIME

The disintegration times of 6 tablets were determined in distilled water at 37±0.5°C, using a Manesty® tablet disintegration test unit (Manesty Machines LTD., Liverpool, England) without disks, fitted with a thermostat to regulate the temperature.

2.4 DISSOLUTION STUDIES

2.4.1 APPARATUS AND DISSOLUTION CONDITIONS

Dissolution studies were performed in a six-station Erweka® dissolution apparatus with paddles motor (model DT6R, Erweka, Heustenstamm, Germany), fitted with a thermostat and variable speed synchronous. The dissolution studies were done in 900 cm^3 0.1 M HCl at a temperature of 37 ± 0.5 °C (regulated by a thermostat) and at a rotational speed of 75 rpm (kept constant by a synchronous motor). As dissolution medium 0.1 M HCl was used because furosemide is only sparingly soluble in a weak

acid, and this provides enough time during dissolution to observe and compare the effect of different excipients on dissolution time.

2.4.2 METHOD

The rods were pushed down into the medium to about 5 cm from the bottom of the glass beaker. The motor was started, and as soon as it reached the required speed (75 rpm), the tablets were introduced to the medium. The time was recorded at t = 0. At times t = 1, 2, 4, 5, 6, 10, 20, 30, 45 and 60 minutes, 5 cm^3 samples were withdrawn through a filter unit containing a Millipore® prefilter and transferred to 10 cm^3 glass poly tops. Immediately after sampling, the volume lost was replaced with an equal volume of fresh, preheated dissolution medium. During dissolution calculations, a correction was made for the amount of drug lost through sampling (see section 2.4.4.1).

The UV-absorbencies of the samples were measured in duplicate at 273 nm against 0.1 M HCl as blank, using a Helios α Unicam®-spectrophotometer fitted with a super sipper and a 1 cm^3 quartz flow-through cell (Unicam Ltd, Cambridge, UK).

2.4.3 STANDARD CURVE

Standard curves were drawn up each day prior to dissolution testing. Standard solutions with concentrations ranging from 1 to 12 $\mu m.cm^{-3}$ were prepared from a stock solution containing 50 mg of furosemide dissolved in ± 50 cm^3 absolute ethanol, and diluted to 250 cm^3 with 0.1 M HCl. The UV-absorbencies of the standard solutions were determined spectrophotometrically at 273 nm against 0.1 M HCl as blank. The absorbencies were plotted against concentration and the best straight line through the data points was fitted, using linear regression. All standard curves obeyed Beer's law in the concentration range employed, with correlation coefficients (r^2) of ≥ 0.9999. The slope (m) and the y-axis intercept (c) were used to calculate the furosemide concentration at each sample time (section 2.4.4.1).

2.4.4 CALCULATIONS

All the calculations were done using Microsoft® Excel 97 for Windows (Microsoft Corporation, Seattle, Washington, USA).

2.4.4.1 Dissolution data

The amount of furosemide dissolved ($mg.cm^{-3}$) at each sampling time was calculated, using equation 2.3, while equation 2.4 was used to correct for the drug lost through sampling.

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

Where y^* is the corrected absorbency (from equation 2.4), 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.

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

Where y^*_n is the corrected absorbency of the n^{th} sample, y_n is the measured absorbency of the n^{th} sample; V_s is the sampling volume; V_m is the dissolution medium volume and $\Sigma^{n-1}y^*$ 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 of each formulation.

2.4.4.2. 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 various formulations, while the area under the dissolution profile up to 60 minutes (AUC) would be an indication of the extent of drug dissolution at the end of the dissolution test.

The DR_i ($mg.cm^{-3}.min^{-1}$) of furosemide from each tablet formulation at every pressure setting was determined from the slope of the dissolution curve between t_0 and t_6, while the AUC ($mg.min.cm^{-3}$) of the drug between t_0 and t_{60} was determined and calculated using the trapezoidal rule, which is given by:

$$AUC = 0.5 * \sum_{t=n}^{t=0} (t_n - t_{n-1}) * (c_n + c_{n-1}) \qquad [2.5]$$

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 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 is 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* (Rescigno, 1992:925).

2.5 STATISTICAL EVALUATION OF THE EXPERIMENTAL DATA

Statistical analysis was performed using the statistical option available in Microsoft® Excel 97 for Windows (Microsoft® Corporation, Seattle, Washington, USA). A 95% confidence level ($p < 0.05$) was considered satisfactory for indicating significant differences. The mean values of the parameters determined, i.e., initial dissolution rate (DRi) and area under the dissolution curve (AUC) were compared for significant differences using one-way analysis of variance (ANOVA) for single factor comparisons.

3. CHAPTER 3

PHYSICAL CHARACTERISATION OF AVICEL® PH 200 AND TABLETTOSE® AS TABLET FILLERS

3.1 INTRODUCTION

The physicochemical properties of the filler/binder in directly compressed tablet formulations play an important role in the release (disintegration) and dissolution of the active ingredient, especially in formulations containing low drug doses, where the filler comprises more than 80% of the tablet composition. In this study, the effect of soluble (Tablettose®) and insoluble (Avicel® PH 200) fillers on the dissolution of furosemide was evaluated. This chapter deals with the powder properties of these two fillers, (i.e. density and particle size) and their compressibility and physical properties of compacts (tablets) in order to determine basic physical characteristics of each.

3.2 POWDER CHARACTERISTICS

The bulk and true densities and mean particle size of Avicel® PH 200 and Tablettose® were determined as described in sections 2.3.2 and 2.3.1 respectively, and the results are presented in table 3.1.

Table 3.1: *Physical properties of Avicel® PH 200 and Tablettose®.*

Properties	**Filler/Binder**	
	Avicel® PH 200	**Tablettose®**
Bulk density ($g.cm^{-3}$)	0.390	0.637
True density ($g.cm^{-3}$)	1.708	1.450
Mean particle size (μm)	202.51±1.09	163.43±4.56

The differences in the density and particle size of these two materials suggested a higher weight at a constant die fill volume for Tablettose® tablets due to its higher bulk density and smaller particle size compared to Avicel® PH 200 (table 3.1).

3.3 PHYSICAL PROPERTIES OF AVICEL® PH 200 AND TABLETTOSE® TABLETS

Tablets containing only Avicel® PH 200; Avicel® PH 200 and magnesium stearate (0.5% w/w) and Tablettose® and magnesium stearate (0.5% w/w) were prepared at a constant die fill volume and at different compression settings as described in section 2.2.1 and 2.2.2. The inclusion of magnesium stearate as lubricant was necessitated because Tablettose® could not be tableted without a lubricant due to high ejection forces after compression, which caused cracking of the tablets during ejection. The tablets were evaluated in terms of weight variation, crushing strength, friability and disintegration time as described in section 2.3. The results are tabulated in tables 3.2-3.4.

Table 3.2: *Tablet properties of pure Avicel® PH 200 tablets at various compression settings. The values in brackets represent the percentage relative standard deviation.*

Compression setting*	Tablet properties			
	Average weight (mg)	Crushing strength (N)	Friability (%)	Disintegration time (sec)
18	205.54 (0.3)	30.71 (4.3)	1.47	8.83 (18.1)
19	204.80 (0.4)	40.57 (3.6)	0.60	10.50 (10.0)
20	204.62 (0.3)	54.49 (3.2)	0.49	14.50 (18.4)
21	205.07 (0.2)	62.06 (2.8)	0.32	16.17 (13.8)
22	206.98 (0.3)	68.81 (3.4)	0.44	18.67 (14.2)
23	204.08 (0.3)	94.71 (4.1)	0.20	38.00 (21.8)
24	202.56 (0.6)	118.01 (5.8)	0.19	88.67 (7.5)

** An increase in compression setting represents an increase in upper punch depth into die, i.e. an increase in compression pressure*

Table 3.3: *Tablet properties of Avicel® PH 200/magnesium stearate (0.5% w/w) tablets at various compression settings. The values in brackets represent the percentage relative standard deviation.*

Compression setting*	Tablet properties			
	Average weight (mg)	Crushing strength (N)	Friability (%)	Disintegration time (sec)
23	234.17 (0.4)	21.87 (4.6)	3.66	15.33 (7.9)
24	229.43 (0.8)	24.59 (3.3)	2.38	13.33 (9.1)
25	229.98 (0.7)	32.04 (4.7)	1.68	13.83 (9.6)
26	228.26 (0.5)	39.27 (4.0)	1.40	13.00 (6.9)
27	231.66 (0.7)	47.96 (3.8)	1.30	15.17 (7.7)
28	227.85 (1.2)	67.26 (6.4)	0.97	25.17 (12.9)
29	225.11 (0.6)	85.77 (3.0)	0.85	45.00 (11.2)

** An increase in compression setting represents an increase in upper punch depth into die, i.e. an increase in compression pressure*

Table 3.4: *Tablet properties of Tablettose®/magnesium stearate (0.5% w/w) tablets at various compression settings. The values in brackets represent the percentage relative standard deviation.*

Compression setting*	Tablet properties			
	Average weight (mg)	Crushing strength (N)	Friability (%)	Disintegration time (sec)
21	364.23 (0.5)	11.56 (20.8)	100.00	1287.33 (6.3)
22	356.43 (0.8)	13.36 (15.6)	69.40	1194.00 (4.0)
23	354.25 (1.2)	14.62 (11.3)	35.19	1262.83 (2.5)
24	350.40 (1.0)	19.72 (14.3)	7.80	1270.33 (3.9)
25	349.94 (0.4)	30.84 (8.6)	3.86	1245.00 (3.4)
26	353.51 (0.7)	64.24 (7.8)	1.60	1229.00 (4.4)
27	361.57 (1.7)	52.23 (14.1)	34.87	804.33 (13.2)

** An increase in compression setting represents an increase in upper punch depth into die, i.e. an increase in compression pressure*

At each compression setting, Tablettose® produced heavier tablets than Avicel® at a constant die fill volume with tablet weights averaging 1.73 and 1.55 times higher compared to those obtained for pure Avicel® and Avicel®/magnesium stearate respectively. This difference in tablet weight could be attributed to the higher bulk density

and more dense packing of the smaller particles in the die cavity of Tablettose® compared to Avicel® (table 3.1). The effect of magnesium stearate was demonstrated by the difference in the tablet weights of pure Avicel® and Avicel®/magnesium stearate tablets with the latter averaging 1.12 times heavier at a constant die fill volume than the unlubricated tablets. This could be ascribed to improvement of the packing characteristics of lubricated powder blends compared to unlubricated blends (Shah & Mlodozeniec, 1977:1378).

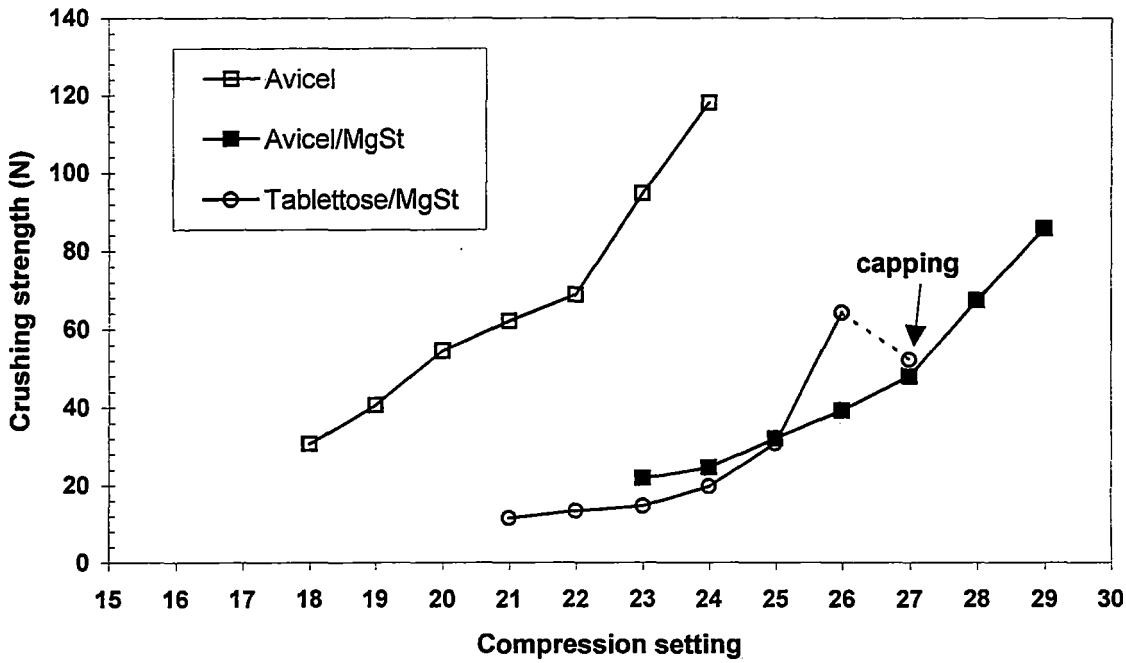

Figure 3.1: *Effect of compression setting on the crushing strength of Avicel®PH 200, Avicel®PH 200/magnesium stearate and Tablettose®/magnesium stearate tablets.*

As expected, the crushing strength of all the tablet formulations increased with an increase in compression force (resulting from an increase in upper punch depth into the die, figure 3.1). The unlubricated Avicel® powder produced tablets with significantly higher crushing strengths at overlapping compression settings (23 and 24) compared to both the lubricated formulations (figure 3.1). Since magnesium stearate is a surface lubricant, it covered the surfaces of individual filler particles, thereby decreasing the contact surface-area necessary for particle binding, which resulted in a decrease in the mechanical strength of the tablets (Shah & Mlodozeniec, 1977:1377; Doelker *et al.*,

1995:643-661). Unlubricated Avicel® produced hard tablets with low friability even at low compression settings (<18) (table 3.2). In lubricated Avicel® tablets friability of less than 1% could only be obtained at pressure settings of 28 and higher (table 3.3). These results confirmed the susceptibility of Avicel® to magnesium stearate (Doelker *et al.*, 1995:643-661). The lubricated Avicel® tablets showed higher friability (>2.38%) at overlapping compression settings, 23 and 24, compared to the unlubricated Avicel® tablets (<0.2%). This was probably due to the lower crushing strengths of the lubricated formulations, resulting in easier destruction of the binding forces between particles. In addition to its negative effect on tablet hardness and friability, magnesium stearate also increased tablet weight variation in Avicel® tablets, as indicated by the %RSD, averaging 0.7% over all compression settings for the lubricated tablets compared to only 0.3% for the unlubricated tablets. Despite its negative effect on the physical properties of Avicel® tablets, magnesium stearate did however increase the upper limit of the compression range from 24 (for the unlubricated tablets) to 29 for the lubricated tablets.

Tablettose®/magnesium stearate blends produced tablets with extremely low mechanical strengths (12-31 N) and high friability (4-100%) up to compression setting 25 (table 3.4), whilst capping occurred at setting 27. The latter was accompanied by a noticeable decrease in tablet crushing strength (figure 3.1), and an increase in tablet friability (table 3.4). These low crushing strengths of Tablettose® formulations could be attributed to the relatively poor binding mechanism of the material, i.e. weak H-bonding (Nyström *et al.*, 1993:2145) which was further reduced by the presence of the lubricant. Comparison of the crushing strengths of the lubricated formulations showed Avicel®/magnesium stearate blends to produce harder tablets at settings lower than 26. Figure 3.1 shows a steep increase in crushing strength of Tablettose®/magnesium stearate above setting 24 resulting in harder tablets compared to Avicel®/magnesium stearate at compression setting 26.

The disintegration results of the Avicel® tablets (figure 3.2) confirmed the excellent disintegration properties of compressed microcrystalline cellulose as described by Battista and Smith (1962:21) and Fox *et al.* (1963:260). This could be attributed to the strong wicking tendency of microcrystalline cellulose which was largely unaffected by an

increase in tablet density (with an increase in compression setting) and the presence of a hydrophobic lubricant like magnesium stearate. Both the lubricated and unlubricated Avicel® tablets disintegrated in less than 90 seconds at all compression settings with the increase in crushing strength having a negligible influence on disintegration. Disintegration times for both the lubricated and unlubricated Avicel® tablets increased with an increase in compression setting due to an increase in mechanical strength, with a more pronounced increase at higher compression settings (figure 3.2). These results confirmed the findings of Fox *et al.* (1963:260) who found that, for Avicel® tablets, disintegration times increased with an increase in compression force, due to a decrease in capillary porosity.

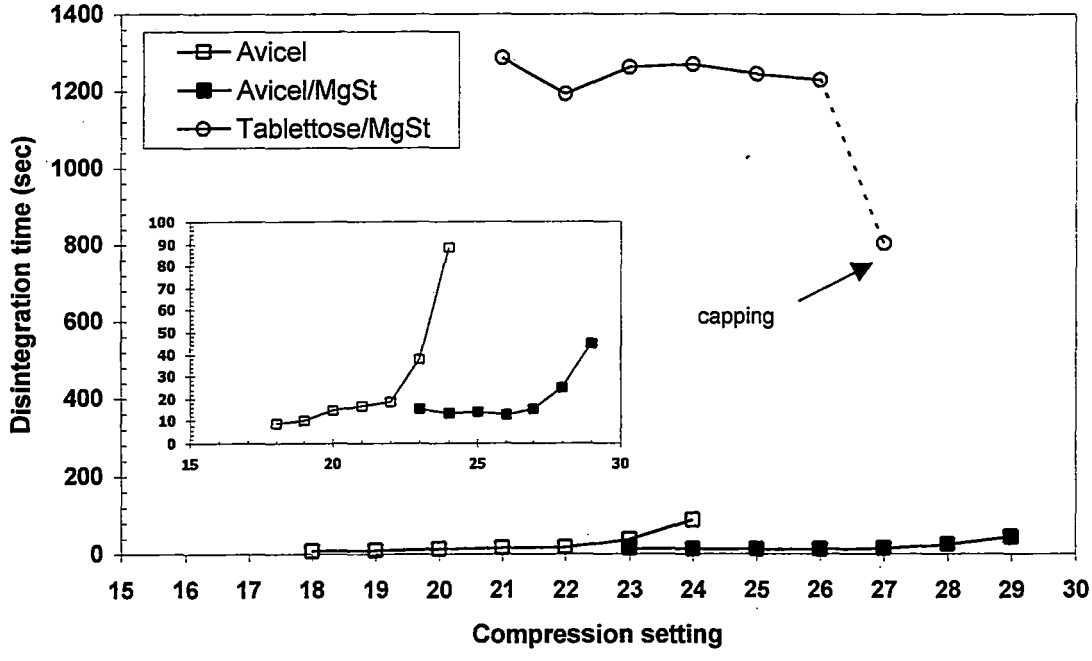

Figure 3.2: *Effect of compression setting on the disintegration time of Avicel® PH 200, Avicel® PH 200/magnesium stearate and Tablettose®/magnesium stearate tablets.*

It might be expected that the hydrophobic lubricant (magnesium stearate) would have a negative effect on disintegration, but this was not the case with Avicel® PH 200, since only a small amount of magnesium stearate (0.5% w/w) was present in the tablets. Figure 3.3 shows a negligible difference in disintegration times for the two formulations at comparable crushing strengths. However, at overlapping compression settings (23

and 24), disintegration times of the lubricated Avicel® tablets were faster (figure 3.2). This could be attributed to the lower crushing strength of the lubricated formulations (figure 3.1) resulting in easier destruction of the cohesive bonding forces in these tablets.

Tablettose® produced tablets with disintegration times exceeding 15 minutes despite the fact that this filler is water-soluble (figure 3.2). These tablets dissolved from the surface without disintegration, and therefore compression force and hardness of the tablet did not influence the disintegration time of the tablet. Lowenthal (1972:1695) stated that disintegration time usually increased with an increase in compression force, but such a relationship could not be found with Tablettose®/magnesium stearate tablets which could be attributed to the lack of disintegrating properties of Tablettose® compared to Avicel®.

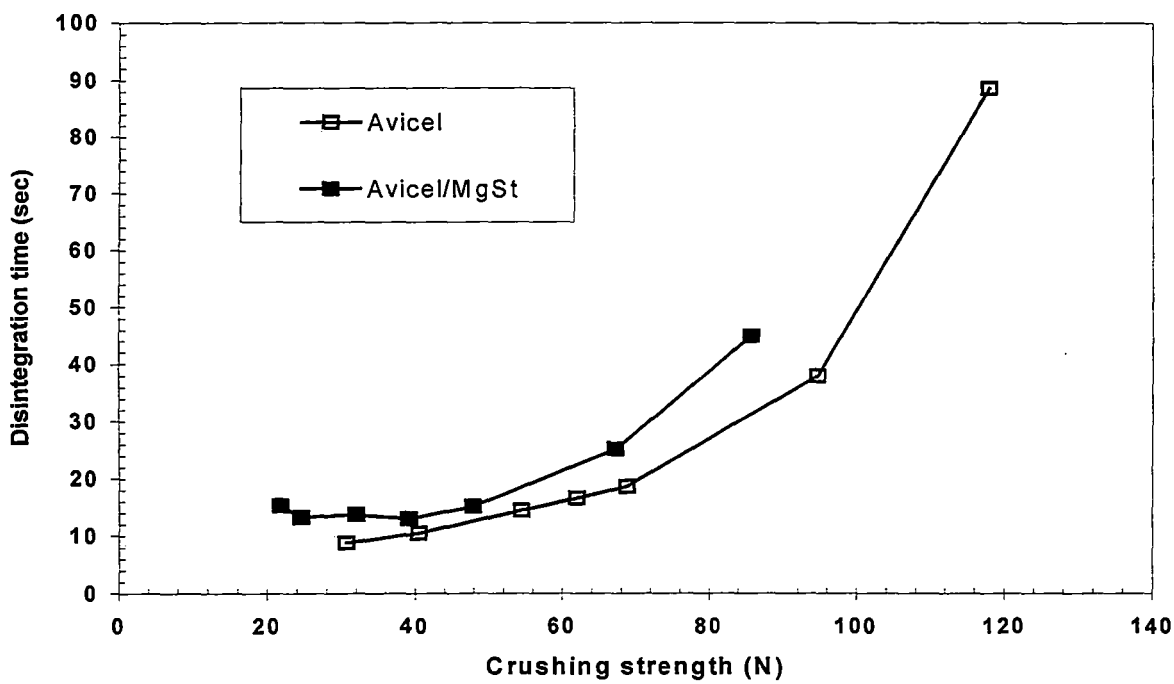

Figure 3.3: *Effect of crushing strength on the disintegration time of unlubricated and lubricated Avicel® tablets.*

3.4 CONCLUSION

Avicel® PH 200 proved to be an excellent directly compressible filler and could be tableted without the addition of a lubricant. It produced tablets with exceptionally fast disintegration times, which was relatively unaffected by an increase in tablet crushing strength or by the presence of a hydrophobic lubricant. Avicel® possessed good flow properties and produced tablets with low weight variation and low friability. The addition of magnesium stearate increased the compression range, without negatively affecting the crushing strength, friability or disintegration times.

Tablettose® showed satisfactory flow properties and produced tablets with low weight variation, but showed certain shortcomings as directly compressible filler, including:

- the necessity of a lubricant (although in low concentrations) for tableting,
- the production of tablets with low mechanical strength and high friability and
- slow tablet disintegration. Tablettose® possesses poor solubility without any disintegration properties, which might result in slow drug release and slow dissolution especially of poorly soluble drugs.

4. CHAPTER 4

EVALUATION OF THE EFFECT OF DRY BINDERS AND DISINTEGRANTS ON THE PHYSICAL PROPERTIES OF TABLETTOSE® TABLETS

4.1 INTRODUCTION

The results from the previous chapter clearly indicated certain shortcomings in the physical properties of directly compressed Tablettose® tablets, in particular high friability resulting from extremely low tablet crushing strengths, and poor disintegration properties despite the solubility of the filler. The current chapter deals with an investigation concerning the evaluation of the effect of the type and concentration of dry binders and superdisintegrants on the physical properties of Tablettose® tablets.

4.2 EFFECT OF BINDERS ON THE PHYSICAL PROPERTIES OF TABLETTOSE® TABLETS

The literature showed that the povidones (commercially marketed under the trade name Kollidon®) are commonly employed as dry binders in directly compressible tablet formulations to increase the mechanical strength of tablets and to reduce tablet friability (section 1.4.1.2). Various grades of Kollidon® are available as dry binders. Kollidon® 30 (povidone) and Kollidon® VA 64 (copolyvidone) were chosen as dry binders in this study due to the fact that they both possess adhesive and binding properties, are water-soluble, show affinity for hydrophilic and hydrophobic surfaces and are effective in relatively low concentrations (2-5%). Furthermore, these two binders have molecular weights of the same magnitude (Bühler, 1993:191).

Mixtures containing Tablettose®, magnesium stearate (0.5% w/w) and either Kollidon® 30 or Kollidon® VA 64 (0, 3.5, 5 and 7% w/w) were prepared and tableted (at a constant die fill volume) at various compression settings as described in sections 2.2.1 and 2.2.2. The tablets were evaluated in terms of weight variation, crushing strength, friability and disintegration as described in sections 2.3.3-2.3.5. The results are tabulated in table 4.1.

Table 4.1: *Tablet weight, crushing strength (CS), percentage friability (%F) and disintegration time (DT) of Tablettose®/magnesium stearate (0.5% w/w) tablets containing different concentrations of Kollidon® 30 or Kollidon® VA 64 at various compression settings. Values between brackets represent percentage relative standard deviation.*

		TABLET FORMULATIONS WITHOUT ANY BINDER							
% Binder	**Compression setting**	**Tablet weight (mg)**		**CS (N)**		**%F**		**DT (sec)**	
0	**23**	347.83 (0.5)		24.04 (10.0)		5.24		1225.17 (4.5)	
	24	346.47 (0.3)		36.68 (7.4)		2.62		1244.50 (2.5)	
	25	341.93 (0.5)		67.25 (7.9)		1.58		1214.50 (1.3)	
		TABLET FORMULATIONS WITH BINDER							
		Kollidon® 30				**Kollidon® VA 64**			
		Tablet weight (mg)	**CS (N)**	**%F**	**DT (sec)**	**Tablet weight (mg)**	**CS (N)**	**%F**	**DT (sec)**
3.5	**23**	335.86 (1.0)	20.15 (19.9)	7.85	1104.67 (2.3)	324.68 (2.5)	19.55 (14.0)	8.40	1030.00 (4.2)
	24	338.72 (0.6)	35.89 (9.1)	3.06	1261.67 (2.6)	326.46 (0.4)	36.04 (6.0)	2.94	1106.17 (1.9)
	25	337.20 (0.8)	66.68 (6.8)	1.49	1302.50 (1.5)	324.73 (0.3)	56.79 (7.9)	1.79	1230.67 (1.9)
	26					325.42 (0.5)	102.35 (7.2)	1.00	1300.67 (1.5)
5	**23**	338.59 (0.6)	20.09 (10.5)	6.57	1220.67 (2.2)	318.45 (0.3)	19.13 (11.7)	8.74	1068.50 (2.1)
	24	339.48 (0.4)	37.09 (6.9)	2.48	1219.67 (2.2)	319.50 (0.5)	35.76 (8.8)	3.34	1031.17 (2.3)
	25	336.55 (0.5)	67.11 (5.9)	1.53	1291.67 (2.9)	320.68 (0.4)	59.87 (5.0)	1.71	1161.83 (1.6)
	26					316.48 (0.4)	99.28 (6.7)	1.10	1212.17 (1.8)
7	**23**	334.54 (0.5)	19.87 (13.1)	7.06	1218.17 (2.2)	312.30 (0.3)	21.27 (9.0)	6.92	1009.17 (1.6)
	24	338.82 (0.4)	40.54 (9.7)	2.52	1322.17 (3.4)	312.51 (0.4)	36.52 (6.7)	3.30	1086.50 (1.2)
	25	337.73 (0.4)	68.16 (6.4)	1.34	1352.67 (3.0)	312.12 (0.4)	60.22 (5.2)	1.87	1140.17 (2.2)
	26					308.24 (0.5)	90.93 (6.1)	1.10	1188.33 (1.5)

For all the formulations the addition of any one of the two binders (and independent of the concentration) resulted in a noticeable decrease in the average tablet weight at each compression setting compared to the values obtained for the basic formulation, i.e. the formulation containing no (0%) dry binder. Comparison of the effect of the binder type on the observed decrease in average tablet weight indicated a larger decrease for tablets containing Kollidon® VA 64 compared to the Kollidon® 30 tablets, the reason being the higher bulk density of Kollidon® 30 (Bühler, 1993:31,198). Furthermore, the tablets containing Kollidon® VA 64 showed a marked decrease in average tablet weight with an increase in the percentage of the binder, averaging 325 mg at 3.5% and 311 mg at 7%. This was due to the high bulk density of Kollidon® VA 64, which had a more pronounced effect on tablet weight in formulations containing higher concentrations of Kollidon® VA 64. Kollidon® 30 did not have the same effect. Most surprisingly, neither of the two binders at any concentration between 3.5 and 7%, showed any significant effect on the crushing strength (and therefore also on the friability) of the tablets. The most significant difference between the two binders were found in terms of the maximum compression setting at which tablets could be produced without capping. At all concentration levels used, tablets containing Kollidon® VA 64 could be tableted at a setting of 26 (and even higher), compared to a maximum setting of 25 for both the Kollidon® 30 formulation and the basic formulation containing no dry binder. At setting 26 both the latter formulations capped. The reason for the increase in compression setting was Kollidon® VA 64's plasticity, a property that Kollidon® 30 does not possess. This property gave granules and mixtures that were less susceptible to capping during compression (Bühler, 1993:214). The increase in compression setting from 25 to 26 for the Kollidon® VA 64 formulations produced a significant increase in tablet crushing strength from about 55-60 N at setting 25 to >90 N at setting 26 at all concentration levels. Once again there was no correlation between percentage Kollidon® VA 64 present and the resulting crushing strength.

Relatively high tablet friability (>1.7%) was observed for both binders and at all concentration levels used, except for Kollidon® VA 64 at compression setting 26 where acceptable values (≤1.10%) were obtained at all concentrations. These results indicated the inability of the binders to improve (reduce) tablet friability in Tablettose® tablets, due to their inability to increase the mechanical strength of the tablets.

The inclusion of binders did not adversely affect the disintegration times of the tablets due to the fact that neither binder at any concentration resulted in any significant increase in tablet crushing strength. Disintegration times for all the tablets were longer than 16 minutes,

mainly due to the fact that these tablets slowly dissolved, rather than disintegrated. These results ones again confirmed the absence of any disintegrating properties of Tablettose®, and emphasised the necessity for the inclusion of a disintegrant in tablet formulations containing this filler.

4.3 EFFECT OF DISINTEGRANTS ON THE PHYSICAL PROPERTIES OF TABLETTOSE® TABLETS

Previous results (chapter 3 and section 4.2) showed long disintegration times for Tablettose® tablets and indicated the necessity of the inclusion of a disintegrant in Tablettose® formulations. Swelling disintegrants swell when in contact with water, exert pressure on the tablet structure and cause disintegration. These disintegrants are highly effective in low concentrations in directly compressed formulations and have little effect on the physical properties of the compact (Marais, 2000:64).

Mixtures containing Tablettose®, magnesium stearate (0.5% w/w), Kollidon® VA 64 (3.5% w/w) and either Ac-Di-Sol®, sodium starch glycolate or Kollidon® CL (0, 0.5, 1, and 2% w/w) were prepared and tableted (at a constant die fill volume) at various compression settings as described in sections 2.2.1 and 2.2.2. From the results in the previous section (4.2) Kollidon® VA 64 was used as dry binder due to the fact that it increased the compression range and produced tablets with low friability and acceptable mechanical strength. Since the concentration of the binder did not have an influence on disintegration, the lowest concentration (3.5% w/w) was used to minimise the influence of the binder on physical properties of the tablets. The tablets were evaluated in terms of weight variation, crushing strength, friability and disintegration as described in sections 2.3.3-2.3.5. The results are tabulated in table 4.2.

A general tendency of a decrease in tablet weight with an increase in compression setting could be seen in formulations containing disintegrant. There were no marked differences between tablet weights in formulations containing different disintegrants or different concentrations of the same disintegrant. The %RSD were below 1%, confirming the good flow properties of Tablettose®, which was unaffected by disintegrants added. As expected, crushing strength increased with an increase in compression setting in all formulations. Crushing strength was generally unaffected by the type or concentration of disintegrant included in the formulation. However, crushing strength decreased markedly in all formulations containing disintegrant compared to formulations containing no disintegrant.

Table 4.2: *Tablet weight (TW), crushing strength (CS), percentage friability (%F) and disintegration time (DT) of Tablettose®/magnesium stearate (0.5% w/w)/Kollidon® VA 64 (3.5% w/w) tablets containing different concentrations of Ac-Di-Sol®, Kollidon® CL or sodium starch glycolate at various compression settings. Values between brackets represent percentage relative standard deviation.*

		TABLET FORMULATIONS WITHOUT ANY DISINTEGRANT											
% D*	C**	TW (mg)		CS (N)		%F		DT (sec)					
0	26	342.75 (1.3)		44.50 (13.1)		2.17		1292.50 (1.7)					
	27	347.81 (0.5)		98.95 (6.9)		1.00		1275.17 (1.0)					
		TABLET FORMULATIONS WITH DISINTEGRANT											
		Ac-Di-Sol®				Kollidon® CL				Sodium starch glycolate			
		TW (mg)	CS (N)	%F	DT (sec)	TW (mg)	CS (N)	%F	DT (sec)	TW (mg)	CS (N)	%F	DT (sec)
0.5	26	346.69 (0.5)	22.88 (22.6)	6.65	49.67 (18.8)	350.77 (0.5)	32.14 (8.5)	3.86	72.00 (15.7)	346.39 (0.9)	27.45 (10.4)	4.55	63.50 (4.2)
	27	345.98 (0.3)	48.74 (9.4)	2.14	35.83 (5.1)	349.21 (0.7)	61.13 (6.5)	1.68	44.17 (5.0)	345.94 (0.6)	55.61 (4.8)	1.87	119.50 (6.3)
1.0	26	345.45 (0.5)	25.30 (16.6)	6.25	90.67 (7.8)	343.32 (0.6)	27.13 (16.9)	4.96	60.83 (8.7)	348.39 (0.7)	25.72 (8.8)	4.65	46.83 (4.8)
	27	341.96 (0.5)	45.32 (4.0)	2.21	40.00 (14.7)	347.51 (0.4)	57.12 (7.5)	1.80	34.50 (4.8)	343.23 (0.5)	51.64 (6.9)	1.93	58.50 (3.9)
2.0	26	343.81 (0.4)	25.50 (19.1)	6.76	128.83 (1.8)	342.73 (0.6)	23.33 (15.3)	6.07	84.17 (14.9)	343.50 (0.6)	21.24 (9.8)	5.87	48.67 (1.7)
	27	342.56 (0.5)	46.32 (5.6)	2.26	104.00 (6.6)	340.27 (0.3)	46.00 (8.9)	2.04	58.67 (11.9)	343.30 (0.6)	38.89 (7.0)	2.24	44.83 (2.2)

* *% Disintegrant*
***Compression setting*

Figure 4.1 shows the effect of disintegrant type and concentration on disintegration time and crushing strength of Tablettose®/magnesium stearate/Kollidon® VA 64 tablets at compression settings 26 and 27. Crushing strength of tablets containing Ac-Di-Sol® was the least affected (at both compression settings) by a change in disintegrant concentration. For each compression setting and for all concentrations of disintegrant, the percentage friability increased in formulations containing disintegrant compared to formulations without disintegrant (table 4.2). However, all formulations showed a decrease in percentage friability with an increase in compression setting. Formulations containing Kollidon® CL or sodium starch glycolate showed an increase in percentage friability with an increase in disintegrant concentration. Friability in Ac-Di-Sol® tablets was unaffected by disintegrant concentration, but showed the highest percentage friability at both compression settings and at all concentrations employed.

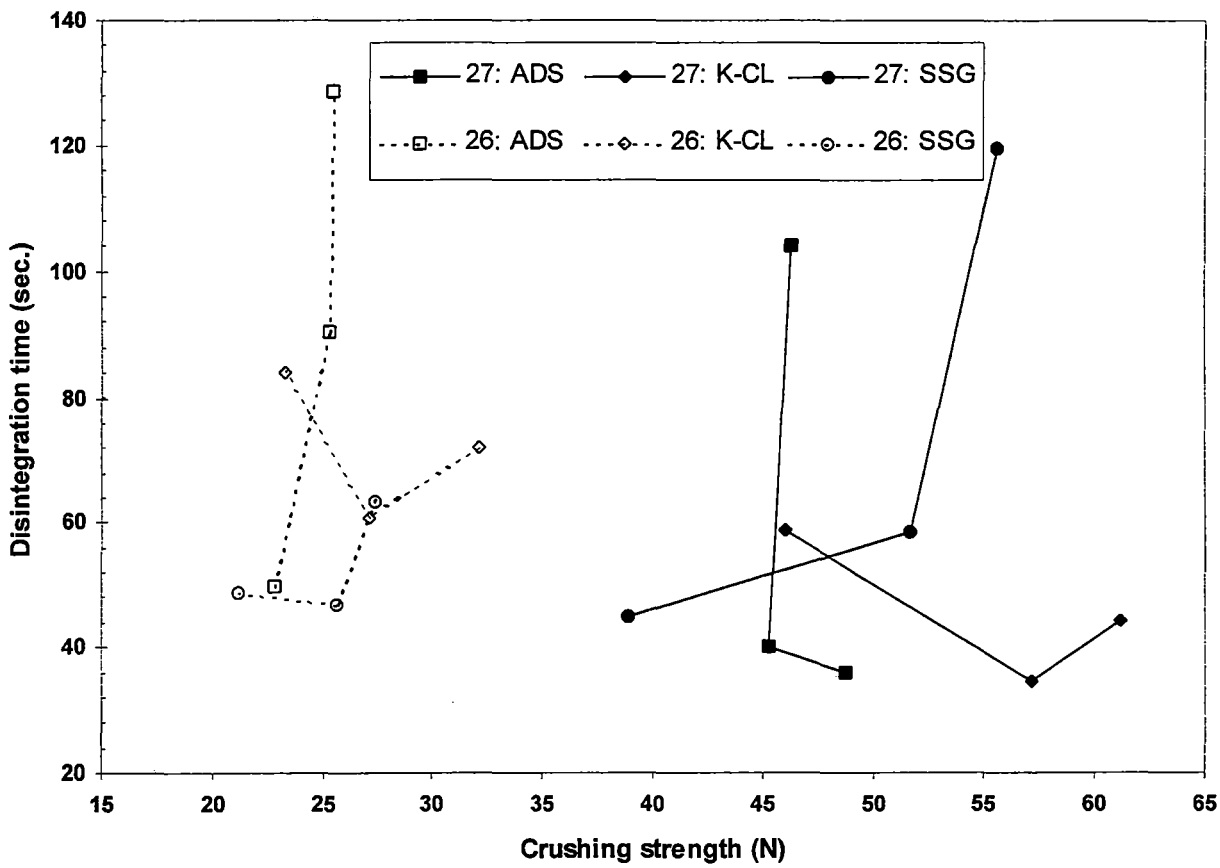

Figure 4.1: *Effect of disintegrant type and concentration and compression setting on disintegration time and crushing strength of Tablettose® tablets. Disintegrant concentration increased from left to right.*

Disintegration times decreased significantly from longer than 21 minutes in formulations without disintegrant, to less than 3 minutes in all formulations containing disintegrant (table 4.2). Figure 4.2 shows the effect of disintegrant type and concentration on disintegration time of Tablettose®/magnesium stearate/Kollidon® VA 64 tablets at compression settings 26 and 27. Although disintegration times for all types and concentrations of disintegrant were fast, there were significant differences between disintegration times of different disintegrants. From figure 4.2 it is evident that higher concentrations of disintegrant are not necessary, as the percentage disintegrant in the formulation had a negligible influence on disintegration times at both compression settings.

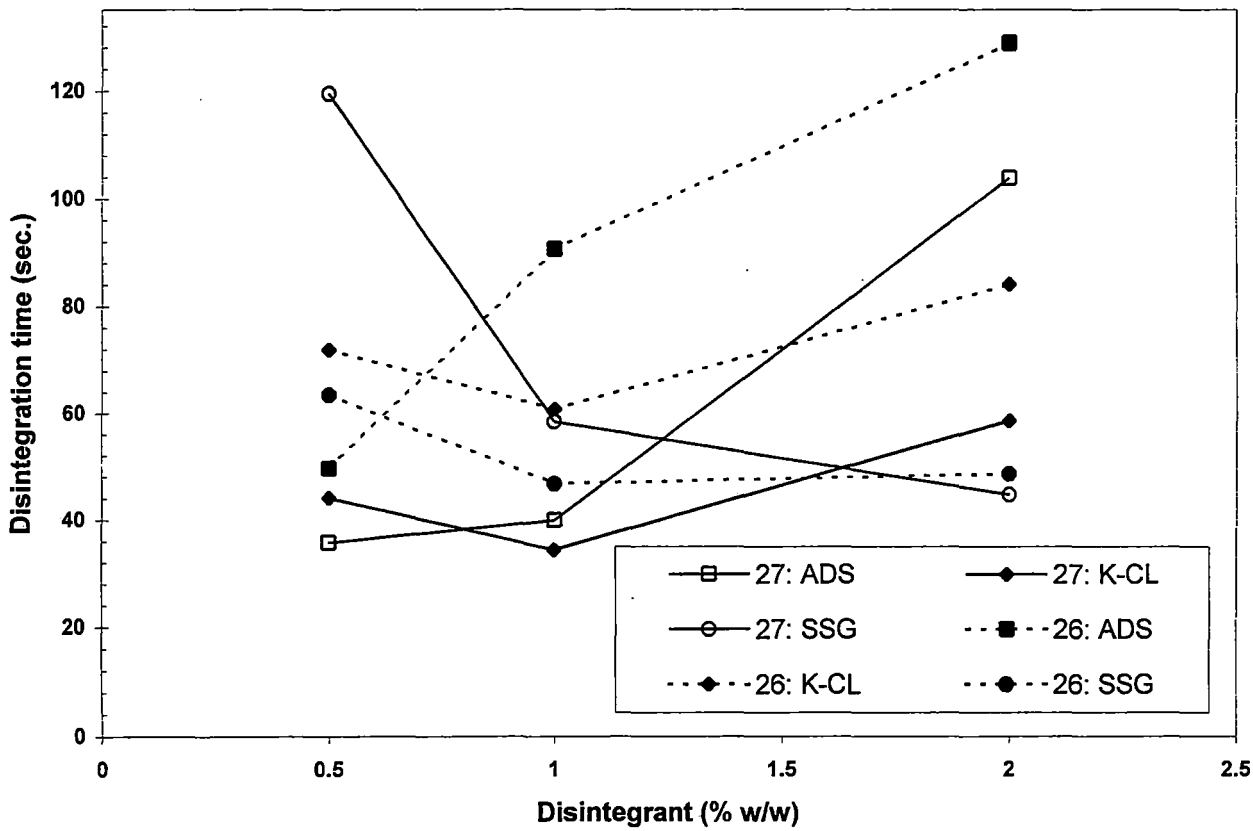

Figure 4.2: *Effect of disintegrant type and concentration on disintegration time of Tablettose® tablets at different compression settings.*

Tablets containing Ac-Di-Sol® showed a slight increase in disintegration time with an increase in concentration. Figure 4.2 also shows an improvement in disintegration with an increase in compression setting in tablets containing Ac-Di-Sol® and Kollidon® CL in all concentrations employed, the reason being a more porous structure at a low compression setting (26), and a certain swelling volume vanished into the numerous voids of the compact causing prolonged disintegration (Schmidt & Rubensdörfer, 1994:2913). At compression

setting 27, there was less accommodation by the tablet matrix of the swelling of the disintegrant, and a significant force of swelling could be expended on the system to cause faster disintegration (List & Muazzam, 1978:161). This tendency was not observed in tablets containing sodium starch glycolate, where an increase in compression setting caused an increase in disintegration time (0.5 and 1% sodium starch glycolate), with no difference in disintegration times when 2% sodium starch glycolate was present. This might be due to the fact that this disintegrant have the smallest swelling capacity of the three disintegrants studied (Caramella *et al.,* 1984:137), and was therefore less affected by the porosity of the tablet structure. For all disintegrants used, 1% seemed to be the optimum concentration with faster disintegration times at all compression settings compared to the other concentrations employed in the formulations.

4.4 CONCLUSION

Neither the addition of Kollidon® 30 nor Kollidon® VA 64 as binders to Tablettose® tablets had any significant effect on the crushing strength (and therefore also on the friability) of the tablets. The most significant difference between the two binders were found in terms of the maximum compression setting at which tablets could be produced without capping. Tablets containing Kollidon® VA 64 could be tableted at higher (≥26) compression settings than tablets containing Kollidon® 30. This increase in compression setting resulted in an improvement in the physical properties of the tablets (increase in crushing strength and decrease in percentage friability).

The addition of Ac-Di-Sol®, Kollidon® CL or sodium starch glycolate as disintegrants to Tablettose® tablets did not have a marked influence on the physical properties of the tablets. However, the addition of disintegrants to Tablettose® formulations resulted in the tablets changing from slowly dissolving to rapidly disintegrating systems with disintegration times of less than 3 minutes. This rapid disintegration may result in fast drug release from the tablets and consequently fast drug dissolution. The type and concentration of disintegrant were not important in decreasing disintegration time.

5. CHAPTER 5

COMPARISON OF THE DISSOLUTION PROFILES OF A POORLY WATER SOLUBLE DRUG FROM DIRECTLY COMPRESSED AVICEL® PH 200 AND TABLETTOSE® FORMULATIONS

5.1 INTRODUCTION

For sparingly water-soluble drugs, like furosemide, dissolution is the rate-limiting step during absorption (preceding appearance of the drug in the systemic circulation). These drugs usually exhibit slow dissolution rates and a low extent of dissolution due to their inherent poor solubility (C_s) and low concentration gradient (C_s-C_t). According to the general dissolution equation (equation 1.2), the rate of dissolution of these drugs depends primarily on the effective surface-area of the drug, i.e. the surface-area in contact with the surrounding medium. It could therefore be assumed that any factor which affects the establishment of rapid contact between drug particles and the surrounding medium, could influence both the rate and extent of drug dissolution. During tablet formulation the aim is to optimise drug release and dissolution through manipulation of formulation variables (choice of excipient type and concentration) and process variables (especially compression force). These factors not only determine the physical properties of the tablet, but also contribute or govern the release and dissolution of the drug from the tablet matrix. It could therefore be deducted that the main contributing factors would include:

- the physicochemical properties of *the filler* due to its high content in directly compressed formulations;
- *the binder* due to its effect on the mechanical strength of the tablets;
- *the disintegrant* due to its effect on the release rate of the drug from the tablet matrix, and
- *compression* force due to its effect on mechanical strength of the tablets, tablet porosity and disintegrant efficiency.

The results from the previous chapter clearly indicated significant differences between the physical tablet properties of directly compressed Avicel® and Tablettose® tablets, especially in terms of the mechanical strength and tablet disintegration, with pure Tablettose® performing less favourably compared to Avicel®. Since tablet properties have a significant effect on drug dissolution, it was expected

that drug dissolution profiles from tablets containing these two fillers would also differ significantly.

In this chapter the dissolution profiles (in terms of rate and extent) of a sparingly water-soluble drug from pure Avicel® and Tablettose® tablets were compared and related to the physical properties of these two fillers and their tablet properties. Furthermore, the effect of the major contributing formulation variables on drug dissolution from Tablettose® tablets was evaluated.

5.2 COMPARISON BETWEEN DRUG DISSOLUTION PROFILES FROM AVICEL® AND TABLETTOSE® TABLETS

Tablets containing furosemide (20 mg), magnesium stearate (0.5% w/w) and either Avicel® PH 200 or Tablettose® were compressed at compression setting 26 as described in section 2.2.2. The physical tablet properties and dissolution in 0.1 M HCl were determined as described in sections 2.3 and 2.4 respectively. From the dissolution data two dissolution parameters were calculated, namely the DRi (indicating the rate of drug dissolution) and the AUC (representing the extent of drug dissolution) (see section 2.4.4.2). The dissolution data is presented in annexure A1 and the physical properties and dissolution parameters are given in table 5.1.

Table 5.1: *Physical properties of Tablettose® and Avicel® tablets with or without furosemide at compression setting 26. The values in brackets represent the percentage relative standard deviation.*

	Without drug		**With drug**	
	Tablettose®	**Avicel®**	**Tablettose®**	**Avicel®**
Crushing strength (N)	64.24 (7.8)	39.27 (4.0)	49.53 (10.0)	54.88 (1.9)
% Friability	1.60	1.40	1.54	1.09
Disintegration time (sec.)	1229.00 (4.4)	13.00 (6.9)	797.67 (3.0)	10.33 (5.0)
AUC $x10^{-1}$ ($mg.min.cm^{-3}$)	ND*	ND	1.65 (14.8)	3.46 (0.8)
DRi $x10^{-4}$ ($mg.cm^{-3}.min^{-1}$)	ND	ND	0.387 (33.8)	4.21 (1.4)

**ND – No dissolution data due to the absence of drug*

Addition of furosemide to Avicel® tablets increased the crushing strength of the tablets, but reduced the strength of the Tablettose® tablets compared to tablets without the drug (table 5.1). These changes in crushing strength, however, had little effect on the friability of any of the formulations, but slightly decreased the disintegration times (from >20 minutes to ≈13 minutes) of the Tablettose® tablets. This was probably due to the decrease in the crushing strength of these tablets, which allowed for faster solution of the tablets.

The dissolution profiles of furosemide from the Avicel® and Tablettose® tablets in 0.1 M HCl are shown in figure 5.1. The inherent poor solubility of the drug (a weak acid with pKa ≈ 3.6-3.9) in the dissolution medium (pH ≈ 1) is reflected in the fact that only 25% and 37% of the available drug dose (20 mg in 900 cm^3) dissolved within 60 minutes from the Tablettose® and Avicel® tablets respectively.

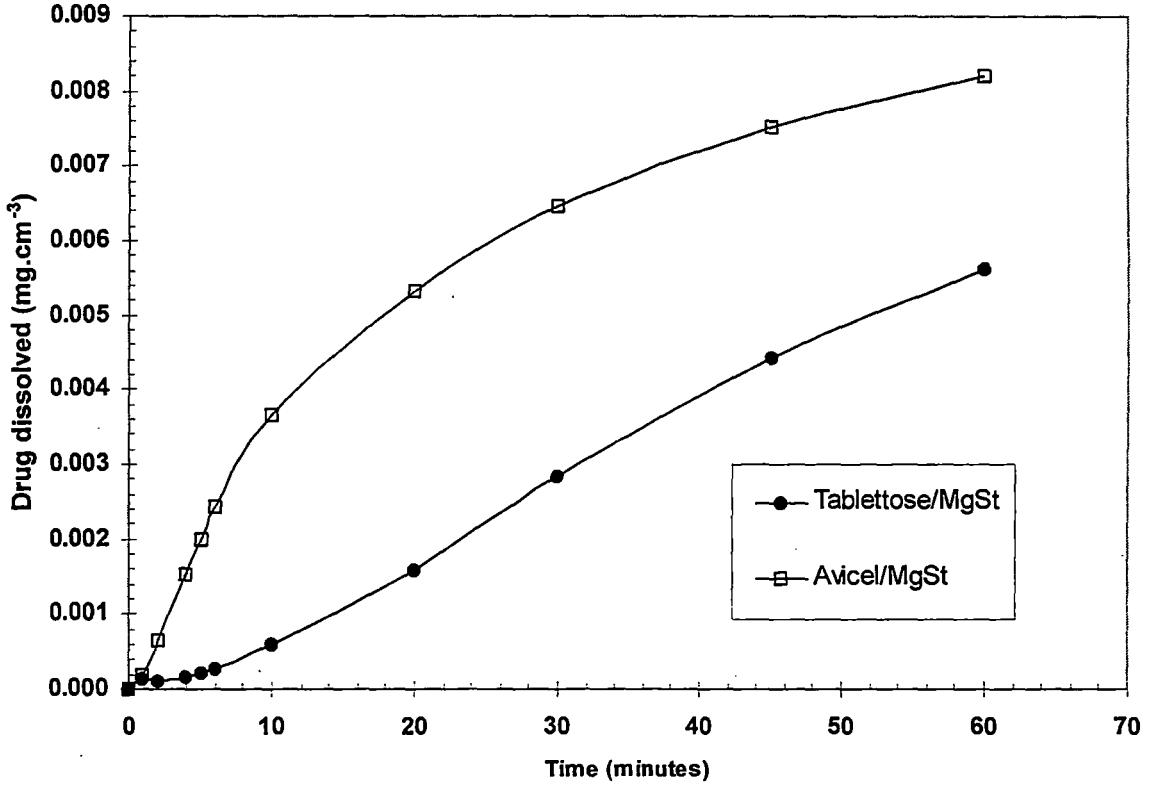

Figure 5.1: *Dissolution profiles of furosemide in 0.1 M HCl from Tablettose® and Avicel® tablets, both containing magnesium stearate (0.5% w/w) at compression setting 26.*

The dissolution profiles of furosemide from the Avicel® tablets is typical for disintegrating tablets and confirmed the disintegrating properties of compressed microcrystalline cellulose (Battista & Smith, 1962:21). Conversely, the dissolution profile from the Tablettose® tablets represented the typical profiles from dissolving compacts, with the slope of the dissolution curve remaining almost constant between all time intervals. The rapid disintegration of the Avicel® tablets (≈10 seconds) resulted in the rapid establishment of contact between drug particles and the medium, which lead to an initial dissolution rate (DRi) for furosemide (4.21×10^{-4} $mg.cm^{-3}.min^{-1}$) that was almost 11 times faster compared to the rate from the Tablettose® tablets (0.387×10^{-4} $mg.cm^{-3}.min^{-1}$), with a disintegration time ≈13 minutes. The slow dissolution rate for the drug from the Tablettose® tablets could be attributed to the restricted contact between drug particles and the dissolution medium due to the fact that these tablets slowly dissolved from the surface, rather than disintegrated.

Comparison of the extent of drug dissolution (represented by the calculated AUC) from the two formulations, showed a significantly higher value (46%) for the Avicel® tablets than for the Tablettose® tablets (table 5.1). These results could be related to the rate at which contact was established between the drug and the dissolution medium, i.e. the initial dissolution rate. These results confirmed the findings of Marais (2000:93) and Miny (2001:67) who showed the dependency of the AUC on the DRi.

5.3 EVALUATION OF FORMULATION VARIABLES ON DRUG DISSOLUTION FROM TABLETTOSE® TABLETS

Results obtained from the evaluation of the physical properties of pure Tablettose® tablets (chapter 3) suggested possible poor drug dissolution profiles due to the fact that the tablets dissolved slowly rather than disintegrated (with resulting disintegration times exceeding 20 minutes). This was confirmed during dissolution testing (section 5.2). In chapter 4 the results of a study on the effect of excipients (dry binders and disintegrants) on Tablettose® formulations showed the advantages of the inclusion of a dry binder to increase compression force (resulting in elimination of capping and reduction in tablet friability) and the addition of super disintegrants (resulting in rapid tablet disintegration). From these results Tablettose® formulations containing furosemide (20 mg per tablet), 3.5% w/w Kollidon® VA 64 (as dry binder)

and 1% Ac-Di-Sol®, sodium starch glycolate or Kollidon® CL (as disintegrant) were prepared and tableted at compression settings 26 and 27. The physical properties (crushing strength, friability and disintegration times) of the tablets were determined as described in section 2.2.2 and compared with formulations without drug and/or disintegrants. The results are presented in table 5.2.

Table 5.2: *Tablet properties of Tablettose®/magnesium stearate (0.5% w/w) tablets containing Kollidon® VA 64 (3.5% w/w) and disintegrant (0 or 1% w/w) with or without furosemide. Values between brackets represent the percentage relative standard deviation.*

Disintegrant		Compression setting			
		26		27	
		Without drug	With drug	Without drug	With drug
Without disintegrant	Crushing strength (N)	44.50 (13.1)	25.65 (14.0)	98.95 (6.9)	41.06 (6.2)
	% Friability	2.17	5.15	1.00	2.36
	Disintegration time (sec.)	1292.50 (1.7)	644.67 (4.5)	1275.17 (1.0)	837.17 (5.0)
Ac-Di-Sol®	Crushing strength (N)	25.30 (16.6)	22.58 (2.6)	45.32 (4.0)	37.43 (7.0)
	% Friability	6.25	5.48	2.21	3.13
	Disintegration time (sec.)	90.67 (7.8)	112.33 (3.6)	40.00 (14.7)	103.50 (2.7)
Kollidon® CL	Crushing strength (N)	27.13 (16.9)	23.09 (14.3)	57.12 (7.5)	36.41 (12.8)
	% Friability	4.96	7.49	1.80	3.34
	Disintegration time (sec.)	60.83 (8.7)	72.17 (6.0)	34.50 (4.8)	62.17 (6.2)
Sodium starch glycolate	Crushing strength (N)	25.72 (8.8)	25.09 (14.2)	51.64 (6.9)	45.06 (7.1)
	% Friability	4.65	5.28	1.93	2.51
	Disintegration time (sec.)	46.83 (4.8)	60.67 (3.4)	58.50 (3.9)	59.50 (0.9)

Incorporation of the drug (20 mg per tablet) into the formulations resulted in a significant decrease in crushing strength, an increase in friability and a decrease in disintegration time in all formulations without a disintegrant at both compression settings. These changes in the physical properties were probably interdependent. The decrease in crushing strength (resulting from interference by the drug with the binding between filler particles) could be responsible for the increase in tablet friability, whilst it also led to faster solution of the tablets (reflected by a decrease in disintegration time).

In formulations containing a disintegrant, the incorporation of the drug had the same effect on the crushing strength (i.e. a decrease) but to a lesser extent. All these tablets were markedly softer compared to the tablets without a disintegrant, which led to the conclusion that the presence of the disintegrant had a more pronounced effect on crushing strength than the drug. The fact that the crushing strengths of the formulations containing both the drug and a disintegrant were significantly lower than those containing neither of these two compounds could be the reason for their higher friability. This difference in crushing strength however was less at compression setting 27 than at 26, with the friability at compression setting 27 also significantly lower than at 26.

The most significant change in the physical properties of the tablets was however observed in the disintegration times of the different formulations. The presence of a disintegrant once again significantly reduced the disintegration times (as has been shown in section 4.3) from more than 20 minutes to less than 2 minutes. This effect could be attributed to the fact that the presence of the disintegrant changed the tablets from slowly dissolving to rapidly disintegrating systems. Although the presence of the drug slightly increased the disintegration times at both compression settings, the tablets still disintegrated in less than 2 minutes. The slight increase in disintegration time of the tablets containing the drug might be due to the hydrophobicity of furosemide, which slightly retarded liquid penetration into the tablets.

The effect of compression force (induced by changing the upper punch depth into the die through an increase in the compression setting) on disintegration times followed the same tendency as was observed in section 2.4, with a slight decrease in

disintegration time for each specific tablet formulation at setting 27 compared to setting 26. As discussed previously, this was the result of an increase in disintegrant efficiency due to less accommodation in the tablet matrix of the swelling of the disintegrants, resulting in the development of an effective swelling force in the tablets, which caused faster disintegration.

In the context of the rapid disintegration times of the tablets this effect of the drug was however almost insignificant. It could therefore be concluded that the incorporation of the drug had little significance in terms of the physical properties of the Tablettose® formulations, and that any observed differences in the dissolution profiles of the drug from the various formulations could be attributed to the effect of the excipients and/or compression force.

The dissolution profiles of furosemide from these formulations in 0.1 M HCl were determined as described in section 2.4 and the results are presented in annexure A2. The two dissolution parameters, i.e. the initial dissolution rate (DRi) and the extent of dissolution (AUC) were calculated from the dissolution data. The calculated values are presented in table 5.3.

Table 5.3: *Dissolution parameters of Tablettose® formulations containing 20 mg furosemide per tablet. Values in brackets represent the percentage relative standard deviation.*

Formulation composition			**Dissolution parameters**			
Filler/Lubricant (0.5% w/w)	**Binder (3.5% w/w)**	**Disintegrant (1% w/w)**	**DRi x10^{-4} (mg.cm^{-3}.min^{-1})**		**AUC x10^{-1} (mg.min.cm^{-3})**	
			Compression setting			
			26	**27**	**26**	**27**
Tablettose®/ Magnesium stearate	None	None	0.39 (33.8)	Capped	1.65 (14.8)	Capped
	Kollidon® VA 64	None	3.83 (4.1)	2.60 (14.9)	3.66 (3.5)	3.34 (2.6)
	Kollidon® VA 64	Ac-Di-Sol®	6.79 (4.3)	6.73 (0.2)	4.12 (3.5)	4.09 (3.7)
	Kollidon® VA 64	Kollidon® CL	5.70 (4.9)	5.70 (5.0)	3.82 (6.2)	3.69 (3.6)
	Kollidon® VA 64	Sodium starch glycolate	6.17 (2.4)	6.80 (9.9)	4.02 (2.9)	4.23 (3.7)

The dissolution profiles of furosemide from the different formulations at compression setting 26 are shown in figure 5.2. The most significant increase in drug dissolution was found with the formulation containing the dry binder (without a disintegrant) compared to the basic formulation (containing Tablettose®, magnesium stearate and the drug). This formulation resulted in the DRi and AUC of the drug being 9.8 and 2.2 times higher respectively despite the fact that the tablets slowly dissolved, rather than disintegrated (with disintegration times exceeding 10 minutes). Consulting of the literature provided an explanation for this somewhat unexpected result. According to Bühler (1993:114) Kollidon® VA 64 increase the solubility of furosemide, possibly due to formation of a drug/excipient complex. The presence of a disintegrant in the formulations containing the binder significantly improved drug dissolution with an average increase of 62% in the DRi and 9% in the AUC at compression setting 26 and 146% and 20% respectively at compression setting 27. This could once again be attributed to the presence of the disintegrant which changed tablets from slowly dissolving to rapidly disintegrating systems, resulting in rapid drug release and providing the necessary contact between drug particles and the medium.

There were no significant differences between the dissolution profiles of the drug from the formulations containing the various disintegrants at each compression setting. This suggested that the type of disintegrant used was not as important as the fact that a disintegrant was included in the formulation. In the disintegrating tablets an increase in compression force had little effect on drug dissolution, with no significant differences between the dissolution parameters at compression settings 26 and 27. In the slowly dissolving tablets, however, an increase in compression force significantly decreased both the rate and extent of drug dissolution. This could be attributed to an increase in the time it took for the tablets to dissolve due to a denser tablet core, which retarded liquid penetration and reduced contact between drug particles and the medium. These results confirmed the advantage of incorporating a superdisintegrant in slowly dissolving tablet formulations to minimise the negative effect of compression force.

Figure 5.2 shows the dissolution profiles of furosemide from the basic Avicel®, basic Tablettose®, Tablettose®/Kollidon® VA 64 and Tablettose®/Kollidon® VA 64/sodium starch glycolate formulations at compression setting 27. The inclusion of the dry binder (Kollidon® VA 64) enhanced drug dissolution to a level comparable with the basic Avicel® formulation, due to an increase in drug solubility as described earlier. Taking into account that this Tablettose® formulation was a non-disintegrating (slowly

dissolving) system compared to the rapidly disintegrating Avicel® formulation, clearly demonstrated the dominant and significant contribution of drug solubility compared to the disintegration process during drug dissolution. However, the advantage of inducing rapid disintegration in slowly dissolving tablet formulations containing poorly water-soluble drugs, through the inclusion of an effective disintegrant, cannot be overlooked. In the absence of a solubility-enhancing excipient, drug dissolution can be significantly improved in non-disintegrating or slowly dissolving tablet formulations, simply by ensuring rapid drug release from the tablet matrix and the establishment of maximum contact between primary drug particles and the surrounding medium. Although rapid tablet disintegration does not guarantee dissolution in the case of sparingly water-soluble drugs, the absence or prolongation of tablet disintegration would definitely significantly retard the already slow dissolution rate and low extent of drug dissolution of these drugs.

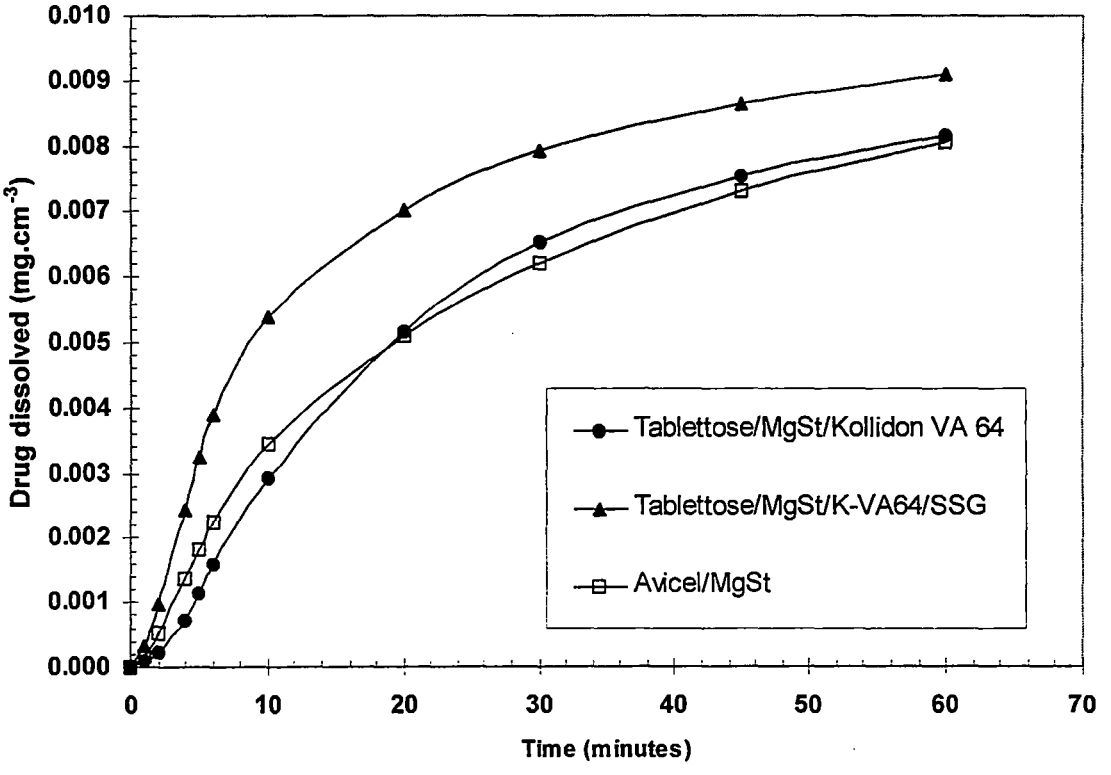

Figure 5.2: *Dissolution profiles of furosemide in 0.1 M HCl from Avicel®/magnesium stearate (0.5% w/w) tablets and Tablettose®/magnesium stearate (0.5% w/w) tablets containing Kollidon® VA 64 (0 or 3.5% w/w) and sodium starch glycolate (0 or 1% w/w) at compression setting 27.*

5.4 CONCLUSION

The addition of furosemide to either Tablettose® or Avicel® PH 200 formulations had little effect on the physical properties of the tablets.

Avicel® produced significantly better drug dissolution compared to Tablettose® tablets. This was due to the inherent disintegration properties of Avicel® compared to Tablettose® tablets, which slowly dissolved from the surface of the tablets rather than disintegrated. The disintegration of the Avicel® tablets established rapid contact between drug particles and the medium, whereas the non-disintegrating Tablettose® tablets showed restricted contact between drug and dissolution medium.

Formulation variables (dry binder and disintegrants) had positive effects on drug dissolution from Tablettose® tablets. The most significant increase in drug dissolution was found with the formulation containing the dry binder (Kollidon® VA 64) due to the fact that Kollidon® VA 64 increased the solubility of furosemide (Bühler, 1993:114). The presence of a disintegrant further improved drug dissolution by changing the Tablettose® tablets from slowly dissolving to rapidly disintegrating systems. The type of disintegrant (Ac-Di-Sol®, Kollidon® CL or sodium starch glycolate) was not important in improving drug dissolution. A change in compression force had no significant effect on drug release from Tablettose® tablets. The results confirmed the dependency of the AUC on the DRi with all dissolution profiles showing a higher extent of dissolution (AUC) with an increase in the initial dissolution rate (DRi).

The results showed that soluble fillers do not guarantee fast disintegration or dissolution, and confirmed the necessity of the inclusion of excipients in slowly soluble tablet formulations to induce rapid tablet disintegration and drug dissolution. It also showed that an insoluble filler with disintegrating properties such as microcrystalline cellulose, does not need the inclusion of excipients to give satisfying drug dissolution.

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7. ANNEXURES

ANNEXURE A: DISSOLUTION DATA OF FUROSEMIDE FORMULATIONS IN 0.1M HCL

ANNEXURE A1: FUROSEMIDE/AVICEL® AND FUROSEMIDE/TABLETTOSE® FORMULATIONS CONTAINING MAGNESIUM STEARATE

Table A1: *Dissolution data of furosemide from Tablettose®/magnesium stearate (0.5% w/w) and Avicel®/magnesium stearate (0.5% w/w) tablets at compression setting 26. The values in brackets represent the percentage relative standard deviation.*

Sample time (min.)	Filler	
	Tablettose®	Avicel®
	Drug dissolved ($mg.cm^{-3}$)	
1	0.0001 (16.6)	0.0001 (14.3)
2	0.0001 (24.9)	0.0001 (9.4)
4	0.0002 (14.7)	0.0002 (3.3)
5	0.00029 (25.4)	0.0002 (2.1)
6	0.0003 (25.7)	0.0003 (1.5)
10	0.0006 (26.7)	0.0006 (2.6)
20	0.0016 (21.1)	0.0016 (1.4)
30	0.0028 (19.0)	0.0028 (1.2)
45	0.0044 (13.7)	0.0044 (0.8)
60	0.0056 (9.7)	0.0056 (1.2)

ANNEXURE A2: FUROSEMIDE/TABLETTOSE®/MAGNESIUM STEARATE-FORMULATIONS CONTAINING KOLLIDON® VA 64 ALONE OR IN COMBINATION WITH AC-DI-SOL®, SODIUM STARCH GLYCOLATE OR KOLLIDON® CL

Table A2.1: *Dissolution data of furosemide from Tablettose®/magnesium stearate (0.5% w/w)/Kollidon® VA 64 (3.5% w/w) tablets containing no disintegrant or different disintegrants (1% w/w), at compression setting 26. The values in brackets represent the percentage relative standard deviation.*

Sample time (min.)	Disintegrant			
	No disintegrant	Ac-Di-Sol®	Sodium starch glycolate	Kollidon® CL
	Drug dissolved ($mg.cm^{-3}$)			
1	0.0001(16.4)	0.0002(16.1)	0.0002(15.8)	0.0002(18.5)
2	0.0003 (7.4)	0.0009 (6.0)	0.0006 (6.5)	0.0008 (5.9)
4	0.0011 (3.6)	0.0025 (3.4)	0.0021 (4.5)	0.0021 (3.2)
5	0.0017 (3.3)	0.0032 (4.0)	0.0029 (3.5)	0.0027 (4.1)
6	0.0023 (3.7)	0.0038 (4.5)	0.0035 (2.0)	0.0032 (6.2)
10	0.0039 (4.2)	0.0053 (3.2)	0.0050 (2.8)	0.0047 (8.5)
20	0.0060 (3.9)	0.0068 (4.5)	0.0066 (3.0)	0.0062 (7.7)
30	0.0070 (3.6)	0.0077 (4.5)	0.0075 (3.8)	0.0071 (7.2)
45	0.0079 (3.5)	0.0084 (2.8)	0.0083 (3.0)	0.0079 (5.3)
60	0.0085 (2.8)	0.0089 (2.3)	0.0087 (2.3)	0.0084 (4.2)

Table A2.2: *Dissolution data of furosemide from Tablettose®/magnesium stearate (0.5% w/w)/Kollidon® VA 64 (3.5% w/w) tablets containing no disintegrant or different disintegrants (1% w/w), at compression setting 27. The values in brackets represent the percentage relative standard deviation.*

Sample time (min.)	Disintegrant			
	No disintegrant	Ac-Di-Sol®	Sodium starch glycolate	Kollidon® CL
	Drug dissolved ($mg.cm^{-3}$)			
1	0.0001 (27.5)	0.0002 (15.6)	0.0003 (44.0)	0.0003 (30.2)
2	0.0002 (8.9)	0.0009 (13.0)	0.0010 (34.8)	0.0009 (13.5)
4	0.0007 (19.2)	0.0024 (5.6)	0.0024 (19.4)	0.0022 (7.2)
5	0.0011 (16.5)	0.0032 (2.1)	0.0033 (13.2)	0.0027 (5.8)
6	0.0016 (11.9)	0.0038 (1.3)	0.0039 (9.6)	0.0033 (6.3)
10	0.0029 (6.6)	0.0052 (4.0)	0.0054 (5.3)	0.0045 (5.0)
20	0.0052 (3.2)	0.0067 (5.0)	0.0070 (2.4)	0.0060 (4.0)
30	0.0065 (2.4)	0.0076 (4.7)	0.0079 (3.3)	0.0068 (4.2)
45	0.0075 (2.4)	0.0084 (3.5)	0.0086 (3.8)	0.0077 (2.8)
60	0.0081 (1.9)	0.0088 (2.9)	0.0091 (3.4)	0.0082 (2.6)