Evaluation and comparison of the physical properties and drug release characteristics of directly compressible lactose-based filler/binders

Bettie van der Walt Erasmus (Alta)

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Bettie van der Walt Erasmus (Alta)

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Supervisor: Prof A.F. Marais

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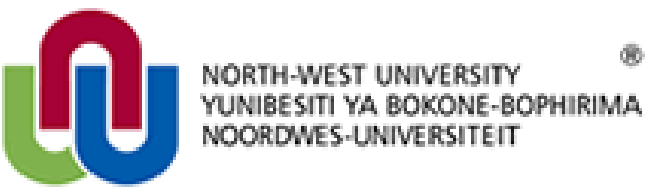

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Then you will have success if you are careful to observe the decrees and laws that the LORD gave Moses for Israel. Be strong and courageous. Do not be afraid or discouraged.

1 Chronicles 22:13

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ABSTRACT

Direct compression has gained significant interest since its advent in the late 1950's due to its potential ease compared to wet granulation. The primary prerequisites for powders used in direct compression are (i) good flow properties (ii) good compressibility and (iii) an acceptable dilution potential to accommodate a relative high percentage of active ingredient. Several filler/binders have been manufactured especially for direct compression and co-processing is one of the recent methods used to produce good compressible excipients with acceptable flow properties. In this study, lactose-based filler/binders were used which included simple and modified lactose materials (Granulac®, Lactopress®, Flowlac® and Tablettose®) as well as co-processed excipients (Starlac®, Cellactose® and Microcelac®).

A comprehensive literature study on direct compression revealed the importance of the physical properties of filler/binders such as interparticle forces, particle shape, particle size and distribution, powder density, particle surface structure and particle packing geometry which influence the flow of powders. All the materials were subjected to the various tests available to evaluate powder flow, namely (i) angle of repose (AoR), (ii) critical orifice diameter (COD), (iii) flow rate and percentage compressibility (%C) in terms of the powders' bulk and tap densities. The results of these tests confirmed the expected flow properties of the various filler/binders, with only one material exhibiting extremely poor flow properties. The following rank order in terms of all flow tests conducted was established; Starlac® >> Microcelac® ≈ Flowlac® >> Cellactose® > Tablettose® > Lactopress® >>> Granulac®. The co-processed filler/binders presented with superior flow compared to the other lactose-based materials.

During the next phase of the study, the compaction properties of the various fillers were evaluated, employing direct compression. Compacts of pure filler were tabletted on an eccentric tablet press at different compression pressures (manipulated by the upper punch setting of the tablet press). The modified lactose filler/binders (Lactopress®, Flowlac® and Tablettose®) exhibited unexpectedly poor compression profiles, where the co-processed filler/binders (Starlac®, Cellactose® and Microcelac®) produced compacts with acceptable appearance and compact properties. Two lubricants (Mg-St or Pruv®), which were tested separately in formulations were added since no compacts could be produced from the pure filler/binders. None of the modified lactose filler/binders, in combination with a lubricant, were able to produce an acceptable compact, since lamination occurred during compression. The co-processed filler/binders produced satisfactory compacts with the addition of a lubricant, but lactose-cellulose fillers (Cellactose® and Microcelac®) also

required the inclusion of a disintegrant (Ac-Di-Sol®) to induce satisfactory compact disintegration.

Poor compressible active ingredients (paracetamol), which exhibit very poor flow properties, are usually difficult to use during direct compression. Many excipients (tested in this study) are formulated to accommodate these drugs and produce acceptable functional tablets. After identifying the best filler/binders (co-processed fillers), according to their flow and compressible properties, paracetamol was added to the formulations. During a pilot study, the percentage paracetamol these fillers could accommodate in a 400 mg tablet was determined. Both Microcelac® and Cellactose® could accommodate 24.5% w/w paracetamol, whilst Starlac® could only accommodated 19.5% w/w. Paracetamol is well known for its tendency to cause tablet capping and lamination. An acceptable upper punch setting range (20-22) was chosen for tabletting, followed by quality control tests done. All three formulations produced suitable tablets for testing and exhibited good tablet properties. All tablets disintegrated within two minutes, with hardness profiles between 120 N and 148 N and friability percentages less than 1%.

Dissolution studies, however, are probably the ultimate test to distinguish between the capability of filler/binders to release the optimum percentage drug after disintegration. Dissolution studies were done on all three formulations using the AUC (area under the curve) and IDR (initial drug release) as parameters to evaluate drug release. All tablets exhibited high initial dissolution rates (between 0.018 – 0.023 mg/min/ml) and 100% drug release was observed. Starlac® presented with a lower amount of drug released compared to the other two, but can be explained by the lower percentage (19.5%) paracetamol present in the formulation.

It was once again confirmed that the physical and compressible properties of potential directly compressible filler/binders play a major role in direct compression. It was concluded that co-processed filler/binders (Starlac®, Microcelac® and Cellactose®) definitely exhibited better tabletting properties during direct compression. They were able to accommodate a certain percentage of paracetamol, although it was expected that they would accommodate a higher amount (at least 50% of total tablet weight).

Key Words: Direct compression; co-processed excipients; lactose-based filler/binders; powder flow; compressibility; dissolution

UITTREKSEL

Direkte samepersing as metode vir die vervaardiging van tablette het baie veld gewen in terme van gewildheid sedert die ontwikkeling daarvan in die 1950's, veral as gevolg van die oënskynlike tydsbesparing in vergelyking met natgranulering. Die vernaamste voorvereistes vir poeiers of poeiermengsels bestem vir direkte samepersing is (i) goeie vloeibaarheid, (ii) goeie saampersbaarheidseienskappe en (iii) 'n groot verdunningspotensiaal om relatief groot hoeveelhede geneesmiddel te kan akkommodeer. Verskeie vulstowwe is spesifiek ontwikkel vir direkte samepersing en saamgestelde vulstowwe (d.i. gekombineerde vulstowwe wat meer as een komponent bevat) is 'n nuwe benadering wat tans gebruik word om direksaampersbare vulstowwe te berei met verbeterde (optimale) vloei-eienskappe. In hierdie studie is vulstowwe met 'n laktose basis ondersoek, insluitend eenvoudige sowel as gemodifiseerde laktose verbindings, naamlik Granulac®, Lactopress®, Flowlac® en Tablettose®, asook saamgestelde vulstowwe (met laktose as hoofbestanddeel), naamlik Starlac®, Cellactose® en Microcelac®.

'n Omvattende literatuurstudie oor direkte samepersing het getoon dat die fisiese eienskappe van die vulstowwe, waaronder bindingskragte, deeltjiegrootte, -vorm, -grootte en grootteverspreiding, -digtheid en pakkingsgeometrie, 'n bepalende rol speel in die vloeibaarheid van die stowwe. Die gekose vulstowwe is onderwerp aan verskillende vloeibaarheidstoetse, waaronder bepaling van die (i) rushoek (AoR), (ii) kritiese openingsdeursnee (COD), (iii) vloeitempo en (iv) persentasie saampersbaarheid (of Carr se indeks) wat gebaseer is op die skynbare en pakkingsdigtheid van poeiers. Die resultate van die toetse op die verskillende vulstowwe het hul goeie vloeibaarheidseienskappe bevestig, met die uitsondering van 'n enkele vulstof (Granulac®) wat in al die toetse swak vloeiresultate gelewer het. Die volgende rangorde in terme van vloeibaarheid kon uit die resultate bepaal word (van goed tot swak); Starlac® >> Microcelac® ≈ Flowlac® >> Cellactose® > Tablettose® > Lactopress® >>> Granulac®. Die saamgestelde vulstowwe het deurgans beter vloei-eienskappe gelewer in vergelyking met die ander laktose-vulstowwe (hoofsaaklik gesproeidroogde en gegranuleerde laktose).

Tydens die volgende fase van die studie is die saampersbaarheidseienskappe van die onderskeie vulstowwe bepaal en vergelyk. Kompakte van die suiwer vulstof is onderwerp aan samepersing by verskillende persdrukke (soos bepaal deur die verstelling van die bo-stempelstand op 'n enkeltabletpers). Die gemodifiseerde laktose (Lactopress®, Flowlac® en Tablettose®) het onverwagte swak saampersbaarheidsresultate gelewer, terwyl die saamgestelde produkte (Starlac®, Cellactose® en Microcelac®) kompakte met goeie fisiese eienskappe gelewer het. Twee smeermiddels (magnesiumstearaat en Pruv®), wat

individueel getoets is, moes egter bygevoeg word aangesien geeneen van die laktoseverbindings getableteer kon word in die afwesigheid van ‘n smeermiddel nie. Nie een van die gemodifisserde laktose produkte kon aanvaarbare kompakte lewer nie, aangesien laminering by almal voorgekom het (ongeag die persdruk wat toegepas is). Die saamgetselde produkte het aanvaarbare kompakte gelewer (in die teenwoordigheid van ‘n smeermiddel), maar die laktose-sellulose produkte (Cellactose® en Microcelac®) het egter ook ‘n toevoeging van ‘n disintegreermiddel vereis (Ac-Di-Sol®) om aanvaarbare disintegrasie van die saamgepersde kompakte te verseker.

Swak saampersbare geneesmiddels (soos parasetamol), wat dikwels ook swak vloei-eienskappe vertoon, lewer dikwels probleme indien hul in direksaampersbare formules geïnkorporeer word (veral hoë dosisse). Die meerderheid van die vulstowwe wat in die studie getoets is, is ontwikkel met die oog op akkommodasie van hierdie tipe “probleem” geneesmiddels in direksaampersbare tabletformules. Na identifisering van die “beste” vulstowwe (naamlik die saamgestelde laktose produkte) op grond van hul vloei- en saampersbaarheidsresultate, is formules berei wat die swak saampersbare parasetamol bevat. ‘n Loodsstudie het getoon dat beide Microcelac® en Cellactose® ongeveer 24.5% m/m parasetamol (in ‘n 400 mg tablet) kon akkommodeer, terwyl Starlac® slegs ongeveer 19.5% m/m kon akkommodeer. Parasetamol is berug vir dekselvorming en laminering tydens samepersing. Die onderskeie parasetamol tabletformules (elk met een van die drie saamgestelde laktose produkte, magnesiumstearaat as smeermiddel en Ac-Di-Sol® as disintegreermiddel, is by die optimum persdruk (20-22) getabletteer, en die tablette is getoets ten opsigte van massavariasie, hardheid, verbrokkeling en disintegrasie. Al drie formules het aanvaarbare tablette gelewer in terme van genoemde fisiese eienskappe, met disintegrasietye binne 2 minute, breeksterktes tussen 120-150 N en verbrokkeling minder as 1%.

Dissolusiestudies is gebruik as finale toetsing van die vermoë van die 3 vulstowwe om optimale geneesmiddelvrystelling te bewerkstellig. Twee dissolusieparameters, naamlik die aanvanklike dissolusietempo (IDR) en die area onder die dissolusiekromme (AUC) is bereken en gebruik om die dissolusieprofiele van die onderskeie formules te evalueer en te vergelyk. Al drie die formules het vinnige IDR-waardes opgelewer (tussen 0.018 – 0.023 mg/min/ml) sowel as volledige dissolusie (100%) binne 64 minute. Hoewel Starlac® se profiel laer vlakke as die van die ander twee formules gelewer het, kan dit toegeskryf word aan die laer parasetamolinhoud in die formule (87 mg in vergelyking met 98 mg).

Die studie het weereens getoon dat die fisiese eienskappe van vulstowwe ‘n baie belangrike (en bepalende) rol speel in hul geskiktheid as direksaampersbare vulstowwe. Die resultate van die studie het getoon dat die saamgestelde vulstowwe, naamlik Starlac®, Microcelac® en

Cellactose® beslis beter geskik is vir gebruik in direksaamgepersde tabletformules in vergelyking met die gegranuleerde en/of gesproeidroogte enkelkomponent laktose produkte (soos Granulac®, Tablettose®, Flowlac® en Lactopress®). Eersgenoemde vulstowwe kon ook hoër persentasies swak saampersbare geneesmiddels akkommodeer, alhoewel daar verwag is dat hulle groter hoeveelhede sou kon akkommodeer, en verdere studies sou waarskynlik nodig wees om hierdie aspek te ondersoek.

Sleutelwoorde: Direkte samepersing; saamgestelde hulpstowwe; laktose-gebaseerde vulstowwe; poeiervloei, saampersbaarheid, dissolusie

AIM

The primary aim of this study was to evaluate and compare the physical, compression and drug release properties of a selection of lactose and lactose-based (single and co-processed) products available on the South African market as directly compressible filler-binders.

BACKGROUND

Traditionally lactose, starch and cellulose were used as fillers and filler-binders in wet granulated formulations. Since the advent of direct compression as a viable alternative for the tedious and time-consuming wet granulation process, manufactures of tablet excipients have spent a lot of time in the development of the ultimate directly compressible filler, possessing the necessary and required flow and compressible characteristics which is the cornerstone of the success of these materials. Starch figured as one of the prominent front runners during this search, for example StaRX®, where lactose products followed with the introduction of products such as Tablettose®, Flowlac® and Ludipress®(a co-processed filler containing a disintegrant and binder). All of the products mentioned had a competent contender, namely microcrystalline cellulose (marketed as Avicel® by the FMC Corporation in the USA) and widely acknowledged as a superior directly compressible filler.

During the past few years, the development of co-processed excipients at a sub-particle level has gained importance in the industry. Co-processed excipients are simple physical mixtures of two or more existing excipients mixed at a particle level (Nachaegari & Bansal, 2004:56). Cellactose®, manufactured by Meggle Corp, Wasserburg, Germany, was one of the first co-processed excipients, containing powdered cellulose and lactose. A starch/lactose-based excipient, Starlac®, soon followed with other meaningful characteristics. Microcelac®, consisting of microcrystalline cellulose and lactose, is one of the most recent co-processed excipients on the market and promise to live up to everyone's expectations.

According to Nachaegari & Bansal, (2004:57), the shift in tabletting from wet-granulation to direct-compression and high-speed manufacturing, forced the industries to come up with new, efficient and effective excipients which are still cost-effective. The success of any pharmaceutical excipient is mainly dependant on the quality, functionality and safety of the compressed tablet.

Flow and packing properties of powders are critical to the successful development and production of solid dosage forms such as tablets (Taylor, 2000:2; Podczeck, 1996:41). A good directly compressible excipient must be able to show physical and chemical

compactibility, flowability, lubricity and the ability to produce a uniform mixture with the active ingredient (Hwang, 2001:1).

Direct compression is a simple technique used in the industry to save manufacturing time and money. Unfortunately this manufacturing process could be problematic if large amounts of poorly compressible active ingredients are incorporated in the formulation (Renoux, 1996:103). Paracetamol is an active ingredient with poor powder flow and compressibility properties which results in many problems during compression, such as capping and lamination.

OBJECTIVES

To achieve the aim of the study, the following experiments have been undertaken:

- Characterization of the physical properties of the lactose based tablet filler/binders, including morphology (utilizing electron microscopy photos, particle size and size distribution analysis) and flow properties (including critical orifice diameter, angle of repose, Carr's index and flow rate);
- Compactibility studies with a variety of different tablet excipients, including fillers, disintegrants and lubricants;
- Compressibility characteristics of pure filler and filler-excipient combinations (determining mechanical strength and friability properties as function of compression force);
- Compressibility properties of fillers including a poorly compressible active ingredient; and
- Drug release properties from tablets containing the above-mentioned drug.

CHAPTER 1
SIGNIFICANCE OF LACTOSE-BASED FILLER/BINDERS AND THEIR PHYSICAL AND COMPRESSION PROPERTIES

1.1 INTRODUCTION

In early days, most tablet formulations required wet granulation processes. Over the past hundred years, manufactures have developed several new excipients, tabletting machines and methods to obtain compressed tablets, containing a precise amount of an active pharmaceutical ingredient (API). Tablets and tablet manufacturing, the most commonly used dosage form, became a science over the past decades (Gohel & Jogani, 2005:76).

Besides the effortless processes and methods used during direct compression, physical factors such as powder flowability, compressibility and dilution play an important role during manufacturing (Nachaegari & Bansal, 2004:52). Direct compression is defined as a process, where pressure is applied, with an upper and lower punch to the powder, held in the die cavity (Zhang *et al*., 2003:2). It involves the compression of a powder mixture containing the active pharmaceutical ingredient and suitable excipients. No pre-formulation is required during direct compression such as in the case with wet granulation. Table 1.1 shows the comparison between the steps that are involved in the manufacturing of tablets by dry granulation, wet granulation and direct compression techniques (Gohel & Jogani, 2005:77).

Direct compression has some merits over wet granulation. Wet granulation is a much more multifaceted process and each stage gives rise to its own difficulties and complications. Granulation consists of a size enlargement process, where small particles are converted to larger and physically stronger agglomerates. There are mainly three categories of granulation namely; wet granulation, dry granulation and dry granulation incorporating bound moisture. Wet granulation is generally used worldwide and includes the wetting of a powder mass with a granulating liquid followed by wet sizing, sieving and drying. The production of granules is a completely new physical entity and good quality assurance is needed to make sure this new material is reproducible. Problems during wet granulation include blending procedures, the concentration, addition rate, massing time, viscosity and distribution of the binder solution. Other factors to keep in mind are temperature effects, drying-rate to ensure drug stability and the granule size and segregation during drying screening (Gohel & Jogani, 2005:77).

All the above-mentioned can contribute to the changing of the granule density, particle size, their filling weight and their compaction qualities. The drying process can also cause unbending due to the fact that soluble API's migrate to the surface of the drying granules (Shangraw, 1989:197). Table 1.2 and gives a brief comparison between the properties of direct compression and wet granulation. It is important to know these differences before any manufacturing can begin. In this study, the focus was mainly on the behavior of tablets conducted from direct compression.

Table 1.1: *Comparison of the major steps involved in the manufacturing methods (Gohel & Jogani, 2005:77).*

Step	Direct Compression	Dry Granulation	Wet Granulation
1	Blending/Mixing of API's and excipients ↓	Blending/Mixing of API's and excipients ↓	Blending/Mixing of API's and excipients ↓
2	**Compression**	Compression into slugs ↓	Preparation of binder solution ↓
3		Size reduction of slugs and sieving ↓	Massing of binder solution of Step 2 with powder mixture of Step 1 ↓
4		Mixing of granules with pharmaceutical excipients ↓	Wet screening of damp mass ↓
5		**Compression**	Drying of wet granules ↓
6			Resifting of dried granules and blending with pharmaceutical excipients ↓
7			**Compression**

During the direct compression process, pressure is applied to the powder mixture held in the cavity by the use of an upper and lower punch. Steps that occur during the process of compression are (1) transitional repacking, (2) deformation at the point of contact, (3) fragmentation and/or deformation, (4) bonding, (5) solid body deformation, (6) decompression, and (7) ejection (Zhang *et al*., 2003:1). Figure 1.1 describes the basic steps during direct compression.

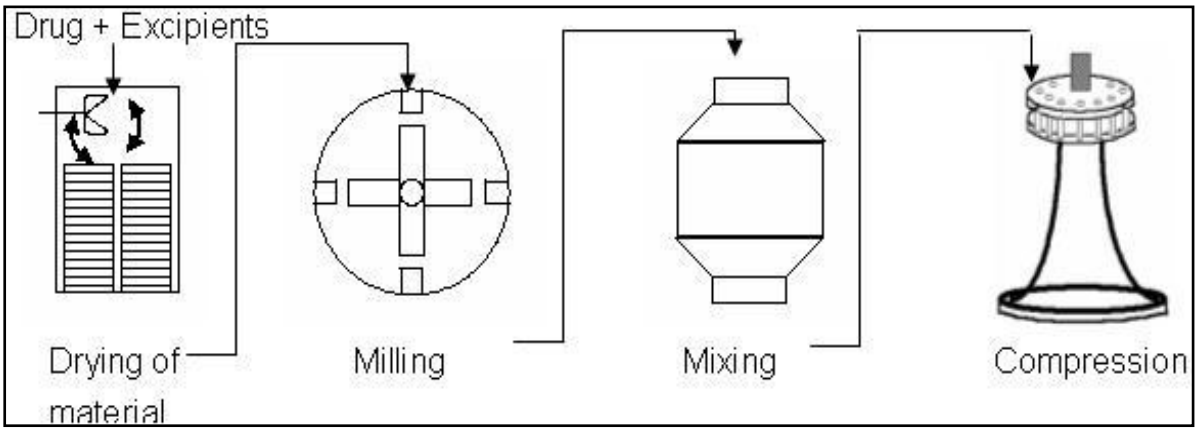


Figure 1.1: *Manufacturing steps during direct compression*

More and more manufacturers at pharmaceutical companies are using the direct compression method due to the availability of directly compressible excipients with both good compressibility and flowability characteristics

The principles of direct compression have been well known for several years; however, the technique used have recently became understandable and was established as a result of the introduction of specially designed excipients for direct compression (Jivraj *et al*., 2000:59). It is important to keep in mind that the quality of the dosage form is not only determined by the characteristics of the active ingredient and the manufacturing processes, but also by the quality of the excipients used (Pifferi *et al*., 1999:1). Pifferi *et al*. (1999:3) stated that excipients are no longer an only inert product, but developed to an essential and functional component in modern dosage designs. Pharmaceutical dosage forms can mainly be divided into three categories namely liquid disperse, solids and semi-solids, where the active substance is partly diluted. This implies that the excipients need to function as diluents, fillers and solvents. These functions are important to give the dose of active suitable weight, uniformity and volume from the galenic point of view, and to make it easier for the administrator (Pifferi *et al*., 1999:3).

1.2 ADVANTAGES AND DISADVANTAGES OF DIRECT COMPRESSION

The main advantage of direct compression compared to wet granulation is the relatively low cost; therefore, it is safe to utter that there would be a minor interest in direct compression if the economic factor had not played such a major role. Since direct compression only involves dry blending and the compaction of the active ingredient and necessary excipients, savings occur in many areas. A lot less unit operations are required during this process, which mean reduced processing time and labor costs, fewer manufacturing steps, less equipment is necessary, reduced consumption of power and less process validation are needed. Although several equipment such as granulators and dryers, are not needed in preparing tablets, more sophisticated blending and compaction equipment are needed for direct compression (Shangraw, 1989:198).

One of the most significant advantages is the exclusion of heat and moisture factors, which decrease thermo labile and moisture sensitive active ingredients' stability and their suitability for the process. The avoidance of high compaction pressure during slugging and roller compaction contributes to the many advantages. Perhaps the least familiar advantage of direct compression is the optimization of tablet disintegration. It enhances the disintegration and dissolution process, because each primary drug particle is separated from the mass and available for dissolution (Shangraw, 1989:198).

The official compendium (USP) now requires dissolution specifications in most solid dosage forms. In the case of directly compressible tablets, the dissolution profile is less likely to change during storage, compared to granulated tablets. Tablets prepared by direct compression have a faster dissolution rate than tablets prepared by wet granulation. Direct compressible tablets disintegrate directly into active ingredient particles instead of granules, thus the active ingredient particles are directly in contact with dissolution fluids. Due to the absence of water in granulation and shorter time periods during processing, microbial growth and cross contamination are less likely to occur in direct compressible tablets (Zhang *et al*., 2003:1).

Table 1.2: *Comparison of direct compression and wet-granulation processes (Shangraw, 1989:202-203).*

Direct Compression	Wet Granulation
Compressibility	
Potential problem for high-dose drugs	Harder tablets for poor compressible drugs
Fluidity	
Formulations may require glidants	Excellent in most cases
Particle Size	
Lower with narrow range	Larger with wide range
Content uniformity	
Segregation may occur	Massing and drying induced
Mixing	
Low shear with ordered blending	High or low shear
Lubricant	
Minimal blending with magnesium-stearate	Less sensitive to lubricant softening and over blending
Disintegration	
Lower levels of disintegrant are necessary	Problems with granules
Dissolution	
No wetting, need a surface active agent **Larger size drug crystals may cause slower dissolution** **Generally faster**	During processing, drugs are wetted Dissolution of granules causes problems Generally slower
Costs	
An increase in raw materials and their quality control	An increase in equipment, labour, time, validation and energy
Formulation flexibility	
Properties of raw materials must be carefully defined	Granules covers the raw material flaws
Stability	
No heat and moisture added **Dissolution rate rarely altered**	Heat and moisture problems Decrease in dissolution rate with time
Tableting speed	
Require lower speed	Fast
Dust	
Very dusty	Less dusty

The moisture present in direct compression excipients are tightly bound, either as water of hydration (e.g. lactose monohydrate) or by hydrogen bonding (e.g. starch, microcrystalline cellulose) and prevents chemical degradation (Shangraw, 1989:199).

Disadvantages of direct compression include the segregation that occurs due to the difference in density of the API's and excipients. The dry state of the powder during the mixing process causes static charge on the powder particles and leads to segregation. The static charges on particles may interfere with the mixing process, which causes agglomeration and could be reduced by creating similar particle size and density of the active drug substance with excipients. Direct compression is not suitable for powders with a low bulk density, because the tablets produced after compression, are too thin. Drug compounds with poor flow properties are not suitable for direct compression (Jivraj *et al*., 2000:59).

In this specific study it was important to be aware of the ideal requirements of directly compressible adjuvants, in particular the fillers. Gohel & Jogani, (2005:78) explained the ideal properties of direct compressible excipients comprehensively in their article.

Direct compressible adjuvants must have good flowability, in other words, free flowing, to ensure that the powder is homogenous and contribute to rapid flow to guarantee identical die filling. To ensure adequate tabletting, good compressibility is required in order to keep the powder mass in the compact form once the compression force is removed. A directly compressible adjuvant requires a high dilution potential and the potential is influenced by the active pharmaceutical ingredient's compressibility. Dilution potential can be defined as "the amount of an active ingredient that can be satisfactorily compressed into tablets with the given directly compressible excipients (Gohel & Jogani, 2005:78). A high dilution potential contributes to a final dosage form with the minimum possible weight.

The particle size of the adjuvants used in a tablet formulation must be in correlation with the particle size of the active ingredient present. Similar particle size distribution is necessary to achieve homogenous blending and the avoidance of segregation, which produces many complications during tabletting. Table 1.3 gives a short summary of the specific requirements, limitations and advantages of an ideal directly compressible adjuvant.

One of the most common problems during tabletting is the capping and lamination of tablets. There are several options to reduce this mechanical failure, but not all of them can guarantee to overcome lamination and capping. Some of the options are reducing compression pressure and decompression speed, increasing or adding a binder, increasing the moisture content; but this can cause stability problems. Many theories and explanations have been given regarding the cause of capping and lamination (Kuppuswamy *et al.,*

2001:1). A theory that is not widely accepted anymore is that air is trapped in the compact during compression. As soon as the upper punch retreats, the trapped air tries to escape causing the tablet to cap. This usually happens during high-speed compression, where the air has not enough time to escape.

Table 1.3: *Ideal requirements, advantages and limitations of direct compression (Gohel & Jogani, 2005:78).*

Requirements	Advantages	Limitations
Compressibility	Cost effective	Segregation
Controlled particle size	Better stability of API	Variation in functionality
Dilution potential	↓ Microbial contamination	↓ Dilution potential
Flowability	↓ Wear and tear of punches	Poor compressibility of API
Reworkability	Simplified validation	Reworkability
Stability	Faster dissolution	Lubricant sensitivity

Capping and lamination occur during low speed compression, which led to further investigation. Kuppuswamy *et al.* (2001:1) confirmed the possible theory for capping and lamination of Mann *et al.* (1983:44), who stated that capping is related to the amount of air present in the granule bed before compression starts. Removing the air before compression, reduced capping but lamination still occurred. Kremer, (2006:7977) did studies on airflow during compression and that a significant amount of air remained in die punch-die cavity as the punch concavity increases. This study confirmed the fact that air entrapment can occur during compression resulting in capping and lamination of tablets. Other possible theories described by Kuppuswamy *et al.* (2001:1) stated that lamination can occur because of radial elastic recovery during ejection of tablets. This is a widely accepted explanation for lamination and attributed to capping caused by internal shear pressure, which initiate cracks in the tablet. Plastic relaxation of shear stresses is one solution to prevent cracking. Materials with a plastically origin are less likely to cap or laminate (Kuppuswamy *et al.,* 2001:2).

1.3 PHARMACEUTICAL EXCIPIENTS

According to Chang and Chang, (2007:1) pharmaceutical excipients can be defined as any substance other than the active drug or prodrug that is included in the manufacturing process, or is contained in a finished pharmaceutical dosage form. Required functions of an excipient, includes increased lubrication, enhanced flowability, improved compressibility and compatibility. They can be categorized as diluents, sweeteners, binders, disintegrants,

lubricants, glidants, emulsifying-solubilizing agents, coating agents, and so forth. In addition to their functional performance, ideal excipients must be chemically stable, nonreactive with the active ingredient and other substances, and inert in the human body (Chang & Chang, 2007:1).

There are several functions and specifications for excipients. Excipients are used to perform different and specific functions and can be categorized in three categories. The three groups consist of the excipients' that influence stability, the release, availability and absorption of the active ingredient and their manufacturability during the production process. The focus was on solid-state excipients. The manufacturing of tablets and capsules require modern excipients that are appropriate to produce a homogeneous and flowable powder mixture. It is essential to make sure that the modern tabletting and capsulation machines are fed swiftly and smoothly with the powder mixture (Pifferi *et al*., 1999:5).

Solid-state excipients have different physical properties that need to be considered during manufacturing. The general Pharmacopoeia monographs indicate the tests that need to be done to determine the technological functionality of the specific material. The functionality of the material can be described as the powders' physical, physico-mechanical and biopharmaceutical properties (Pifferi *et al.*, 1999:6). It is essential to keep in mind that excipients are not made up of single chemical entities but consist of several mixtures of polymers, synthetic and semi-synthetic natural derivatives. Some properties of excipients have a remarkable influence on the intermediate and final products. The properties of the excipients and the active ingredients are clearly visible in the various parameters such as flowability, compressibility, fluidity, uniformity, lubrication, mixing and the weight and content of the pharmaceutical dosage form. Other parameters where these properties are reflected in the hardness and speed of tablet disaggregation, the chemical and physical stability of the manufactured product, the coating of the active ingredient and the bioavailability of the active ingredient (Pifferi *et al.*, 1999:6).

During tablet manufacture, the choice of excipients plays a key role to ensure the most appropriate and effective tablet. There are a great number of highly potent drugs that must be used in very low dosages. Fillers are a main component that must be considered during the formulation of tablets. Their main function is to make the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size. Both organic and inorganic materials are used as fillers and binders. Carbohydrates are a known organic resource with the ability to enhance the mechanical strength of the product and the products' toxicity freedom. It ensures an acceptable taste and delivers sensible solubility profiles (Kottke *et al*., 2002:293)

Lactose is the most commonly used carbohydrate in compressed tablets. Lactose is a disaccharide of galactose and glucose and is present in cow's milk. The two main grades of lactose are the amorphous lactose and the isomeric forms of lactose. If amorphous lactose is in contact with moisture, recrystallization occurs due to the hygroscopic property of anhydrous lactose. The two stereo-isomers of lactose are α and β isomers and differ only in their hydroxyl-group's positioning. Lactose α-monohydrate can be sieved such as Inhalac® where as Capsulac® and Granulac® are examples of milled lactose. Lactochem® is available as milled and sieved α-lactose monohydrate. Gohel and Jogani, (2005:81) stated that α-lactose monohydrate shows relatively poor binding properties and compared to the other forms of lactose, it has a very high brittle index. The above-mentioned fillers, especially the milled lactose, are mainly used in wet granulation.

Anhydrous α-lactose are obtained from dehydrated α-lactose monohydrate, where the single crystals change to aggregates and are then responsible for a higher binding capacity. These changed crystals are much softer, weaker and less elastic. One of the major disadvantages of anhydrous lactose is the relative slow disintegration of tablets (Gohel & Jogani, 2005:81).

Widely commercially used lactose is anhydrous β-lactose and consists of agglomerates of exceptionally fine crystals. Anhydrous β-lactose is created by the crystallization of α-lactose monohydrate above 93˚C by roller drying. The moisture content of this powder is very low and makes it a suitable excipient for moisture sensitive API's. Known products are Supertab Anhydrous® and Lactopress Anhydrous®. Tablettose® is a recognized excipient used during direct compression. It is an agglomerated form of α-lactose monohydrate and was especially developed for direct compression due to its good binding properties. Coarse lactose has good flowability and milled lactose shows good compression. This combination in Tablettose® attributes to its good properties and efficiency as excipient in tablets (Gohel & Jogani, 2005:82).

One of the universally used lactose forms is spray-dried lactose. According to Gohel and Jogani (2005:82), Guncel and Lachman were the first people to describe the process of spray-dried lactose. Many people are not familiar with the spray drying process. Spray-dried lactose made its appearance in the early 1960's and was the first product specially designed for direct compression (Takeuchi *et al*., 1998:91-92). In short, spray drying is a method where different solutions are swiftly dried by atomizing the liquid in a heated chamber until it reached a particulate form. It is also possible to spray dry solvent-based systems under controlled conditions (Takeuchi *et al.,* 1998:92).

There are a few standard unit operations during the spray-dry process. This procedure begins with the pre-concentration of the liquid; evaporation was used previously but is

currently too expensive. Atomization is the next step and consists mainly out of the creation of droplets. A few atomization techniques are used in the industry such as pressure nozzle atomization, two-fluid nozzle atomization and centrifugal atomization. All of the mentioned techniques give a relatively good average particle size control. The particle distribution differs a lot if you compare the techniques. This step is the most critical step during the spray-dry process.

The third major step during spray drying consists of drying the droplets in a stream of hot, dry gas, usually air. Separation of powder from the moist gas follows, where cooling and the packaging of the product completes the process. One of the most commonly used spray-dryers is the cyclone spray dryer, figure 1.2. In short, a liquid product concentrate is pumped into the atomizing device, where small droplets are formed. A stream of hot gas meets these droplets and causes it to lose moisture rapidly while in dry air. The dry powder is then separated from the moist air by centrifugal actions. Lastly, the atomizer compromises either a spinning disc with a rotation between 2000 – 20,000 rpm, or static high velocity jet nozzles (Broadhead, *et al.,* 1992:1170).

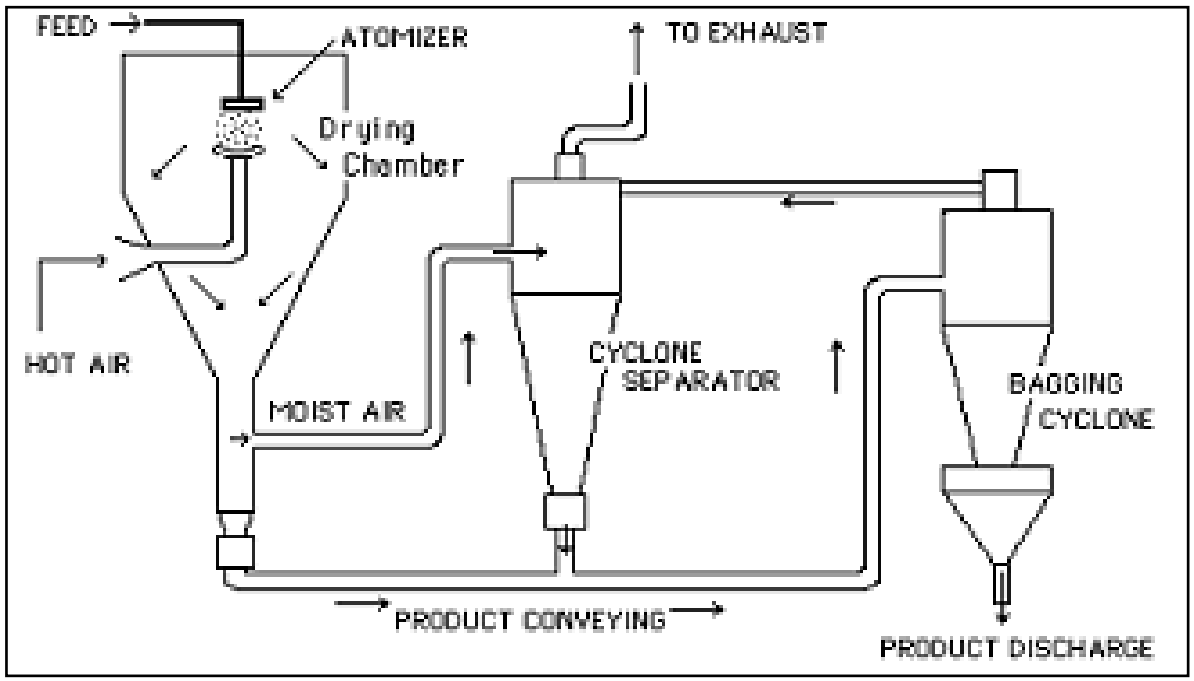


Figure 1.2: *Cyclone spray dryer.*

Lactopress® is a good example of spray-dried lactose. It consists mainly of α-lactose monohydrate spherical particles and contributes to excellent flowability and binding. This excipient is highly effective in modern, high-speed tabletting machines due to the presence of 15% amorphous lactose, which ensures low friction with the die wall.

Nachaegari and Bansel, (2004:54) stated that there is lack of new chemical excipients on the market. The main reason for this occurrence is the shortage of money due to the high costs involved in excipient discovery and development.

New combinations of existing excipients are a bright suitable option for improving the functionality of excipients in a tablet formula. There are many possible combinations which will contribute to the desired performance characteristics, however, this is a very complex process because of the possibility that one excipient may interfere with the other excipients properties and functions. Co-processing dates back to the late 1980's, when the first co-processed excipient made its appearance. Cellactose®, a mixture of powdered cellulose and lactose, was the second excipient discovered, in the 1990's, after co-processed microcrystalline cellulose and calcium carbonate (Nachaegari & Bansel, 2004:58). Starlac®, a combination of maize starch and spray-dried lactose, is one of the recent co-processed excipients on the market. All these co-processed excipients need to be developed on a sub-particle level where particle engineering takes place.

Particle engineering is a very broad concept that involves the manipulation of particle parameters such as shape, size, and size distribution; and changes the polytypic and polymorphic parameters on a molecular level. All of the above mentioned parameters are translated into bulk-level changes such as flow properties, compression, moisture sensitivity and the ability to use a machine. A more understandable explanation for co-processing is that the process is based on a novel concept of two or more excipients, interacting on a sub-particle level to provide a synergy of functional improvements and the masking of the undesirable properties of each individual excipient (Nachaegari & Bansel, 2004:58-59). The methods and techniques used during co-processing are represented in figure 1.3.

Before any co-processing can take place, it is important to keep the individual materials' characteristics in mind. Some materials have the tendency to show a dominant response over the other materials. Co-processing of two or more individual excipients is generally a mixture of a brittle material for example lactose (75%), and a plastic excipient, such as cellulose (25%) to obtain Cellactose®. The ratio in which these materials are used, is an important parameter to gain specific properties. In this particular case, the ratio of brittle and plastic materials used, prevent the storage of elastic energy during compression. There are also extreme cases where the ratio changes drastically to ensure optimum results. The fact remains that it is important to use materials with plastic deformation and brittle fragmentation (Nachaegari & Bansel, 2004:59).

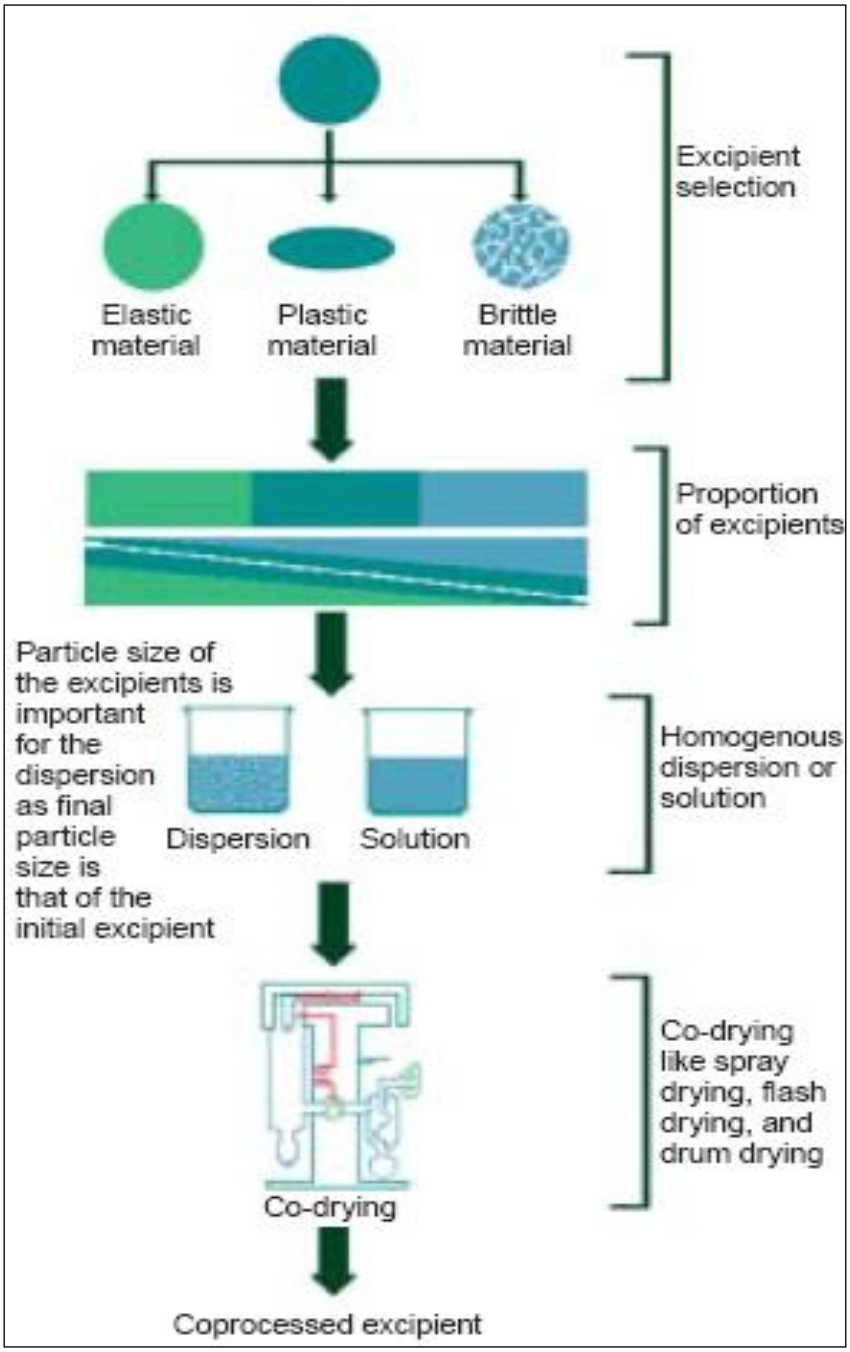


Figure 1.3: *Schematic explanation of the co-processing method (Nachaegari & Bansel, 2004:58).*

The big question still remains, why co-processed excipients are much better and more favorable than the individual excipients. So many studies lead to several experiments, conclusions, advantages, limitations and reasons for using co-processed excipients during direct compression. There are a few advantages and possible limitations of co-processed excipients according to several authors. These advantages and limitations are disputable and every individual excipient will manifest with different properties, advantages and disadvantages (Gohel & Jogani, 2005:80).

Using co-processed excipients in tablet formulations, combines wet granulation and direct compression advantages. The advantages can be summarized in a few sentences. The products obtained are modified and improved without altering the chemical structure. A homogenous distribution is obtained through embedding mini-granules and segregation is prevented by adhesion of the actives on porous particles (Gohel & Jogani, 2005:80).

This reduces companies' regulatory concerns. In general, the physical and mechanical properties of the individual materials are improved. Flow properties, compressibility and dilution potential are few of the many physical properties that are enhanced. An important advantage involving tabletting is that fewer fill-variations are shown during manufacturing. The primary reason for this is the impregnation of one particle in the matrix of another particle. This reduces the rough particle surfaces, which contributes to a high fill-variation. Lubricant sensitivity is a large problem with individual excipients, which is less in co-processed excipients. This is because co-processed excipients consist out of a brittle component such as α-lactose monohydrate and a plastic component such as cellulose. The brittle friction lowers the sensitivity to lubricants while the plastic component provides a big surface on the matrix to ensure good particle bonding (Nachaegari & Bansel, 2004:60).

There are some economical and manufacturing advantages for using co-processed excipients in the industry. Nachaegari and Bansel, (2004:61) avowed that manufactures use a single excipient with functional properties instead of many different excipients. Although these excipients are more expensive, the final product is much less due to the fewer tests and requirements to get the product on the market. Literature reveals and clarifies some limitations regarding co-processed adjuvants. In perspective to the single excipients, the disadvantages are much less. The most common disadvantage is the fixed ratio of excipients in a mixture. This fixed ratio of individual adjuvants may not be the optimum choice for the active pharmaceutical ingredient and the dose per tablet during the development of a new formulation (Gohel & Jogani, 2005:80). One of the major obstacles that co-processed excipients are currently facing, is to find their way into official monographs in the pharmacopoeia. The pharmaceutical industry will not accept combination fillers, unless it produces momentous advantages towards tablet compaction in comparison to the physical mixture of the adjuvants. Due to this problem, many pharmaceutical manufactures refuse to use co-processed excipients in their formulations. Once these problems are solved, the use of combined adjuvants will grow dramatically (Nachaegari & Bansel, 2004:62).

Curiosity about the effect of these highly rated co-processed adjuvants in tablet-form is enormous. There are a number of specifications regarding a tablet's chemical, physical and biological properties, which are extremely important before a tablet could reach the market.

Quality assurance regarding the final product must be considered during the early stages of the development process. It clarifies the goal to be achieved during development and manufacturing (Alderborn, 2002:398). The pharmacopoeias give all the information about the tests and specifications for tablet testing. The uniformity of drugs is tested by two separate methods: uniformity of weight and uniformity of active ingredient.

The main purpose for this study was to compare the different lactose fillers and co-processed fillers where lactose was one of the ingredients. The three co-processed fillers and their composition, tested in this study are explained in the following paragraphs.

As previously mentioned, Cellactose® was one of the first co-processed excipients manufactured. It contains 25% powdered cellulose and 75% α-monohydrate lactose; and exhibit good flow properties. Starlac® contains 15% corn starch and 85% α-monohydrate lactose, whereas Microcelac®, one of the most recent fillers, contains 25% microcrystalline cellulose and 75% α-monohydrate lactose. Our main objective during this study was to find out why companies are producing these co-processed fillers and if there are any relevance to use it as a first choice excipient (Meggle Excipients and Technology).

During the tabletting process, adhesion forces tend to form between the solid particles and die-wall, causing friction. This problem can be reduced by adding a lubricant, which forms a smooth layer between the compact surface and die wall (Shah & Mlodozeniec, 1977:1377). During this study two lubricants namely: magnesium stearate and sodium stearyl fumarate (Pruv®) were used in the formulations.

According to Shah and Mlodozeniec, (1977:1377) the mixing time of lubricants tends to influence the properties of a tablet and the properties of the blended mixture. Alderborn (2002:408) described the mechanisms of lubricants thoroughly and explained that there are mainly two mechanisms, fluid and boundary lubrication. Boundary lubrication is more relevant to this study due to the use of dry ingredients and the direct compression method. The mechanism of a boundary lubricant is to reduce the friction force needed to overcome the shear strength of the die wall (Shah & Mlodozeniec, 1977:1377).

Magnesium-stearate (Mg-St) is a hydrophobic lubricant, which is normally used in the range of 0.25 – 1.0% (w/w) for tablet compression. It has a crystalline structure where its particle size and specific surface area contribute to its lubrication efficiency. Mg-St, no matter in what amount, causes different tablet hardness profiles, tablet disintegration and tablet dissolution (Barra & Somma, 1996:1106). It is generally accepted that Mg-St has a negative effect on tensile strength and tablet hardness, especially in materials where deformation occur. Brittle materials handle Mg-St better because they are more likely to fracture and fragment during compression. When Mg-St is mixed with plastically deformable materials

(microcrystalline cellulose, lactose and pre-gelatinized starch), the tensile strength decreases with a lubricant increase. Thus, lubricant sensitivity depends on the portion of brittle and deformable materials present during formulation (Wang *et al.,* 2010:10).

Sodium stearyl fumarate (Pruv®) is less hydrophobic than Mg-St, with a fatty acid ester component. In comparison to Mg-St it shows less interference with tablet strength and tablet dissolution (Saleh & Aboutaleb*,* 1984:589). Both Pruv® and Mg-St increase disintegration times as their concentrations increase, thus disintegration is dependent on the amount of lubricant used (Kuno *et al.*, 2008:991).

1.4 POWDER FLOW

Before any formulation and manufacturing can take place, several tests and experiments need to be done on the excipients and active ingredients. The most important aspect is the flowability of the powders and substances. A straightforward definition for flowability, is the ability of powder to flow freely or without any interference. The powders can be arranged on a scale from free flowing to non-flowing (Prescott & Barnum, 2000:59). Powder-flow is complex and there is no single test to quantify the flow characteristics of a powder. Due to this multivariable difficulty, it is important to include all possible tests and values to reassure the accuracy of the flowability characteristics of powders. Flowability is not an inherent substance property, but a combination of a substance's physical properties that affect their flow, the apparatus used during experiments, humidity and moisture factors, and the storing of powders. A powders' flow properties include the percentage compressibility, angle of repose, critical orifice diameter, flow rate, particle size, bulk and tap densities, cohesive strength and wall friction (Prescott & Barnum, 2000:60). In conclusion, flowability of powders plays a crucial role in the manufacturing of tablets, and therefore, it is important to do all possible tests thoroughly. The aim of this study does not include a detailed study about powder flowability, but all tests have been done to determine the characteristics of the different substances used during this experimental study.

1.5 COMPRESSION PROPERTIES AND INTERPARTICLE FORCES

1.5.1 Mechanisms of compression of particles

Compaction properties of pharmaceutical powders play an important role during tabletting. There are two different definitions concerning the compaction properties of a powder i.e. the compressibility is the ability of a powder to deform under pressure and compactibility are a powders' ability to form coherent compacts (Sonnergaard, 2006:270). Looking at the

tabletting process, the particles in the die will be rearranged to form a less porous structure, thus the voids between the particles are occupied. When the elastic limit of the powder is reached, deformation of the material occur plastically or destructively (fragmentation or brittle fracture).

The mechanisms that take place are dependent on the characteristics of the material, the compaction speed, compaction pressure and particle size and distribution (Jivraj *et al*., 2000:58). According to De Boer (1986:148), fragmentation can be described as the formation of smaller, discrete particles from an initial grain. Fragmentation is a permanent process where it is impossible for the fragmented particles to return to their original shape when the force is removed. During the fragmentation process new particle surfaces are formed which lead to strong bonding forces between particles. Lactose tends to merge by fragmentation as described by Vromans *et al.* (1985:192). This causes strong binding forces which are independent of moisture absorption and crystallization.

Plastic deformation is also a permanent process where the particles will stay deformed after the force has been removed. The factors, which determine the amount of plastic deformation, are the total compression time, surface contact time, dwell time and the rate of compression. Microcrystalline cellulose is an example of a material that undergoes plastic deformation which results in strong particle-particle bonds. Plastic deformation is a major factor concerning a tablet's mechanical strength or brittle fracture, which produces poor quality tablets that crumble during handling (Kottke & Rudnic, 2002:310). Elastic deformation is mainly dependent on time and particle deformation is reversible if the force is removed. During the relaxation phase of compaction, the particles can create residual stresses within the tablet (Jain, 1999:21). Due to the ability of the particles to go back to their original shape after compression, coherence will be lost because of the reduced interparticulate contact surface.

1.5.2 Interparticle forces in tablets

There are five dominant mechanisms which tend to adhere particles together, namely; (i) distance attraction forces, (ii) solid bridges, (iii) non-freely-movable binder bridges, (iv) bonding due to movable liquids as capillary and surface tension forces, and (v) mechanical interlocking. Capillary and distance attraction forces are naturally cohesive and restrict the relative movement of particles which result in the formation of agglomerates and affect the packing of particles during compression (Yu *et al.,* 2003:70).

Distance attraction forces are divided in three groups: Van der Waals forces, electrostatic forces and hydrogen bonding. The strength of these forces is mainly determined by the

material type and the distance between particles and the surrounding medium (Israelachvili, 1992:11).

Van der Waals forces are the most dominant force between dry fine spherical particles. Li., *et al. (*2004:92) found that the compact strength has a direct correlation with van der Waals forces, theoretically and experimentally. Van der Waals forces operate over short distances where the compression energy is translated to adhesion energy in order to produce a strong binding force between particles (Vachon & Chulia, 1999:184).

Hydrogen bonds are mainly present between molecules containing electronegative and hydrogen atoms in their molecular structure (Pauling, 1960:25). The hydrogen bonds between the hydrogen groups in a particle (cellulose) contribute to the strength and cohesiveness of compacts (Carlin, 2008:188). Electrostatic forces have no major effect on the tensile strength of tablets (Nyström & Karehill, 1986:20).

1.5.3 Summary

To reach the outcome of this study, it was important to be familiar with the chemical, physical and tabletting properties of lactose-bases filler/binders. By comparing the filler/binders, it was possible to distinguish between the different fillers and their suitability for direct compression. All the lactose-based fillers used in this study, except for one, Granulac®, are specially manufactured for direct compression. Another crucial parameter of comparing filler/binders is their ability to accommodate active ingredients (good or poor compressible drugs) during direct compression and is dependent on the compressibility of fillers and their drug release properties.

CHAPTER 2
MATERIALS AND METHODS

2.1 INTRODUCTION

The materials used in this study were different lactose-based fillers which are used during the manufacturing of tablets through wet granulation and direct compression. The diverse lactose-fillers differ according to their production method, composition, particle shape and size, densities, and their molecular- and interparticle forces.

This chapter focuses on the different materials used during this study and the various methods utilized to determine and compare the flow and compression properties of the powders and the dissolution profile of a tracer drug (API) from tablet formulations containing the various fillers.

2.2 MATERIALS

Table 2.1 presents the various materials used during this study with reference to composition, batch numbers, the manufacturers and suppliers. Analytical grade materials were used in all experiments.

2.3 SCANNING ELECTRON MICROSCOPY (SEM)

The characteristics and behavior of pharmaceutical powders are to a large extend dependant on their physical properties such as particle size, size distribution, shape and surface structure. In order to explain powder behavior and to explain differences in the behavior of different powders, knowledge about their physical characteristics is essential.

Scanning electron micrographs (SEM photos) were prepared from the various powders studied in this project which provided much needed information about the particle properties of each powder, especially particle shape and surface structure.

Small amounts of each powder were used for this experiment. Fractions of the different powders were affixed on a double-sided conductive carbon tape on a sample tray. The samples were dusted with an inert gas. Powder fractions were accordingly sputter-coated with a gold/palladium (80:20) mixture to form an approximately 28 nm layer on the surface of the powder fractions. An Eiko® ion coater (model IB-2, Eiko Engineering, Japan) was used in the coating procedures. The coating process operated under a vacuum higher than 0.06 Torr. A *GUANTA FEI SCANNING ELECTRON* microscope was used to study the particles of each powder and displayed on a computer (Eindhoven, The Netherlands).

Table 2.1: *The various raw materials used in this study.*

Material	Composition	Batch Number	Manufacturer
Granulac® 200	Fine, milled lactose monohydrate	022 – 4990	Meggle GmbH & Co., Wasserburg, Germany
Tablettose® 80	Agglomerated lactose monohydrate	022 – 4999	Meggle GmbH & Co., Wasserburg, Germany
FlowLac® 100	Spray-dried lactose, anhydrous and monohydrate	022 – 04492	Meggle GmbH & Co., Wasserburg, Germany
Lactopress®	Spray-dried amorphous lactose	615825	Frieslandfoods , DOMO, Zwolle, Holland
Cellactose® 80	Lactose monohydrate and cellulose	022 – 27973	Meggle GmbH & Co., Wasserburg, Germany
Starlac®	Lactose monohydrate and corn starch	022 – 0013622	Meggle GmbH & Co., Wasserburg, Germany
Microcelac® 100	Spray-dried lactose monohydrate and cellulose	022 – 0987	Meggle GmbH & Co., Wasserburg, Germany
Magnesium Stearate®	Lubricant	624489	Warren Chemicals Specialities Ltd, Durban, South Africa
Ac-Di-Sol®	Disintegrant	T017C	FMC International, Wallingstown, Little Island, Cork, Ireland
Paracetamol®	Active Ingredient	0815107	SRI KRISHNA Pharmaceuticals Ltd, Hyderabad, India

2.4 POWDER FLOW METHODS

This section describes the different methods utilized to determine the flow characteristics of the various powders. This section is divided in two sub-sections, namely (2.4.1) the preparation and treatment of the materials before testing and (2.4.2) the methods used to determine the flow characteristics and the calculations of the different flow factors from the results.

2.4.1 Preparation of materials before testing

Flow characteristics of materials are affected by environmental factors such as humidity, temperature and moisture absorption. The materials in this study are sensitive to humidity changes, (effect of moisture in the atmosphere which is directly influenced by the temperature). All experiments were carried out in a temperature controlled laboratory. The particle size and size distribution of each powder are important characteristics, because of their effect on the flow properties of the materials.

2.4.1.1 Particle size and size distributions

Particle size analysis was conducted with a Malvern Mastersizer 2000 (Malvern Instruments Ltd, Malvern, UK) fitted with a Hydro 2000SM wet accessory and a computer. Results were obtained with software for the Mastersizer 2000 version 5.31.

The dispersant used for all the materials was a volume of 100 ml ethanol for each experiment. For every measurement, background measurements were taken in each case. After completion of the background measurement a sufficient quantity of the raw material was added to render an obscuration of 10-20% after which particle size measurement was made. Two measurements, 20 seconds apart, consisting of 12000 sweeps each, were taken. All samples were analyzed in duplicate for each material.

2.4.1.2 Pre-treatment of powders

Each powder was placed on a drying pan and dried in an oven fitted with an extraction fan (Labotec Ecotherm) at a temperature of 50˚C for 8 hours. The oven was pre-heated for 30 minutes to the required temperature. The powders were removed from the ovens after 8 hours and were taken to the temperature controlled room. Powders were carefully poured into clean, dry glass containers, after which the openings were covered with Parafilm®, and the lids were screwed on tightly. All experiments were done in the temperature controlled room at 25 ± 1˚C, where the relative humidity was 40 – 60%.

2.4.2 Flow Tests

The following powder flow tests were conducted during this study: critical orifice diameter (COD); angle of repose (AOR); flow rate (FR) and percentage compressibility (%C), which included the determination of bulk and tapped densities of the powders.

2.4.2.1 Critical orifice diameter (COD)

COD of powders is defined as the smallest orifice diameter through which powder particles can flow freely without application of any external help or interference (Buys, 2006:40).

Apparatus used to determine the COD of the various fillers were designed by Buys (2006:40). The apparatus consists of a set of copper brass discs stacked on top of each other (as illustrated in figure 2.1A). Each disc is between 5 and 15 mm thick and has an opening of a specific size, ranging from 1.5 to 32 mm (see figure 2.1B). During set-up, five discs were stacked with the disc with the smallest opening at the bottom. Due to the angle of the opening in each disc, stacking resulted in the formation of a funnel with a smooth slope of degrees. An aluminum cylinder was fitted at the top of the funnel to create a holding chamber for the powder mass. No static powder areas formed due to the absence of a cylinder floor and base plat (Buys, 2006:41).

A powder volume of 100 ml was gently poured into the holding cylinder, while the opening on the bottom disc was kept shut. Opening the bottom orifice resulted in the discharge of the powder (if possible) from the holding chamber. Interchanging the stacked discs allowed for changing the bottom orifice diameter, whilst keeping the slope of the funnel constant. This provides a means to find the critical orifice diameter for each individual powder, whilst keeping the set-up conditions (i.e. internal slope and height) constant.

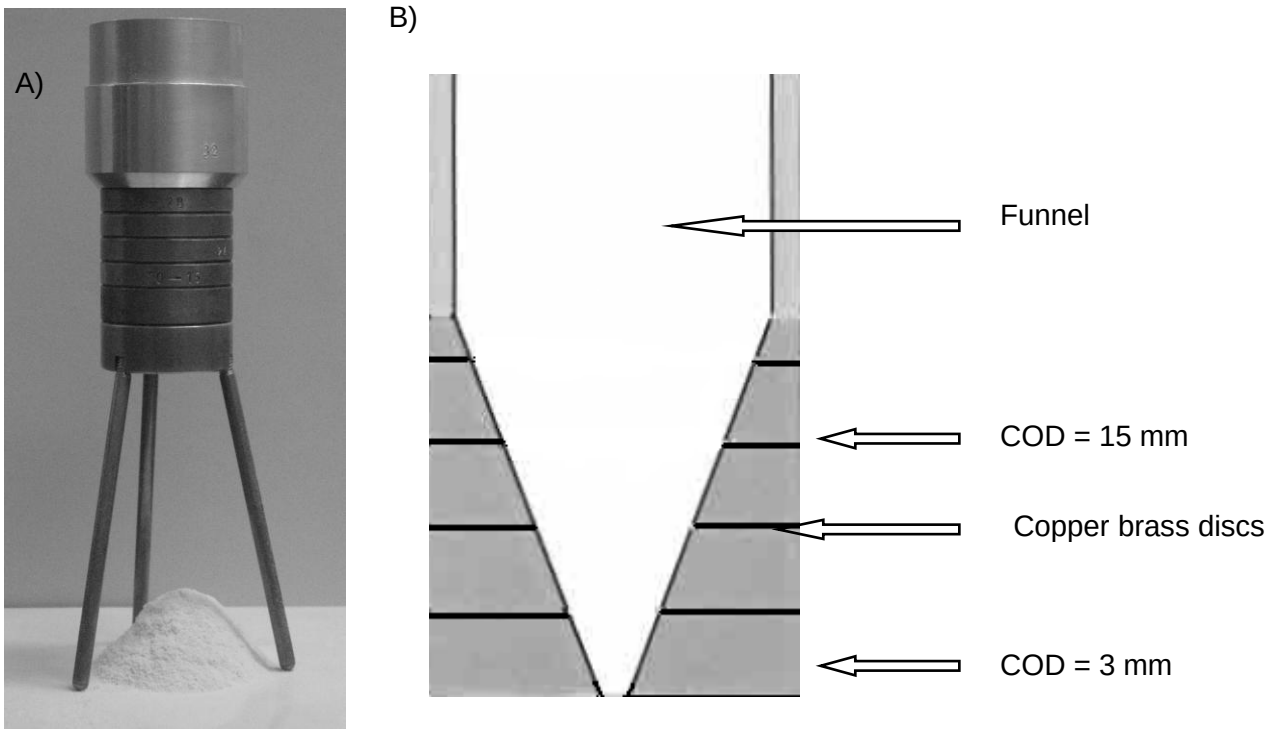


Figure 2.1: *A) Critical orifice diameter apparatus; B) Copper brass discs.*

Each powder was analyzed for its COD in triplicate according to table 2.2 (using different volumes during each run), and the average COD, standard deviation and percentage relative standard deviations were calculated.

Table 2.2: *Ranking index used to classify flow according to the critical orifice diameter.*

Flow description	Critical orifice diameter (mm)
Excellent	1 – 5
Good	6 – 9
Average	10 – 15
Poor	16 – 20
Very poor (cohesive)	20

2.4.2.2 Angle of repose (AoR)

A powder's angle of repose describes the frictional forces between the powder particles. The angle of repose is the maximum angle between the surface of the powder cone and the powder cone's horizontal plane (Wong, 2002:2636). Table 2.3 gives an indication how to classify powders according to their angle of repose. The same apparatus used for determination of the COD of the various powders was employed during this experiment.

An amount of powder was allowed to flow freely from the apparatus from a height of 15 cm onto a flat surface (white paper on a square of glass), as seen in figure 2.2.

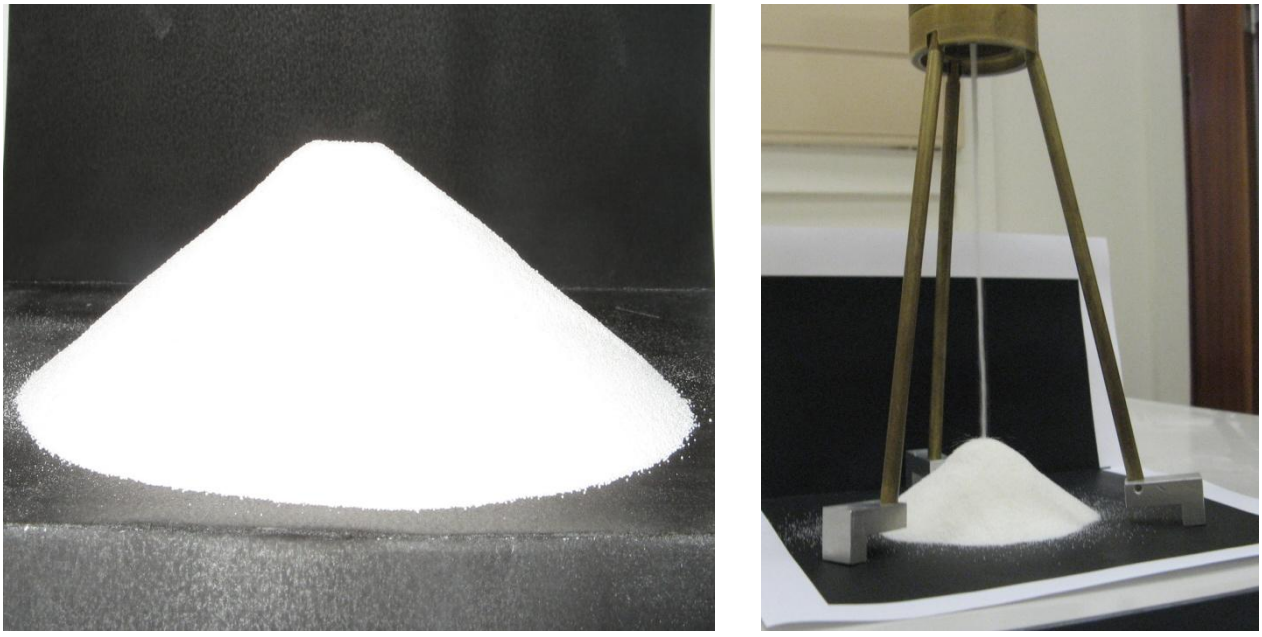


Figure 2.2: *Measurement of the angle of repose of powders.*

The size of the bottom orifice was chosen two sizes larger than the COD (as determined for each powder in section 2.4.2.1). The diameter of the cone formed by the dispersed powder was marked on the paper, and the cone height was measured using a ruler. After all measurements were taken, a pencil was forced through the center of the cone to mark the middle point of the cone on the paper. This midpoint of the cone in relation to the edges of the cone was used to determine the diameter of each powder heap. The results were transformed to the angle of repose for each powder using equation 2.1 as described by Wong (2002:2636). The average AoR, standard deviation and percentage standard deviation of three determinations of each powder were calculated.

– [2.1]

Where:

h represents the height of the powder cone and *r* is the radius (½ x diameter) of the cone base.

As a general rule, powders with an AoR greater than 50˚ are classified to have poor flow properties (also termed as cohesive powders), whilst those with an AoR in the magnitude of 25˚ or less are considered to passss satisfactory flow (sometimes termed as free-flowing powders) (Staniforth, 2002:207).

Table 2.3: *Flow properties and corresponding angle of repose (USP, 2007:644).*

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

2.4.2.3 Percentage compressibility (%C) or Carr's index (CI)

Carr's index comprises of the determination of the bulk and tapped density of a powder. The bulk or poured density of a powder refers to the ratio between the volume of a powder mass to its weight (including both intra- and inter-particle voids), whilst the tapped density refers to

the ratio between the volume occupied by same powder bed after being tapped to a constant volume (thus including intra-particle voids, but excluding most inter-particle voids).

To determine the bulk density of the powders, a volume of powder (100 ml) was gently poured into a graduated cylinder and the weight of the powder was recorded. Then the powder bed was densified by vibrating the cylinder until the powder volume reached a constant volume, and the volume was noted. Vibration was done using a Fritsch analysette (type 30.502) at an amplitude setting 7. The bulk and tapped density of each powder were calculated using equations 2.2 and 2.3, respectively, whilst Carr's index for each powder was calculated using equation 2.4. Each powder was analyzed in triplicate and the average standard deviation and percentage relative standard deviation were calculated.

— [2.2]

Where:

ρ_b is the bulk density (g.cm^{-3}), w is the weight (g) and V_b is the bulk or poured volume (cm^3) of the powder.

— [2.3]

Where:

ρ_t is the tapped density (g.cm^{-3}), w is the weight (g) and V_t is the tapped volume (cm^3) of the powder.

——— [2.4]

Where:

ρ_t is the tapped density (g.cm^{-3}) and ρ_b is the bulk density (g.cm^{-3}).

The index shown in table 2.4 was used to characterize powder flow.

Table 2.4: *Indication of powder flow by means of Carr's index (Wells, 2002:134).*

Flow description	Carr's index (%)
Excellent	5 – 15
Good	12 – 16
Fair to passable	18 – 21
Poor	23 – 35

2.4.2.4 Flow rate (FR)

The flow rate describes the amount of powder that could be discharged through a funnel in a specific time unit (normally per second). The same apparatus was used as for the determination of the COD, except that the powder was discharged into a beaker which was placed on the pan of an analytical balance. The balance was connected to a computer fitted with a chart recorder program which could record the change in the powder mass on the balance as a function of time (seconds). The experiment was repeated in triplicate for each powder at different critical orifice diameters, and the average flow rate (gram.second $^{-1}$) and standard deviation (SD) were calculated. The ranking index used to classify flow according to flow rate is presented in table 2.5.

Table 2.5: *Ranking index used for flow rate (Horn, 2008:60).*

Flow description	Carr's index (%)
Excellent (free flowing)	20
Good	10 – 20
Average	5 – 10
Poor	2 – 5
Very poor (extremely cohesive with little or no natural flow)	<2

2.5 COMPRESSION STUDIES

Compression studies during this project was divided into two sections, namely (A) compression of pure fillers (with the addition only of excipients necessary to produce acceptable compacts regarding ease of compression, mechanical strength and/or disintegration, and (B) compression of mixtures of the filler and a poorly compressible active ingredient (paracetamol).

Although all fillers initially included in this study (pure lactose or lactose- based combination fillers) were subjected to direct compression during stage (A), only those who produced acceptable compacts were used during the second stage (B).

2.5.1 Compression studies on lactose-based fillers (no active ingredient [stage A])

Compacts with a constant weight (400±10 mg) were compressed on an eccentric tablet press (Cadmach®) using flat-faced punches with a diameter of 10 mm (figure 2.3). Due to

differences in the particle size, shape and density of the fillers, the fill volume was adjusted to produced tablets within the desired weight range (390-410 mg). Since the strike depth of the upper (i.e. the depth the upper punch move into the die during compression), the upper punch setting (with a range of 0 to 50) was considered to determine the force exerted on the powder. For each powder the lowest upper punch setting (UPS) was determined which produce a compact of measurable mechanical strength. After setting the lower punch (to produce the desired tablet weight) and upper punch (to produce an acceptable compact) for a specific filler, the press was started and at least fifty compacts were produced (of which the first 20 compacts were discarded). The compacts were transferred to glass containers, sealed with Parafilm®, sealed with a screw cap and stored at room temperature for at least 24 hours before analysis.

Figure 2.3: *The eccentric tablet press.*

2.5.1.1 Experimental variables used in compression studies during stage A

Compression variables

At least three UPS were employed for each filler (ranging from 15 [low], 20-22 [intermediate] to 27 [high]); and the specific settings for each filler were determined (at least 2-3 UPS per filler).

Formulation variables

Since no compacts could be produced with any one of the fillers, a lubricant was added. Two commonly employed tablet lubricants, namely magnesium stearate and Pruv® (sodium stearyl fumurate), were evaluated during a pilot study and a concentration of 0.75% or 1% w/w of either was eventually included in each compact (see table 2.6).

To facilitate disintegration in all the compacts, a disintegrant (0.5% or 2% w/w Ac-Di-Sol®) was included in some compacts (see table 2.6).

2.5.1.2 Mixture composition and preparation

Table 2.6 presents the mixture composition prepared for the production of compacts of each filler.

The required amount of each mixture component (to produce at least 50 tablets) was accurately weighed on an analytical balance (Mettler Toledo, model PB303-S) in 1000 cm^3 glass jars. The jars were covered with Parafilm®, and mixed in a Turbula® mixer (model T2C, W.A. Bachhofen, Basle, Switzerland) at 69 rpm for 10 minutes. The mixtures were stored in the glass jars at room temperature until compression.

Table 2.6: *Mixture composition.*

Component	Function	Percentage w/w
Granulac® 200 **Tablettose® 80** **Flowlac® 100** **Lactopress®** **Cellactose® 80** **Starlac®** **Microcelac® 100**	Fillers	qs to 100%
Magnesium stearate or Pruv®	Lubricant	0.75 or 1%
Ac-Di-Sol®	Disintegrant	0.5 to 2%

2.5.2 Compression studies on lactose-based fillers (active ingredient included [stage B])

During stage B of the compression studies, selected fillers (based on the results from stage A) were combined with a tracer drug, namely paracetamol, a poorly compressible active ingredient. Paracetamol, also known as acetaminophen, is a white crystalline powder with a

monoclinic crystal system, resulting in high elastic deformation during compression (Gonnissen *et al.;* 2007:22). It has anisotropic properties (Lennartz & Mielck; 1998:76) which weakens tablet structure and negatively affect the physical properties of tablets. The poor plastic deformation ability of paracetamol as well as its irregular particle shape, size and structure contribute to its poor powder flow characteristics and compression properties. Paracetamol is also known for its high capping tendency and lamination during direct compression. It is an ideal material to test and compare the compression characteristics of fillers, especially those employed in direct compression. The same flat-faced punches were used as in stage (A) and tablets with a constant mass (400±10 mg) were produced.

The objective of these studies was to determine the percentage of paracetamol that one filler could accommodate in one tablet (generally known as the dilution potential of the filler). Paracetamol has poor flow and compression properties and therefore it is generally granulated before tabletting (Kaerger *et al*., 2004:174). However, to avoid the time-consuming and expensive granulation process, direct compression was employed, combining the drug with the various combination lactose-based fillers.

2.5.2.1 Experimental variables used in compression studies during stage B

Compression variables

At least three upper punch settings (UPS) were employed for each filler (ranging from 15 [low], 20-22 [intermediate] to 27 [high]); and the specific settings for each filler were determined (at least 2-3 UPS per filler).

Formulation variables

The active ingredient (paracetamol) was added to the three selected fillers from stage A. The amount of the paracetamol content was determined through a pilot study until a smooth compaction was obtained. During the pilot study, the difference between Mg-St and Pruv® (sodium stearyl fumurate) was determined, where Mg-St 0.75% was selected as the lubricant. According to the results of stage A, 2% Ac-Di-Sol® was added as disintegrant (see table 2.7).

2.5.2.2 Mixture composition and preparation

Table 2.7 presents the mixture composition prepared for the production of tablets of each filler (containing paracetamol as tracer drug / active ingredient).

The required amount of each mixture component (to produce at least 50 tablets) was accurately weighed on an analytical balance (Mettler Toledo, model PB303-S) in 1000 cm^3 glass jars. The jars were covered with Parafilm®, and mixed in a Turbula mixer (model T2C, W.A. Bachhofen, Basle, Switzerland) at 69 rpm for 10 minutes. The mixtures were stored in glass jars for at least 24 hours at room temperature until compression.

Table 2.7: *Composition of paracetamol mixtures used in tablet formulation during stage B.*

Formula	Ingredients	Function	% w/w	Amount (mg) per 401 mg tablet
1	Paracetamol	Drug	24.4	98
	Microcelac®	Filler	qs to 100	292
	Magnesium stearate	Lubricant	0.75	3
	Ac-Di-Sol®	Disintegrant	2	8
2	Paracetamol	Drug	24.4	98
	Cellactose®	Filler	qs to 100	292
	Magnesium stearate	Lubricant	0.75	3
	Ac-Di-Sol®	Disintegrant	2	8
3	Paracetamol	Drug	19.5	78
	Starlac®	Filler	qs to 100	312
	Magnesium stearate	Lubricant	0.75	3
	Ac-Di-Sol®	Disintegrant	2	8

2.5.3 Analysis of tablets

Each batch of tablets was analyzed for the following physical properties and according to the methods described below: individual tablet; crushing strength; diameter; thickness; friability and tablet disintegration.

2.5.3.1 Weight variation

Twenty tablets from each batch were randomly selected. Each tablet was individually weighed on a Precisa® analytical balance (model 240A, PAG OERLIKON AG, Zurich, Switzerland) and the reading was recorded. The average weight of twenty tablets, the standard deviation and the percentage relative standard deviation were calculated.

2.5.3.2 Crushing strength, diameter and thickness

A PharmaTest® (model PTB-311, Switzerland) tablet test unit was used to determine the crushing strength, diameter and thickness of the tablets. Ten tablets randomly selected from the batch were used. The readings were recorded and the average of ten tablets, the standard deviation, and the percentage relative standard deviation of the parameters were calculated.

2.5.3.3 Friability

Ten tablets from each batch were randomly selected and lightly dusted with a soft brush. The ten tablets were weighed on a Precisa® analytical balance (model 240A, PAG OERLIKON AG, Zurich, Switzerland) and the reading recorded. The ten tablets were placed in a Roche® friabilitor for four minutes at 25 revolutions per minute. After four minutes, the tablets were lightly dusted and only the intact tablets were weighed again and the reading recorded. Equation 2.5 was used to calculate the percentage friability.

[2.5]

Where:

%F is the calculated percentage; W_B and W_A are the total weight of dusted tablets before the onset of rotation and after completion of rotation, respectively.

2.5.3.4 Tablet disintegration

The disintegration times of six tablets were determined using an Erweka® D63150 disintegration machine (model ZT503, GmbH, Heusenstamm, Germany), with distilled water at 37 ± 0.5 ˚C as disintegration medium. The disintegration time was taken as the time needed for a tablet to be completely defragmented and able to pass through the 2 mm sieve openings at the bottom of the tubes.

2.6 DISSOLUTION STUDIES

2.6.1 Apparatus

Dissolution studies were performed in a six-station Erweka® (model DT6R) dissolution apparatus fitted with a thermostat and variable speed synchronous motor (Erweka®, Heusenstamm, Germany).

2.6.2 Settings and conditions for dissolution studies

The dissolution studies were done in 900 cm³ phosphate buffer (pH 5.8) at a temperature of 37 ± 0.5 ˚C (regulated by the thermostat) and at a rotational speed of 50 rpm (kept constant by the synchronous motor).

2.6.3 Method

Prior to each dissolution run, the dissolution medium was pre-heated to 37 ± 0.5 ˚C. The motor was started and as soon as the paddles reached the required speed (50 rpm), the tablet was submerged into the medium. The time was recorded as t = 0 with a stopwatch. At times, t = 1, 2, 4, 8, 16, 32 and 64 minutes, 10 cm³ samples were withdrawn with a pipette through the filter unit containing a Millipore® pre-filter and transferred to 10 cm³ glass poly tops. Immediately after each sampling, the volume lost was replaced with an equal volume of fresh, pre-heated dissolution medium.

2.6.4 Sample analysis

From each sample, 5 cm³ was withdrawn and transferred to a 50 ml volumetric flask and diluted to 50 ml with phosphate buffer (pH 5.8).

The UV-absorbencies (ultra-violet) of the samples were measured in triplicate at 243 nm against phosphate buffer (pH 5.8) as blank, using a UV-1700 (E) PharmaSpec® spectrophotometer fitted with a super sipper and a 1 cm³ flow-through quartz cell. Three dissolution profiles for each tablet were determined to obtain an average dissolution profile.

2.6.5 Standard curve

A standard curve was drawn up prior to dissolution testing of the various tablets. Standard solutions of pure paracetamol (with concentrations ranging from 2.5 to 12.5 µg/ml), were prepared from a stock solution containing 50 mg paracetamol dissolved in 200 cm³ phosphate buffer (pH 5.8). UV-absorbencies of the standard solutions were determined spectrophotometrically at 243 nm against the phosphate buffer as blank. The absorbencies were plotted against concentration and the best straight line through the data points was fitted using linear regression. A standard curve exhibited Beer's law relationship in the concentration range employed, with correlation coefficients (R^2) of ≥ 0.999. The slope (*m*) and *y*-axis intercept were used to calculate the paracetamol concentration of each sample time (section 2.6.7).

2.6.6 Calculations

All the calculations were done using Microsoft ® Office Excel 2007 for Windows Vista.

2.6.7 Dissolution data

The amount of paracetamol dissolved (mg/ml) at each sampling time was calculated using equation 2.6, whereas equation 2.7 was used to correct for the drug lost through sampling.

[2.6]

With:

*y** the corrected absorbency, *x* the drug concentration (mg/ml) and *m* and *c* the slope and y-axis intercept, respectively, obtained from the standard curve.

$$y_n^* = y_n + \frac{v_s}{v_m} \cdot \sum^{n-1} y^* \qquad [2.7]$$

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 is the sum of all the corrected absorbencies prior to the n^{th} sample.

Dissolution profiles in this study are presented as paracetamol (in mg/ml) as function of time (minutes) and are the means of at least three runs of each formulation.

2.7 DISSOLUTION PARAMETERS (AUC AND IDR)

The area under the dissolution profile up to 64 minutes (AUC) is an indication of the extent of drug dissolution, whereas the initial slope of the dissolution curve between t_0 and t_4 is a fair estimate for the initial dissolution rate (IDR) of a drug from a solid dosage form.

The IDR ($mg.ml^{-3}.min^{-1}$) of paracetamol from the various tablet formulations was determined from the slope of the dissolution curve between t = 0 and t = 4; while the AUC ($mg.min.ml^{-3}$) of the drug (between t = 0 and t = 64) was determined and calculated using the trapezoidal rule, which is given by formula 2.8.

[2.8]

Where:

$t_n - t_{n-1}$ is the time difference between two consecutive sampling times and c_n and c_{n-} is the drug concentration (mg/ml) in samples at sampling times corresponding to t_0 and t_{n-1}.

2.7 STATISTICAL ANALYSIS

The data calculations were done using the Microsoft® Office Excel® 2007 for Windows® XP (Microsoft Corporation, Seattle, Washington, USA). Statistical analysis was performed with STATISTICA® 6.1 (Statsoft®, Inc., 2003). A confidence level of 95% ($p<0.05$) was considered satisfactory for determining significant differences between various powders. One-way analysis of variance (ANOVA) was used as single factor to determine the mean values of the various parameters, i.e., angle of repose, percentage compressibility and flow rate.

CHAPTER 3
FLOW PROPERTIES OF VARIOUS LACTOSE-BASED FILLER/BINDERS

3.1 INTRODUCTION

The involvement of powder handling is present in several pharmaceutical processes such as blending, transfer, storage, feeding, compaction and fluidization. The quality of a product, in terms of its content uniformity and weight, is determined by the flow of the powder during manufacturing (Prescott & Barnum, 2000:60). The most common used tablet press during manufacturing is a multi-station tablet press, where the tablet die is filled with powders or granules based on the volume. Thus, the flow properties of the powders used are very important, because the powder needs to flow from the hopper into the die to produce a compact tablet (Shah *et al.,* 2008:258). Knowledge about the flowability of powders and mixtures in early stages of preformulation enables the formulator to determine potential problems which may cause deprived tablets with poor tablet and compression characteristics, variation in tablet weight and hardness, and reduced tablet efficiency due to poor distribution of excipients in the tablet structure.

There are various methods available to measure powder flow. These methods include measurement of (i) angle of repose, (ii) bulk density, tapped density, (iii) Carr's compressibility index, and (iv) Hausner ratio (Shah *et al.,* 2008:258). Other measurements that contribute to powder flow evaluation are critical orifice diameter and flow rate. It is of great importance / significance to have knowledge about the powders' physical properties such as their particle shape, particle size and particle distribution.

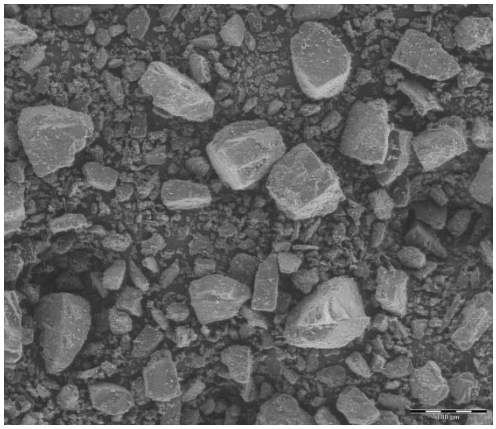
The different methods to determine the flow properties have been discussed in section 2.4. These methods have been applied to a number of pharmaceutical powders used in tablet formulations (direct compressible formulations) as described in section 2.5. All the results of the various physical tests are affected by the particle properties (shape, average size and size distribution).

This chapter presents the results from the various flow tests conducted on the various powders used in this study. Discussions, comparisons and conclusions of the various powders' flow properties were presented, with special attention to presumptions on how these physical properties would affect tabletting.

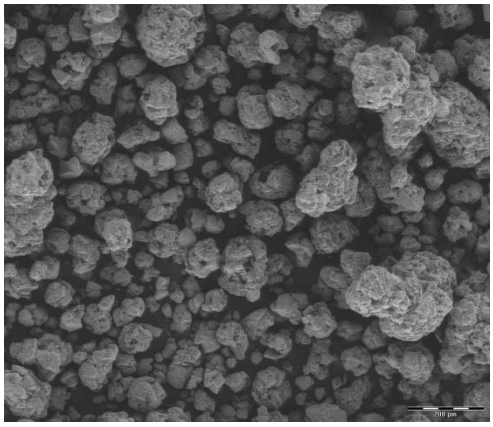
3.2 PARTICLE MORPHOLOGY STUDIES

Scanning electron microscopy (SEM), particle size and distribution analysis were used to determine and study the morphology of the various fillers used during this study. SEM is an excellent method to study the particle shape and structural characteristics. The particle shape can clearly be observed on the micrographs and it is possible to identify prominent differences between the fillers. Particle size and distribution analysis contribute to the differentiating of adhesive and cohesive forces between the particles in the various fillers.

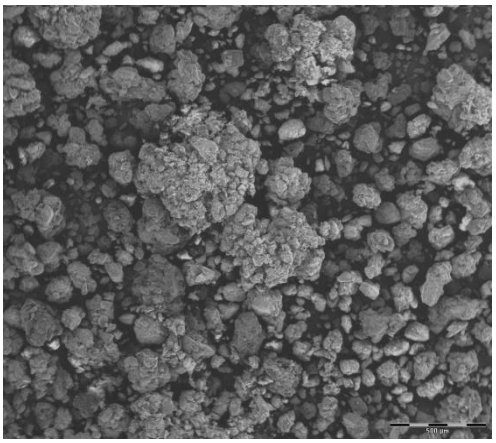
Micrographs were taken of each powder as described in section 2.3, whilst particle size analysis was done employing laser diffraction as described in section 2.4.1.1. The SEM photomicrographs are presented in figure 3.1. (a – g) and the particle size data in table 3.1.



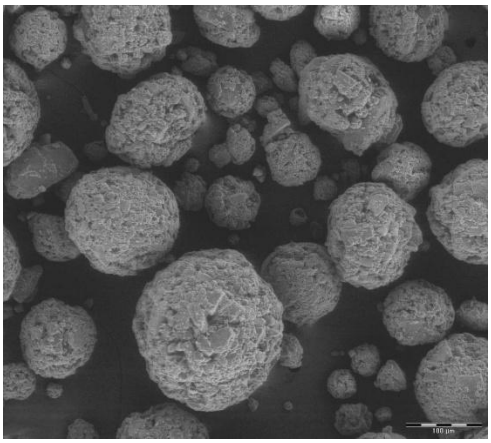
a) Granulac® 200



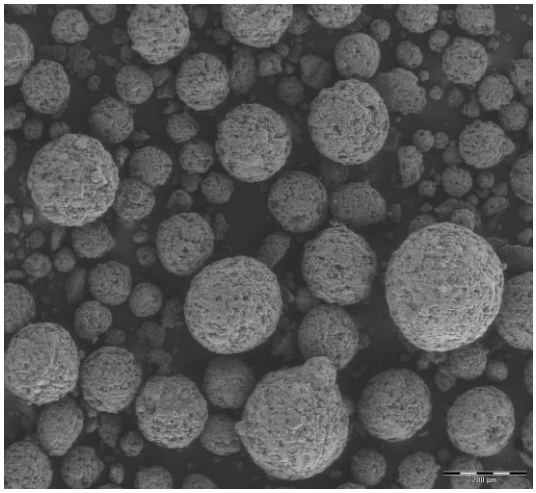
b) Lactopress®



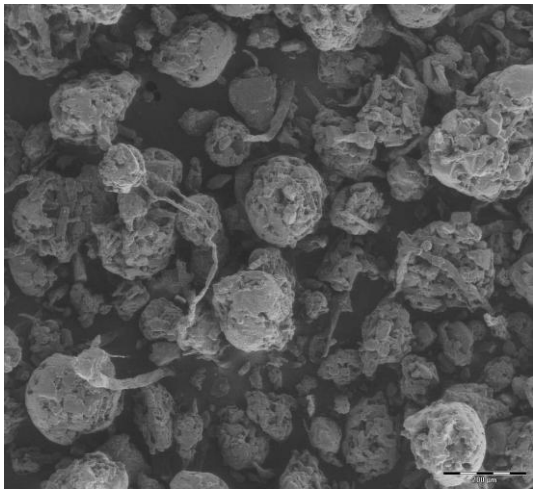
c) Tablettose® 80



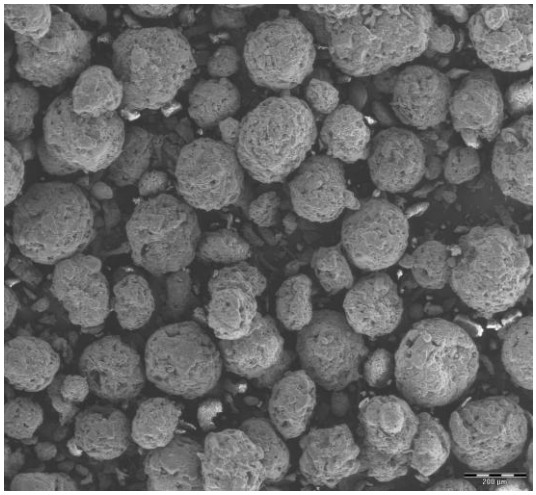
d) Flowlac® 100



e) Starlac®



f) Cellactose® 80



g) Microcelac® 100

Figure 3.1: *Photomicrographs of the various fillers used in this study.*

From the micrographs presented in figure 3.1 and the data in table 3.1 it was clear that there are significant differences between the powders' particle shape, size and distribution. From these results it could be concluded that the various fillers would demonstrate marked / significant differences in their flow properties.

Spherical particles exhibit optimal flow due to their ability to reduce frictional forces through minimizing the contact between particles. Starlac®, Microcelac® 100, Flowlac® 100 and Cellactose® 80 exhibited the most spherical particles compared to the other fillers. The surfaces of these four fillers were smoother than the others, which would suggest increased particle flow.

Table 3.1: *Results of the particle size analysis of powders used in this study.*

Material	10% particles smaller than (µm)	50% particles smaller than (µm)	90% particles smaller than (µm)	Average (volume weighted) particle size (µm)
Granulac® 200	8.57	38.52	99.03	47.22
Lactopress®	49.97	121.52	292.87	150.40
Flowlac® 100	62.70	134.54	246.61	145.86
Tablettose® 80	53.50	193.53	436.48	229.62
Starlac®	52.08	140.44	266.63	151.77
Cellactose® 80	54.52	175.59	347.49	191.29
Microcelac® 100	45.86	152.57	291.75	163.66

It is well documented that powders with different particle sizes show different flow and packing properties, therefore, it is important to define the particle size of a powder before any formulation. Adhesion and cohesion forces between particle surfaces play a crucial role during powder flow. Cohesion is the force that develops between two similar surfaces, such as powder particles, where adhesion can be described as the force between two different surfaces such as the powder and die wall. Fine particles tend to have high surface to mass ratio which make them more cohesive. Coarse particles are more influenced by gravity forces which make it less cohesive (Staniforth, 2000:200).

Particles with a size greater than 250 µm are considered free-flowing, whilst powders with sizes smaller than 10 µm are extremely cohesive and resist any flow under gravity (Staniforth, 2002:200). Therefore, it could be expected that with a decrease in particle size and a deviation from a spherical particle shape, powder flow would be negatively affected.

From the micrographs (figure 3.1) the following rank order could be established for particle shape (in terms of spherical shape): Starlac® ≈ Flowlac® 100 > Microcelac® 100 > Cellactose® 80 > Tablettose® 80≈ Lactopress® >>> Granulac® (irregular, cubical shaped). In terms of surface smoothness both Starlac® and Flowlac® 100 showed exceptional surface smoothness, followed by Microcelac® 100 and Cellactose® 80 exhibiting fair smoothness, but with the presence of some surface roughness. Conversely, both Tablettose® 80 and Lactopress® clearly showed a high extend of uneven surface structure. Although the surface

structure of Granulac® seemed to be quite smooth, its irregular shape could be detrimental to good particle flow.

Since powder flow is dependent on the various physical properties of its particles, it could be expected that Starlac®, Flowlac® 100 and Microcelac® 100 may exhibit better powder flow than the other fillers due to less friction between individual powder particles within the powder bed, which result from their spherical shape, surface smoothness and relative large particle size; whilst Tablettose® 80, Cellactose® 80 and Lactopress® should show poorer flow properties due to unfavorable particle shape and structure, especially surface roughness. Granulac® 200 should present with the poorest flow properties due to its relative small particle size and particle shape (less spherical). These assumptions will, however, be verified from the flow results presented in the following section.

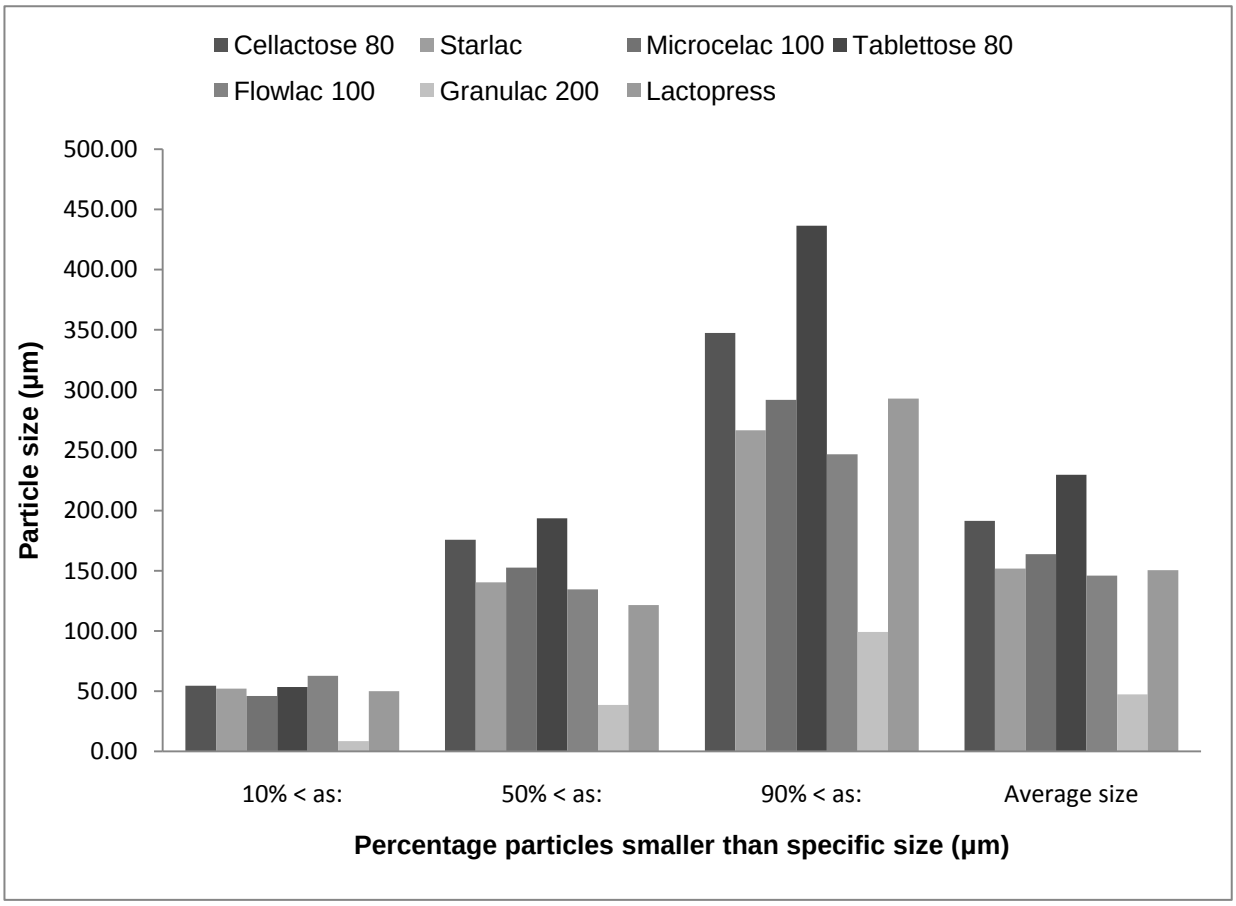


Figure 3.2: *The particle size and distribution of the different powders.*

3.3 FLOW TEST RESULTS

In the following section the results obtained for the various flow tests done are represented and discussed. The results were obtained employing the methods described in section 2.4.2 and are presented in table 3.2; with the raw data presented in annexures B – E.

Table 3.2: *Summary of the flow parameters for the fillers used in this study.*

Material	CI (%)	AoR (°)	COD (mm)	FR ($g.sec^{-1}$)	Density ($g.sec^{-1}$)	
					Bulk	Tapped
Granulac® 200	37.01 ±1.25	47.57 ±	24	0.00 ±0.00	0.531 ±0.012	0.843 ±0.015
Flowlac® 100	15.67 ±1.22	25.40 ±0.38	3	15.67 ±1.23	0.636 ±0.007	0.754 ±0.008
Lactopress®	19.69 ±0.81	29.91 ±1.08	7	9.64 ±	0.626 ±0.006	0.779 ±0.005
Tablettose® 80	21.19 ±0.77	25.40 ±0.38	3	17.20 ±	0.607 ±0.007	0.770 ±0.013
Starlac®	15.25 ±0.74	26.22 ±0.90	2	18.27 ±	0.583 ±0.008	0.688 ±0.012
Cellactose® 80	20.30 ±1.23	30.30 ±0.86	2	17.42 ±0.04	0.405 ±0.004	0.509 ±0.009
Microcelac® 100	19.27 ±1.06	32.65 ±0.91	1.5	20.27 ±1.06	0.496 ±0.004	0.614 ±0.010

CI* = Carr's Index, AoR* = angle of repose, COD = critical orifice diameter

3.3.1 Critical orifice diameter

The critical orifice diameter is defined as the smallest opening through which a powder can flow under the influence of gravity (without any external intervention). This flow parameter is, to a large extent (primarily), dependent on particle properties like shape, size, density and packing geometry within a powder bed. All these factors can be related to internal forces within the powder bed which affect the adhesive / cohesive nature of the powder. It is generally accepted that free flowing powders will flow through the smallest critical orifice diameter, wheras more cohesive powders will flow through larger critical orifice diameters.

Critical orifice diameter is used regularly because of its relative ease of determination and its efficiency and accuracy of measuring powder flow.

Figure 3.3 shows a graphical presentation of the COD data according to the flow description used by Horn (2008:42), indicating the following rank order between the various powders (best to worst): Microcelac® ≈ Cellactose® 80 ≈ Starlac® ≈ Flowlac® 100 ≈ Tablettose® 80>> Lactopress® >>> Granulac® 200.

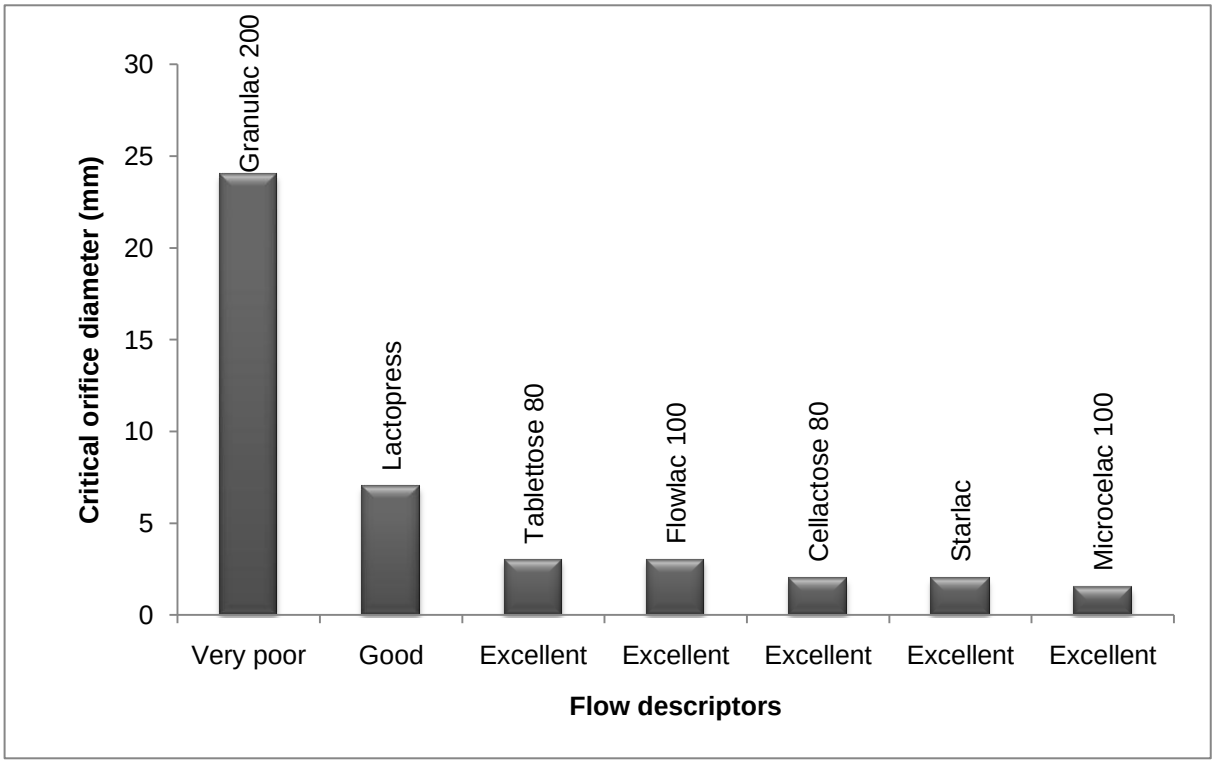


Figure 3.3: *Critical orifice diameter of the various lactose-based filler/binders.*

The extremely poor flow of Granulac® (significantly worse than all the other fillers; $p<0.05$) could be attributed to its irregular shape (figure 3.1a) and relative small particle size (47 µm); both factors which induce attractive forces between particles in a powder bed and inhibit powder flow. The poor performance of Lactopress® (COD = 7 mm) compared to the other fillers (COD ranging between 1.5 and 3 mm) could be attributed to its irregular/rough surface structure (figure 3.1b). Tablettose® 80 (COD = 3 mm) showed unexpected good results despite the fact that its physical appearance, i.e. shape and surface structure (figure 3.1c), is quite similar to that of Lactopress®. The main reason for its increased flow could, however, could be the result of its large average particle size of ±230 µm (table 3.1).

The excellent flow results of all the spray-dried fillers (i.e. Lactopress®, Flowlac® 100, Starlac®, Cellactose® 80 and Microcelac® 100) confirmed the fact that this method of particle manipulation produced free-flowing particles due to its smooth surface structure and spherical shape (Podczeck & Sharma, 1996:194).

3.3.2 Angle of repose

The angle of repose is an indirect method used to measure the flow of powders, utilizing the height and diameter of a cone formed when the powder is released through a funnel from a specific height and determining the angle formed between the side and base of the cone.

This method has been labeled as rather indiscriminative in identifying differences between the flowability of materials with significant different physical properties, and it was observed that different angles of repose could be obtained for the same powder, depending on (i) the experimental setup, (ii) type of material construction of the funnel used in the experiment and (iii) the way the samples were handled prior to measurement (Horn, 2008: 53). Its acceptance as approved method for determining powder flow, however, has been substantiated by its inclusion in official pharmacopoeia, for example the USP (USP, 2007:644). As a general guide, powders with angles of repose greater than 50˚ have unsatisfactory flow, whereas minimum angles close to 25˚ predict good powder flow (Staniforth, 2002:207).

Figure 3.4 presents the data graphically, whilst statistical comparisons are tabulated in table 3.3 Starlac® and Flowlac® 100 presented with significantly better flow than Tablettose® 80, Lactopress® and Cellactose® 80 ($p<0.05$). Whilst the latter three exhibited significantly better flow than Microcelac® 100, with Granulac® markedly worse than all the fillers.

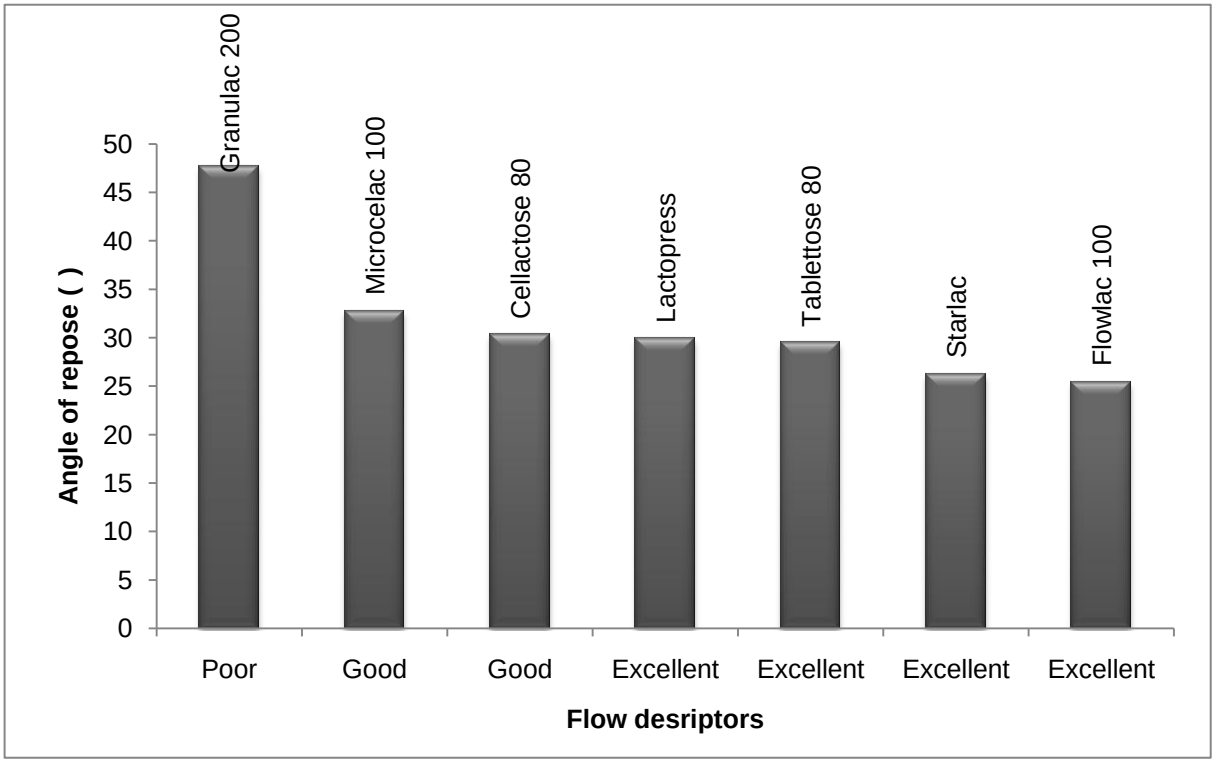


Figure 3.4: *Angle of repose of various lactose-based filler/binders.*

The only powder with exceptionally poor flow properties and with significant difference to the other powders was Granulac® 200. It could be attributed to its rough particle surface (figure 3.1a) and relative small particle size (47 µm). Both these factors add to the forming of small distances between particles, where the interparticle forces increase between particles, resulting in poor flow. Small particles are more cohesive and allow contact between particles, developing high friction between particles forming a high cone beneath the funnel. Microcelac® 100 exhibited significant poor flow in comparison with the other fillers. This unexpected occurrence justified the fact that angle of repose is an indiscriminative way to characterize the differences between the flow properties of materials because Microcelac® 100 are expected to exhibit with very good flowability according to its spherical particles (figure 1.3g) and relative small particle size (163 µm).

Flowlac® 100 and Starlac® presented with extremely good flow and showed a significant difference in comparison with Tablettose® 80 and Cellactose® 80; probably due to their very smooth particle surface and spherical form (figure 3.1 d,e). Although Lactopress® has a rougher particle surface; it still exhibited good flow according to the angle of repose data which could be explained by its very large particle size (229 µm).

It can be assumed that angle of repose are mainly affected by the distances between particles, friction forces and the particle shape and size. Large, smooth, spherical particles flow better than irregular shaped, small particles, due to the large interparticle spaces which decrease the interparticle friction and attractive forces, resulting in good flowability. Table 3.3 indicates the significant differences between the powders' angle of repose results.

Table 3.3: *Turkey's statistical test results for the indication of significant differences (indicated by √) in the angle of repose between the various materials (p<0.05).*

	Granulac® 200	Lactopress®	Tablettose® 80	Flowlac® 100	Starlac®	Cellactose® 80	Microcelac® 100
Granulac®		√	√	√	√	√	√
Lactopress®	√		NSD	√	NSD	NSD	NSD
Tablettose®80	√	NSD		√	√	NSD	√
Flowlac®100	√	√	√		NSD	√	√
Starlac®	√	NSD	√	NSD		√	√
Cellactose®80	√	NSD	NSD	√	√		NSD
Microcelac®100	√	NSD	√	√	√	NSD	

NSD: No significant difference

√: Significant difference

3.3.3 Percentage compressibility (%C)

The percentage compressibility, also known as Carr's index, is an indirect method for determining powder flow and are calculated from the bulk and tapped densities of a powder. It measures the potential powder bridges between the particles and the powders' stability during packing, transport and handling (tapping). This parameter is mainly dependent on the volume reduction during handling and transport, simulated by tapping, and gives an indication of the cohesiveness of powders and the strength of frictional forces between individual particles in the powder bed. Harnby *et al*. (1987:881) explained that powders with a strong structural strength, thus spherical, smooth surfaced particles, will resist collapse when dispersed in a container resulting in a low bulk density (i.e. low mass to volume ratio), whilst a weak powder (irregular, uneven, rough surfaced particles) will collapse easily exhibiting a high bulk density.

Figure 3.5 shows a graphical presentation of the %C data according to the flow description presented in table 2.4, indicating the following rank order between different materials (best to worst): Flowlac® 100 ≈ Starlac® >> Cellactose® 80 ≈ Lactopress® ≈ Microcelac® ≈ Tablettose® >>> Granulac® 200. This data was determined by statistical comparisons between the various powders at a 95% confidence level ($p<0.05$) and tabulated in table 3.4.

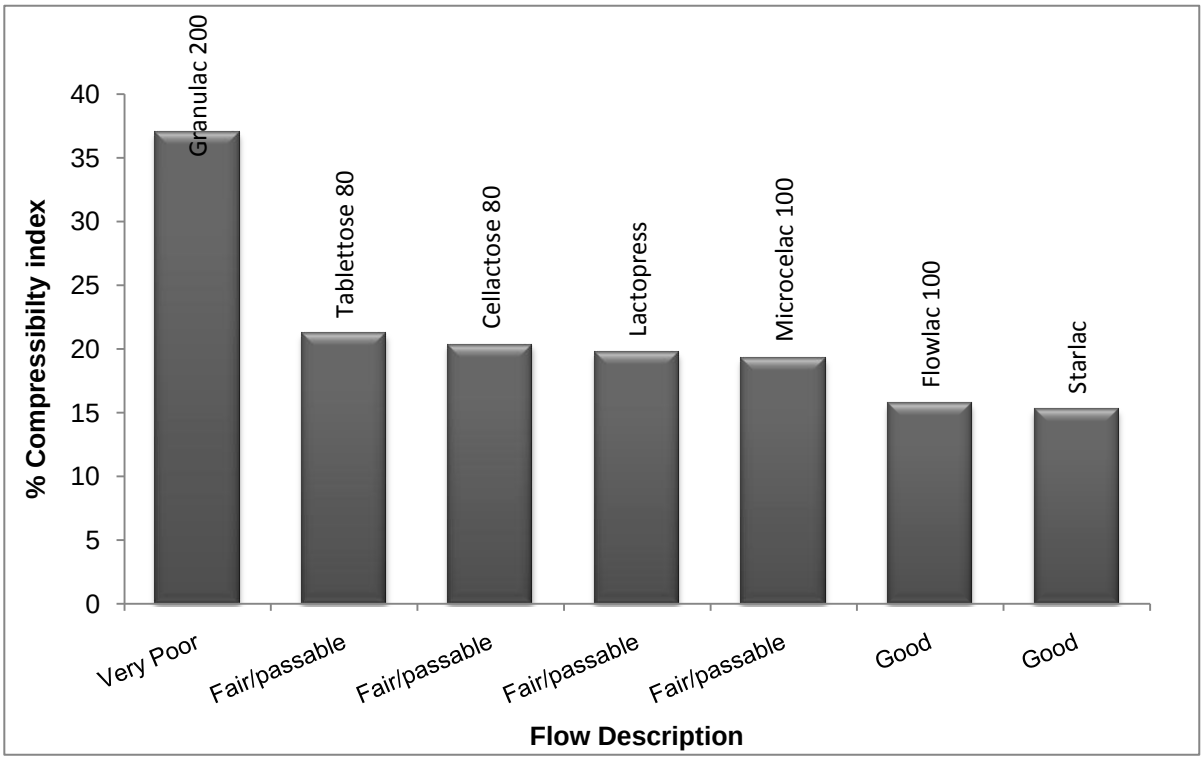


Figure 3.5: *Percentage compressibility of various fillers/binders*

The good flow of Starlac® and Flowlac® 100 is due to their spherical particle shape (figure 3.1d,e) thus a reduction in friction occured, allowing particles to move independently from one another, resulting in good flow. Most of the powders exhibited fair to passable flowability with a %C ranging from 19 – 20%. Cellactose® 80 and Microcelac® 100 were expected to present with good acceptable flow properties due to their spherical, smooth surfaced particles (figure 3.1f,g) and large mean particle sizes (191 µm an 163 µm, respectively). Both Tablettose® 80 and Lactopress® have uneven, rougher particle surfaces but still presented fair to passable flowability. This can be explained by their large mean particle size which probably counteracted the particle shape and resulted into fairly good flow properties. Granulac® 200 exhibited very poor flow which could be attributed to its irregular, uneven particle shape (figure 3.1a) and small average particle size (47 µm). This weak structure enhanced frictional forces between particles, preventing particles to move individually and therefore interfered with the natural flow of powders, presenting with very poor flow.

Table 3.4: *Turkey's statistical test results for the indication of significant differences (indicated by √) in the percentage compressibility (%C) between the various materials (p<0.05).*

	Granulac® 200	Lactopress®	Tablettose® 80	Flowlac® 100	Starlac®	Cellactose® 80	Microcelac® 100
Granulac®		√	√	√	√	√	√
Lactopress®	√		√	√	√	NSD	NSD
Tablettose®80	√	√		√	√	NSD	√
Flowlac®100	√	√	√		NSD	√	√
Starlac®	√	√	√	NSD		√	√
Cellactose®80	√	NSD	NSD	√	√		NSD
Microcelac®100	√	NSD	√	√	√	NSD	

NSD: No significant difference

√**:** Significant difference

By monitoring the change in volume (bulk density) during tapping there may be a relation between the cohesion and frictional forces of a powder, indicating the flowability of a powder. A linear graph (figure 3.6) of percentage compressibility and the percentage bulk volume reduction is a confirmation of the importance of volume changes during handling and transporting of powders. This could be used as a method to predict the percentage compressibility and determining flow properties of various powders. Frictional forces are

famous for their prevention of particles moving individually, causing significant reduction in the volume of powders, exceeding 55%, which is typical of cohesive powders.

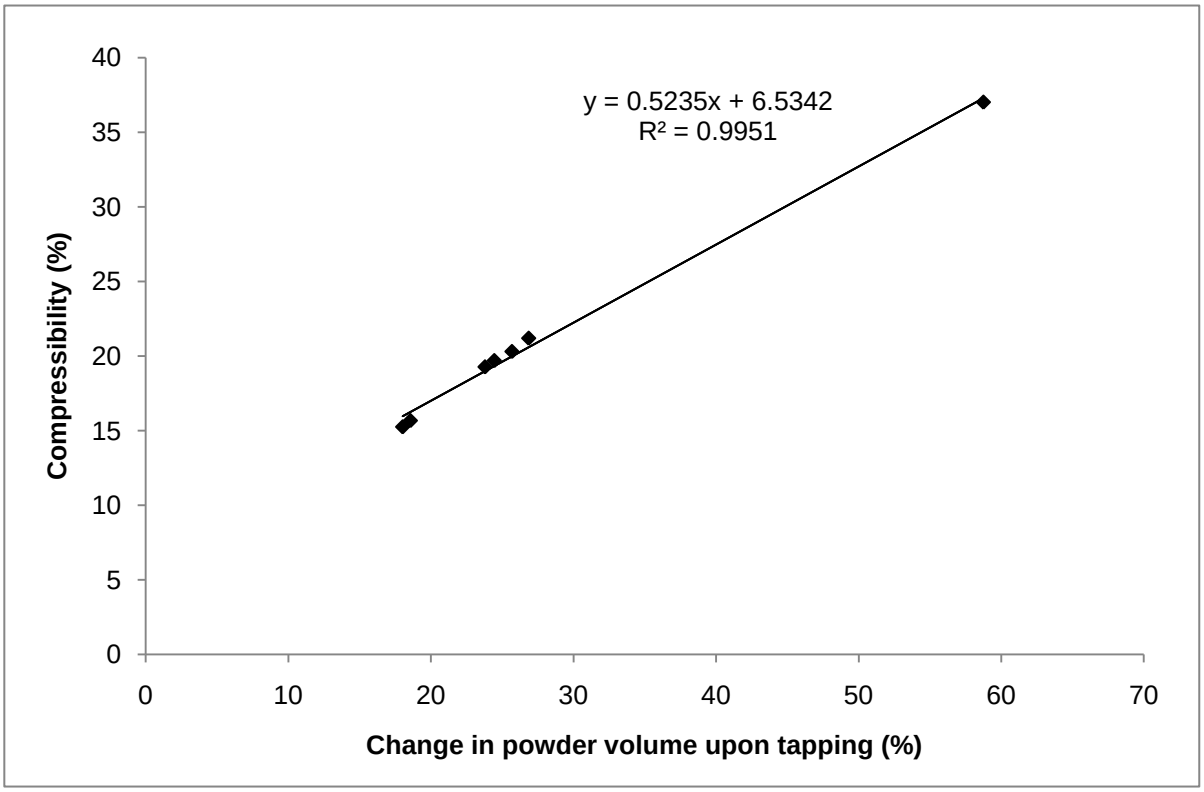


Figure 3.6: *Relationship between %C and percentage change in bulk volume upon tapping for various pharmaceutical materials.*

3.3.4 Flow rate (FR)

Flow rate is one of the simplest methods to determine powder flow and is affected by particle and process related effects as described by Staniforth (2000:204). Particle effects include particle shape, size and density, whereas process effects consist out of orifice diameter, hopper width, height of powder bed and hopper wall angle. The process effect were kept as far as possible identical during determination of powder flow of various materials with different physical properties. It is difficult to choose an orifice diameter which is suitable for all the powders, because an inappropriate orifice diameter may result in false measurements and data. Different orifice diameters were used because of the different physical properties of the powders tested. Flow rate can be defined as the amount (gram) of powder that could be discharged through a funnel in a specific time unit, normally seconds. The flowability of powders according to flow rate is usually dependent on the particle shape, size and the density of the powder. Flow rate is important during direct compression, especially if using the multiple tablet press.

The results of flow rate for the various materials are indicated, graphically, in figure 3.7 and the statistical calculated significant differences between the powders are presented in table 3.5. The rank order for the powders tested was as follow (best to worst): Microcelac® 100 > Starlac® > Cellactose® 80 > Tablettose® 80 > Flowlac® 100 > Lactopress® > Granulac® 200.

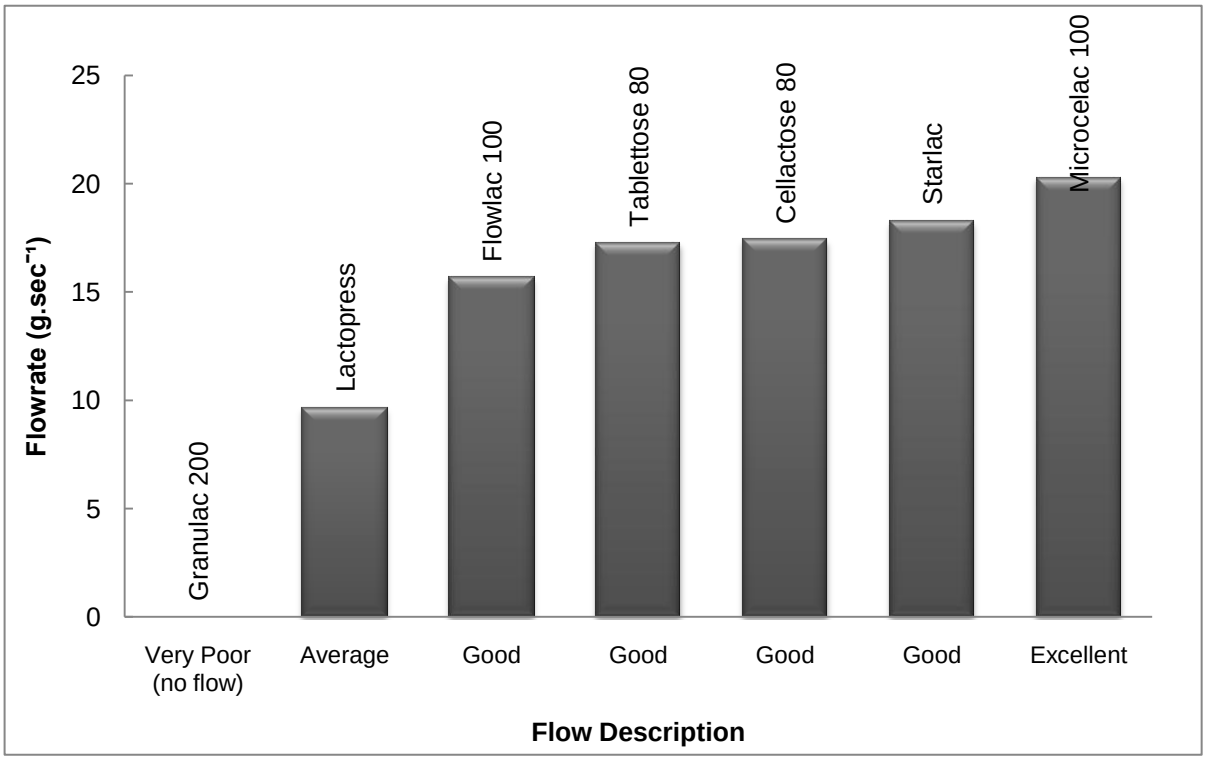


Figure 3.7: *Flow rate of various filler/binders.*

According to table 3.5 there were significant differences between these powders. There was no relationship between powder densities and flow rate, but the particle shape and size definitely played an enormous role. No flow was recorded for Granulac® 200 because of its large COD in comparison to the other powders. Lactopress® exhibited the worst recorded flow rate and this could be explained by its irregular, rough, uneven particles which caused interparticle friction and resulted in poor flow. All the other powders presented with good flow according to their recorded flow rate. The spherical particles and large mean particle size of the various powders were the main reason for their good flow properties. Microcelac® 100 exhibited the best flow and this could be explained by its high percentage spherical particles and large mean particle size.

It was illustrated by figure 3.7, that powders with small particles have poorer flow in comparison to powders with large particles. Flow rate is generally a good parameter to determine flowability. One problem with this method is that powders must have the ability to flow like adhesive powders. This method is not suitable for cohesive powders with no flow, such as Granulac® 200.

Table 3.5: *Tuckey's statistical test results for the indication of significant differences (indicated by √) in the flow rate (FR) between the various materials (p<0.05).*

	Granulac® 200	Lactopress®	Tablettose® 80	Flowlac® 100	Starlac®	Cellactose® 80	Microcelac® 100
Granulac®		√	√	√	√	√	√
Lactopress®	√		√	√	√	√	√
Tablettose®80	√	√		√	√	√	√
Flowlac®100	√	√	√		√	√	√
Starlac®	√	√	√	√		√	√
Cellactose®80	√	√	√	√	√		√
Microcelac®100	√	√	√	√	√	√	

NSD: No significant difference

√**:** Significant difference

3.4 CONCLUSION

Before any compression or tabletting could be done, one has to be familiar with all the powder flow properties of the excipients used in the study. The powder performance has an enormous impact on the development and production of tablets and related products. Powder characteristics are critical to the efficacy of a drug, the efficiency of the manufacturing process and the quality of the finished product (Freeman, 2000:143). From the results given in section 3.3 it is clear that particle size and shape are one of the main factors contributing to the flow properties of powders. Powders with small particle sizes are more cohesive and exhibit marginal to weak flow due to the frictional forces between particles, whereas powders with average sizes exhibit adequate to good flow. Spherical particles are able to move individually, preventing friction between particles and interparticle friction.

Both angle of repose and percentage compressibility are indirect methods for the determination of powder flow. It was clear from the results that the flow classification of powders depend on the method used to determine flowability. The results obtained from the tests done on the various powders, proved that not one of the powders achieved the best flow data from the four tests done (as seen in table 3.6). However, Granulac® 200 definitely exhibited the poorest flow in comparison to the other tested powders. This could be ascribed to its irregular, uneven, small particles and the fact that it is mainly manufactured for

granulation. The relative good flow of the other powders was either because of their large mean particle size (Lactopress®), or their smooth, even, spherical particles.

Table 3.6: *Rank order of the various fillers used in this study*

Material	CI*	AoR*	COD*	FR*	Average Position
Granulac® 200	7	7	7	7	7.00 (7)
Flowlac® 100	2	1	3	5	2.75 (2)
Lactopress®	4	4	6	6	5.00 (6)
Tablettose® 80	6	3	3	4	4.00 (5)
Starlac®	1	2	2	2	1.75 (1)
Cellactose® 80	5	5	2	3	3.75 (4)
Microcelac® 100	3	6	1	1	2.75 (2)

CI* = Carr's Index, **AoR*** = angle of repose, **COD*** = critical orifice diameter, **FR*** = Flow rate

In this study Granulac® 200 and Lactopress® exhibited the poorest flow properties in comparison to the other materials tested. The lactose-combined fillers such as Microcelac® 100, Starlac® and Cellactose® 80 exhibited very good powder flow properties. Flowlac® 100 and Tablettose® 80, which are modified lactose fillers presented with fairly good powder flow properties.

Tablets contain a large percentage of fillers, and that is the reason why the flow properties of these fillers play such an important role during tabletting and manufacturing. From the results obtained it could be predicted that Granulac® 200 would not be suitable for direct compression due to its poor flowability. All the other powders presented with acceptable powder flow properties, which could be suitable for manufacturing tablets using direct compression; especially Starlac®, Cellactose® 80 and Microcelac® 100.

CHAPTER 4
COMPRESSION AND TABLETING CHARACTERISTICS OF CO-PROCESSED FILLER/BINDERS

4.1. INTRODUCTION

Successful compaction and tabletting, using direct compression, require the knowledge and understanding of the fundamental characteristics of powders, in this case especially the properties of fillers. Fillers comprise more than 80% of the tablet composition and therefore play a significant role during compaction and tabletting. One must keep in mind, that the ingredients in a tablet formula play an important part in the release (disintegration) and dissolution of the active ingredient, especially in tablet formulations with a low drug dose and high percentage of fillers. It is of great importance to be familiar with the friction that can develop between the powder or tablet and the die wall of the tablet press. Due to this problem, most formulas require the addition of a lubricant (Kása *et al.,* 2008:859).

The compression behavior of the different lactose and lactose-based fillers was tested in this chapter. This chapter revealed the compression properties of the fillers in combination with a lubricant.

4.2. PILOT STUDIES

An initial pilot study was conducted to determine the suitable punch and die set for evaluation of the compression and tabletting characteristics of the various fillers studied. The aim was to find a punch and die set that would accommodate the same weight for all the fillers and which would provide for a range of compression forces (through changing the upper punch setting on the tablet press). From the results obtained, a set of 10 mm flat-faced punches and corresponding die was chosen which allowed for a powder mass of 400 ± 10 mg to be compacted.

Compacts of pure filler (at an approximate weight of 400 mg) were compacted at different upper punch settings (according to the method described in section 2.5.1) in order to determine:

- compression range (as determined by the upper punch setting on the eccentric tablet press) that was available for each filler to produce acceptable compacts; and
- additional excipients (and their levels) required to produce tablets with acceptable mechanical strength, no capping and/or lamination, low weight variation and disintegration properties.

The results of these initial compression studies showed that none of the fillers could be suitably compacted without the addition of additional excipients. In order to alleviate the physical appearance and properties of the pure filler compacts, the following additions to the pure fillers were tested:

- increasing the UPS, i.e. increasing the compaction pressure;
- addition of a lubricant, namely magnesium stearate or Pruv® (0.75 or 1% m/m) to reduce friction between the compact and the die wall during the ejection phase after compaction or
- addition of a dry binder (Kollidon® 30) to increase particle binding.

Table 4.1 shows a summary of the results of the preliminary compaction studies on the various fillers. The results clearly indicated that none of these changes resulted in the improvement of the physical properties of compacts containing Granulac®, Tablettose®, Flowlac® or Lactopress®. Many authors and researchers believe that capping occurs when air is trapped in the tablet under pressure; and as soon as the upper punch retreat, the air tries to escape causing rupture of the tablet (Kuppuswamy *et al.,* 2001:1). Capping and lamination of tablets are thoroughly described in chapter 1. Since all the tablets were pressed at different upper punch settings, from very soft to very hard, the compression pressure was eliminated as one of the causes. Acceptable compacts were obtained for Cellactose®, Starlac® and Microcelac® when a lubricant was added. Both magnesium-stearate and Pruv® were tested separately in each formula to observe whether there would be any change in the capping problem. Unfortunately there was no improvement regarding these three fillers in tablet form. A dry binder (Kollidon®30) was added to the Lactopress®, Flowlac®100 and Tablettose®100 formulas to see if it would prevent capping due to its ability to increase the mechanical strength between particles in a tablet, but no success was gained by this procedure.

Table 4.1: *Preliminary compaction results of lactose-based filler/binders*

	Granulac® 200	**Lactopress®**	**Flowlac® 100**	**Tablettose® 80**	**Cellactose® 80**	**Starlac®**	**Microcelac® 100**
Pure filler at various UPS* (15 to 27)	No compacts	No compacts	No compacts	No compacts	Lamination	Lamination	Lamination
Addition of glidant (MgSt* or Pruv®	No compacts	Capping	Capping	Capping	Acceptable compacts, No disintegration	Acceptable compacts	Acceptable compacts, No disintegration
Addition of dry binder (Kollidon®30)	No compacts	Capping	Capping	Capping	NA*	NA*	NA*
Addition of disintegrant (Ac-Di-Sol®)	NA*	NA*	NA*	NA*	Acceptable compacts	Acceptable compacts	Acceptable compacts

*UPS = Upper punch setting, *MgSt = Magnesium stearate, NA* = Not applicable

The inability of Granulac® 200 to produce compacts during direct compression could be explained by the fact that it is mainly manufactured for wet granulation. Its' extremely small mean particles could affect the flow of the powder into the die of the tablet press, producing no tablets. There was no meaningful explanation for the poor compaction of Tablettose® 80, Lactopress® and Flowlac® 100 since all three of them are manufactured for direct compression and exhibited acceptable flow properties. Both manufactures, Meggle and Signet, specify these three fillers for oral dispersed tablets and capsule/sachet filling. The large tablet (400 mg) produced in this study could have attributed to the capping of compacts during compression.

Testing the "acceptable" compacts in terms of the various tests described in section 2.5.4 indicated poor disintegration (in excess of 15 minutes) of the compacts at all upper punch settings employed. This necessitated the inclusion of a disintegrant (0.5%, 1% and 2% w/w Ac-Di-Sol®) which produced disintegration of some compacts at different UPS (see following section for results and discussion). The poor disintegration could be due to too high or too low pressures used during tabletting, but this was excluded due to the different punch settings used during compression. As described by Mutasem *et al.* (2006:E6), an increase in crushing force results in increased particle contact, which contributes to reduced tablet porosity. Tablet porosity is when pores forming capillary pathways which allow rapid water penetration through the tablet. A decrease in tablet porosity leads to a decrease in capillary pathways resulting in low water uptake and longer disintegration times (Mutasem *et al.,* 2006:E6).

Due to the poor overall performance of Granulac®, Tablettose®, Flowlac® and Lactopress® in terms of their compaction properties, further compression studies were only focused on the three remaining lactose-based fillers, namely Cellactose®, Starlac® and Microcelac®, which were all combination fillers exclusively designed for direct compression.

4.3 COMPRESSION PROPERTIES OF CO-PROCESSED FILLERS

Mixtures of Cellactose®, Microcelac® and Starlac®, and 0.75% Mg-St or Pruv® (as lubricant) were prepared as described in section 2.5.1, and compressed at at least 3 upper punch settings, which produced acceptable compacts. The lower and higher limits of the UPS for the different fillers were the minimum and maximum settings at which compacts with sufficient mechanical strength could be produced. The compacts were evaluated in terms of target weight (app. 400 mg), weight variation, mechanical strength (hardness), thickness,

Table 4.2: *Summary of the tablet analysis results of the different formulas*

Filler	Glidant	Physical property	UPPER PUNCH SETTING (SIMULATING COMPRESSION FORCE)						
			15	17	20	22	23	25	27
Cellactose® 80	Mg-stearate (0.75% w/w)	Weight (mg)	ND	ND	ND	ND	409.08 (7.69)	415.44 (6.65)	434.09 (16.92)
		FR (%)	ND	ND	ND	ND	0.724	0.060	0.042
		Hardness (N)	ND	ND	ND	ND	71.07 (7.45)	257.13 (15.96)	305.83 (5.85)
		Disintegration (min.)	ND	ND	ND	ND	0.42 (0.05)	15.00	15.00
	Pruv (0.75% w/w)	Weight (mg)	ND	ND	ND	ND	444.48 (5.82)	436.70 (4.44)	423.53 (8.55)
		FR (%)	ND	ND	ND	ND	2.880	0.833	0.163
		Hardness (N)	ND	ND	ND	ND	38.73 (3.01)	104.81 (11.45)	204.06 (23.43)
		Disintegration (min.)	ND	ND	ND	ND	0.27 (0.05)	0.47 (0.40)	15.00 (0.00)
Microcelac® 100	Mg-stearate (0.75% w/w)	Weight (mg)	ND	406.49 (5.07)	402.35 (6.09)	ND	403.57 (2.42)	ND	ND
		FR (%)	ND	0.434	0.097	ND	0.111	ND	ND
		Hardness (N)	ND	87.31 (8.89)	304.81 (2.48)	ND	317.35 (4.61)	ND	ND
		Disintegration (min.)	ND	0.91 (0.29)	15.00 (0.00)	ND	15.00 (0.00)	ND	ND
	Pruv (0.75% w/w)	Weight (mg)	ND	393.01 (2.92)	391.26 (2.18)	ND	391.27 (4.57)	ND	ND
		FR (%)	ND	0.489	0.089	ND	0.084	ND	ND
		Hardness (N)	ND	80.57 (5.47)	312.54 (3.47)	ND	330.89 (5.25)	ND	ND
		Disintegration (min.)	ND	2.46 (0.63)	15.00 (0.00)	ND	15.00 (0.00)	ND	ND
Starlac®	Mg-stearate (0.75% w/w)	Weight (mg)	396.51 (5.77)	ND	400.37 (4.17)	401.22 (2.63)	ND	ND	ND
		FR (%)	1.075	ND	0.232	0.196	ND	ND	ND
		Hardness (N)	66.07 (5.19)	ND	202.85 (13.90)	209.85 (9.26)	ND	ND	ND
		Disintegration (min.)	0.89 (0.08)	ND	1.76 (0.09)	1.95 (0.07)	ND	ND	ND
	Pruv (0.75% w/w)	Weight (mg)	415.92 (1.36)	ND	420.49 (2.67)	428.23 (1.27)	ND	ND	ND
		FR (%)	4.932	ND	0.441	0.416	ND	ND	ND
		Hardness (N)	24.35 (1.21)	ND	199.69 (16.68)	225.98 (15.84)	ND	ND	ND
		Disintegration (min.)	1.26 (0.13)	ND	3.23 (0.16)	3.00 (0.08)	ND	ND	ND

diameter, friability and disintegration according to the methods described in section 2.5.3. The results are presented in table 4.2, with the raw data tabulated in annexure F.

The variation in the compression force range required by the different fillers to produce acceptable compacts, and the effect of compression force on compact hardness are shown in figure 4.1.

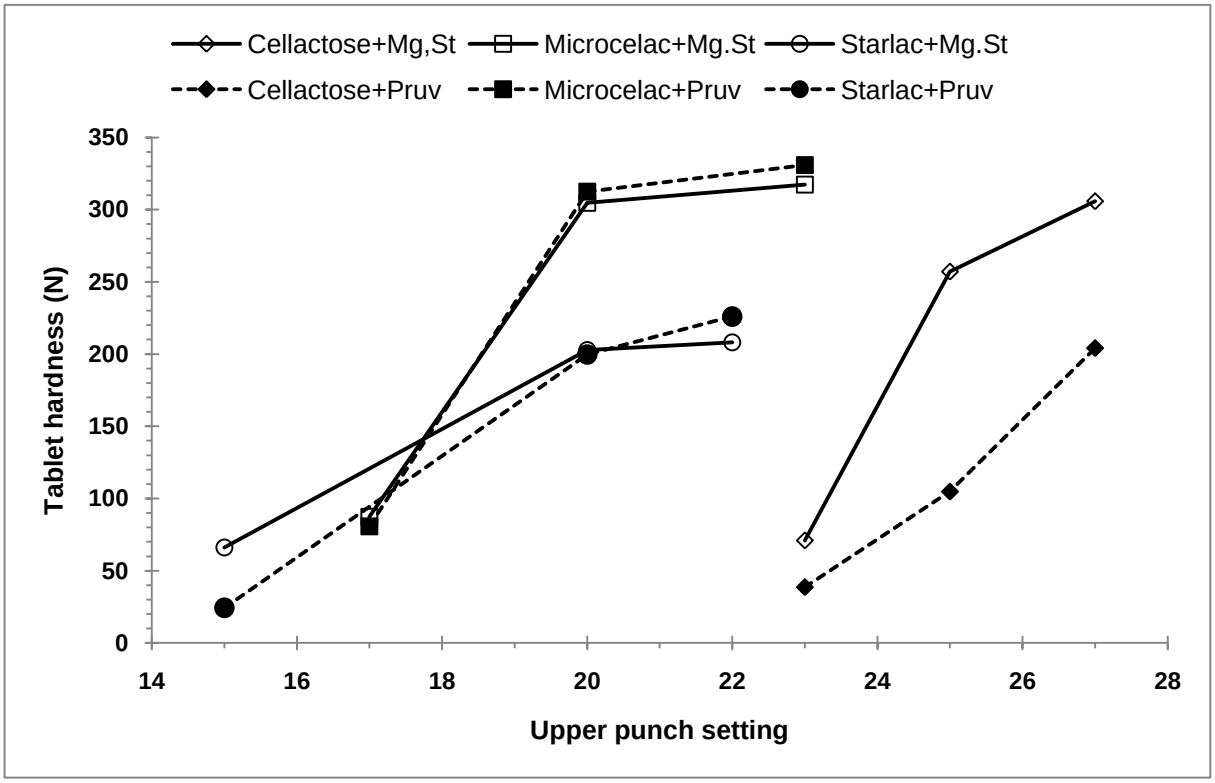


Figure 4.1: *Hardness-compression force profiles of the various co-processed filler/binders. Mixtures contained 0.75% w/w magnesium stearate (solid lines)* ***or*** *0.75% w/w Pruv® (dashed lines).*

The upper punch setting of a tablet press plays a definite role during the determination of tablet hardness, as seen in figure 4.1. A drastic increase in tablet hardness was observed for all the tablets between the first and second upper punch setting, which can be explained by the increase of binding forces between particles during compression. Starlac® presented with significantly lower tablet hardness than the other two fillers and it can be assumed that the tablets were much softer. Cellactose®80 formed compacts at much higher upper punch settings and can be explained by its composition. It contains powdered cellulose which are not a very good directly compressible powder, whereas Microcelac®100 contains microcrystalline cellulose which are formulated for direct compression. There were no meaningful differences between formulas containing Mg-St or Pruv® except for Cellactose®80, where the formula containing

Pruv® presented with significantly lower hardness profile as with Mg-St. Since there are no meaningful explanations for this tendency, further investigation should be done on this topic. Change in tablet hardness at different upper punch settings can be explained by the amount of energy transmitted to the powder bed during compression. The weak van der Waals forces translate the energy into adhesion energy resulting in a cohesive compact. Van der Waals forces are distance related, meaning if the particles are close to each other with minimum air spaces between them, much stronger forces will form between particles, resulting in harder compacts (Vachon & Chulia, 1998:184).

Figure 4.2 indicates the weight variation of the compacted fillers as a function of compression force. Compacts of all the fillers showed a lower weight variation for formulas containing Pruv® compared to magnesium stearate. These results suggested a mechanical interference of magnesium stearate in powder flow, which negatively affected uniform die filling during tabletting.

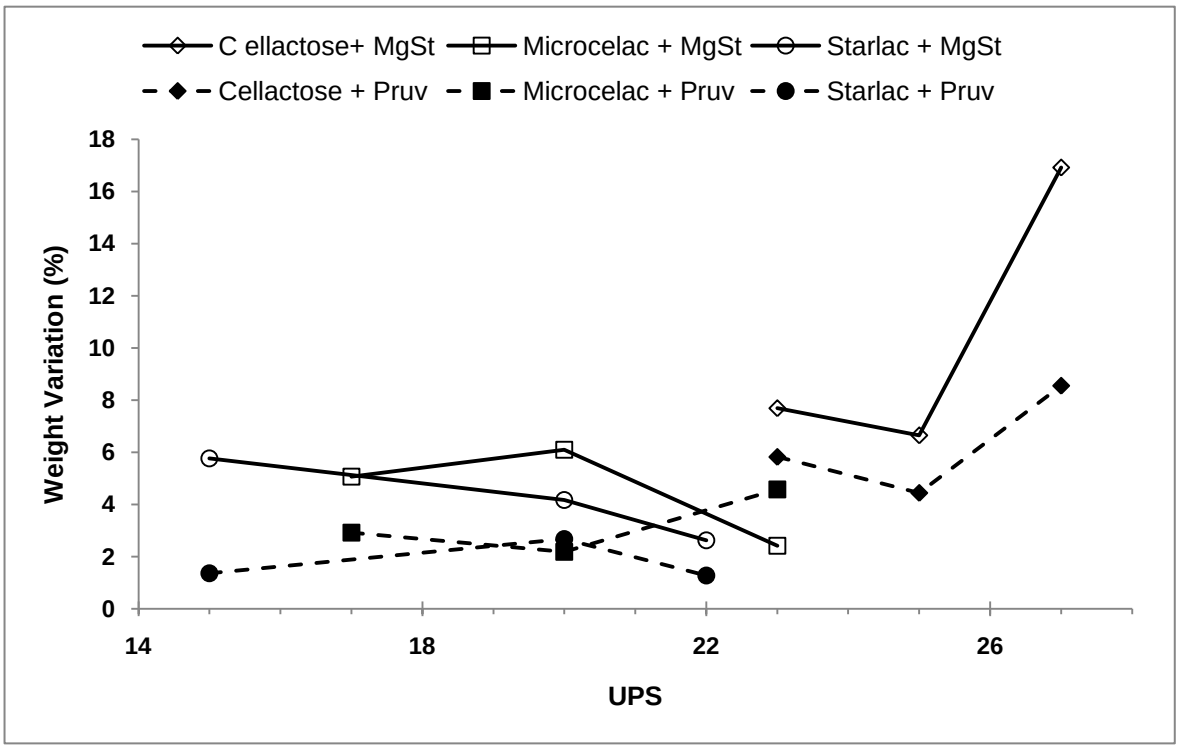


Figure 4.2: *Weight variation of compacts of the co-processed fillers at various upper punch settings (reflecting compression force).*

For both Starlac® and Microcelac® compacts, weight variation decreased or remained relative constant over the compression range employed, whilst both Cellactose® formulations exhibited an unexpected increase in compact weight variation with an increase in UPS from 25 to 27. Overall, Cellactose® compacts exhibited higher weight variation compared to both Starlac® and

Microcelac® containing either Pruv® or magnesium stearate. A large variation in compact weight can be explained by the powder flow and particle size of each powder. It is clear from figure 3.1, that Cellactose® has the most irregular and uneven particle size and distribution compared to Microcelac® exhibit and Starlac® and according to table 3.3 both, Starlac® and Microcelac® have a higher rank order compared to Cellactose® in terms of powder flow. Even though Cellactose® presented with relative good flow properties, it was still not as good as the other two filler/binder compacts and the lack of very good flow could have resulted in uneven, partial die filling during compression, causing a larger weight variation compared to Starlac® and Microcelac®.

The percentage friability represents the tablets' ability to sustain resistance against any mechanical shock or abrasion, thus low percentage friability is an indication of good resistance against mechanical factors. From the results in table 4.2, it could be seen that tablet hardness had an influence on the percentage friability of compacts. An increase in tablet hardness caused a decrease in friability. As previously mentioned, there was no meaningful differences between formulas containing Mg-St or Pruv®, except Cellactose® 80, where further studies need to be done to determine the reason for this occurrence.

Table 4.3 summarizes the disintegration results obtained from the different compacts. The addition of Ac-Di-Sol® (2%) was explained in section 4.2. It was the smallest percentage added where compacts showed disintegration within 15 minutes. During the pilot studies, Ac-Di-Sol® (2%) was only added to the formulas containing Mg-St (0.75%). Poor disintegration was observed for formulas containing Cellactose® 80 and Microcelac® 100 until the disintegrant was added. Starlac® was the only filler which produced compacts that disintegrated within 15 minutes without the addition of a disintegrant.

All particles undergo deformation generated by the magnitude of force, application rate, duration of induced stress, contact time between particles and mechanical properties of components (Jain, 1999:21). Lactose monohydrate, which is present in all three filler/binders, leads to fragmenting resulting in spontaneous disintegration because of the damage done to the intermolecular bonds between particles. Microcrystalline cellulose (Microcelac® 100) undergoes plastic deformation where particles swell during integration which provokes a high swelling force and contributes to disintegration. When lactose monohydrate and cellulose (powdered or microcrystalline) are combined, lactose forms an outside layer around the cellulose nucleus, preventing moisture absorption, making it impossible for cellulose to absorb water and start swelling to induce disintegration. Starlac® consists of corn starch (hygroscopic structure) which

provides a large surface for moisture uptake and is facilitated by lactose monohydrate which has rapid liquid uptake ability, resulting in fast disintegration (Ferrari *et al*., 1996:73; Casalderrey *et al*., 1999:462). The addition of the disintegrant facilitated disintegration in both Microcelac® 100 and Cellactose® 80 formulas. The hardness of compacts could also be a factor during disintegration. Compacts with a high hardness profile, such as Cellactose® 80 and Microcelac® 100 are less porous than softer tablets (Starlac®), which were very porous, causing high water uptake and resulting in quick disintegration.

Table 4.3: *Disintegration results of compacts with and without a disintegrant (Ac-Di-Sol® 2% and Mg-St 0.75%).*

			Upper Punch Setting						
			15	**17**	**20**	**22**	**23**	**25**	**27**
Starlac®	**Without disintegrant**	**0.75% MgSt**	0.89 (0.08)	ND*	1.76 (0.09)	1.95 (0.07)	ND*	ND*	ND*
		0.75% Pruv®	1.26 (0.13)	ND*	3.23 (0.16)	3.00 (0.08)	ND*	ND*	ND*
	2% Ac-Di-Sol®		ND*	ND*	ND*	ND*	ND*	ND*	ND*
Cellactose® 80	**Without disintegrant**	**0.75% MgSt**	ND*	ND*	ND*	ND*	0.42 (0.05)	15.00 (0.00)	15.00 (0.00)
		0.75% Pruv®	ND*	ND*	ND*	ND*	0.27 (0.05)	0.47 (0.40)	15.00 (0.00)
	2% Ac-Di-Sol®		ND*	ND*	ND*	ND*	0.40 (0.11)	7.43 (0.47)	7.50 (0.37)
Microcelac® 100	**Without disintegrant**	**0.75% MgSt**	ND*	0.91 (0.29)	15.00 (0.00)	ND*	15.00 (0.00)	ND*	ND*
		0.75% Pruv®	ND*	2.46 (0.63)	15.00 (0.00)	ND*	15.00 (0.00)	ND*	ND*
	2% Ac-Di-Sol®		ND*	0.84 (0.08)	6.45 (0.07)	ND*	7.38 (0.04)	ND*	ND*

ND* = No data

Another parameter employed as a measuring instrument of mechanical strength, was the hardness-friability index, designated as HFI, (i.e. ratio of hardness to friability at a given compression force. Since most compacts prepared from "good" compressible materials should exhibit an increase in hardness accompanied by a decrease in friability with an increase in

compression force, thus resulting in an increase in the value of the HFI. A higher HFI for a specific compact (or filler) compared to that of another filler at the same compression force can be an indication that the first-mentioned filler possesses better compaction properties than the latter. A decrease in the HFI value, however, could indicate the presence of mechanical weaknesses in the compact structure which could relate to poor compaction characteristics of a filler. This parameter could, therefore, enable us to compare the compressibility of a material in terms of both strength parameters. The results from the calculated values with the HFI of the various fillers as a function of compression force (governed by the upper punch setting) are graphically presented in figure 4.3. The fillers responded markedly different towards this parameter, but a particular filler showed similarities in the HFI/UPS profiles for both magnesium stearate and Pruv® containing compacts.

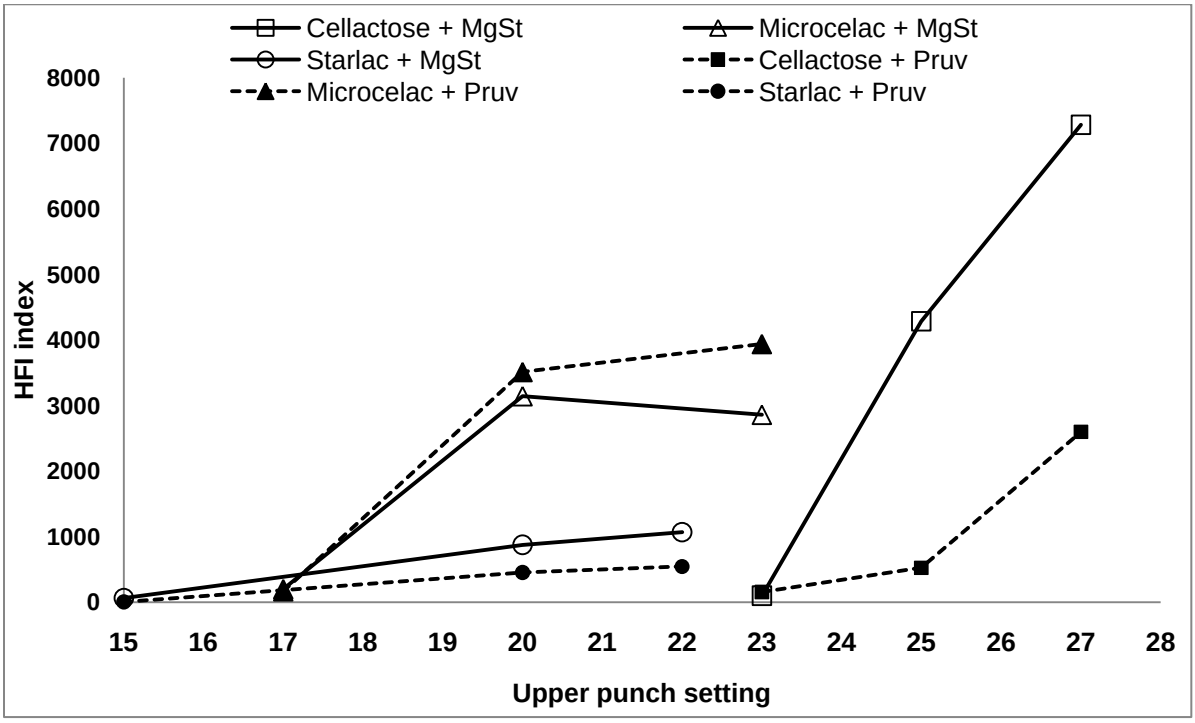


Figure 4.3: *The hardness-friability index versus compression force (UPS) for various compacts.*

Starlac® exhibited an almost linear increase in HFI with an increase in compression force, but with a low gradient, which indicate that the filler did not respond very well towards compression force in terms of an increased in mechanical strength (both hardness and friability changed relatively little with a change in applied force on the powder bed during compaction).

Conversely, Microcelac® exhibited a steep increase in HFI as compression force was increased, indicating a significant increase in compact hardness accompanied by a decrease in compact friability – a profile of a potential excellent directly compressible filler. The negative effect of Mg-

St, at the upper range of the compression force range, on the compactibility of the material could be evident from the decline in the slope of the line at UPS = 23, which resulted from an increase in % friability in these compacts (%F increased from 0.097% to 0.111%) with an increase in UPS from 20 to 23. At this applied upper punch force the compact has already reached a plateau in its hardness.

Cellactose® showed an excellent HFI profile for compacts containing Mg-St (as indicated by the steep gradient of the profile), but compacts containing Pruv® performed significantly poorer as the UPS was increased. This result suggested some interference of the lubricant with binding forces at higher compression forces, resulting in either a tapering in hardness and/or increase in compact friability.

Comparisons of fillers in terms of their HFI at overlapping UPS indicated mechanically stronger compacts for Microcelac® compared to Starlac® (at UPS 22 and 22), and Cellactose® (at UPS 23). Cellactose®, however, could accommodate higher compression forces compared to both the other two fillers, and its compact strength increased markedly at higher UPS (at setting above 23).

Determination of the hardness-disintegration index (HDI) can be used on the same principle as HFI as another parameter to distinguish between the physical tabletting properties of the various fillers (see figure 4.4). The HDI parameter explains the ratio of hardness to disintegration at a specific compression force. It is expected that an increase in crushing strength would cause longer disintegration times as the compression force is increased due to a resultant increase in bonding strength and a decrease in compact porosity. Tablets with a high porosity has the ability to absorb more water than less porous tablets resulting in faster disintegration times due to the weakening of binding forces between particles. At high compression pressures, tablets are likely to present with high crushing strength profiles resulting in less porous compacts causing low water absorption and longer disintegration times. Since “good” compressible materials were used to prepare compacts, they should present with an increase in hardness accompanied by longer disintegration rates with an increase in compression force, thus resulting in an increase in the value of the HDI. A high HDI value at a specific compression force indicates longer disintegration due to the high crushing strength of a compact whereas compacts with extremely high hardness profiles resulted in no disintegration.

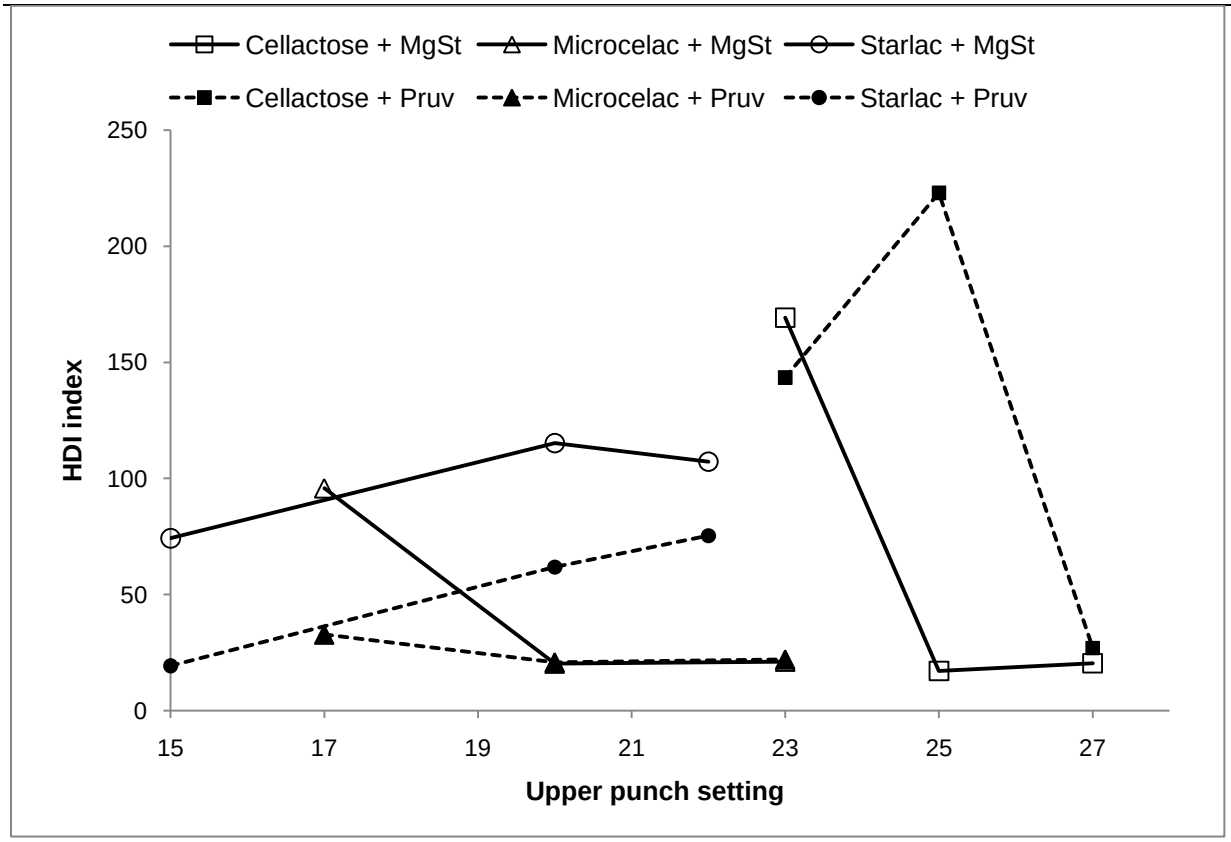


Figure 4.4: *The hardness-disintegration index versus compression force (UPS) for various compacts.*

Starlac® exhibited almost a linear increase in HDI with an increase in compression force, but not with a very high gradient, suggesting that the filler did not show much sensitivity towards a change in compression force in terms of interparticle forces (both hardness and disintegration changed little with a change in the applied force). According to Gohel and Jogani (2005:81), both corn starch and α-lactose monohydrate (components in Starlac®) exhibits good disintegration properties individually. Neither Mg-St nor Pruv® interfered with the behavior of Starlac® regarding the HDI values.

The only meaningful observation that could be made of Microcelac® was at an UPS=17, where a drastic decrease in HDI could be observed with an increase of compression force. These results were unexpected, since microcrystalline cellulose has relative good disintegration ability, but somehow did not exhibit with disintegration at higher upper punch settings. The formula containing Mg-St, had a much higher HDI value than Pruv®, which indicated longer disintegration times for tablets compressed at the same upper punch settings. This could be explained by the effect magnesium stearate has on crushing strength, affecting the binding forces between particles and the ability to absorb enough water (porous) to swell and induce

disintegration. It was clear that Microcelac® does not have the ability to disintegrate if compressed at high upper punch settings.

Cellactose® exhibited an unusual HDI profile, where higher HDI values were observed at low compression forces, indicating softer compacts with low mechanical strength. There was a significant difference between the formulas containing Mg-St and Pruv®, especially at the first two upper punch settings. A steep increase in HDI as compression force increased was observed for the formula containing Pruv® and could probably be explained by the effect magnesium stearate has on hardness during direct compression interfering with the binding forces and causing tablets to be less porous resulting in no disintegration. The only possible reason for Pruv® to exhibit faster disintegration was due to its increased wettability property.

Microcelac® and Cellactose® were the only two filler/binders which exhibited no disintegration at higher upper punch settings and needed a disintegrant to induce disintegration (see section 4.2). Both these fillers contain 25% cellulose in their formulation, which disintegrate by absorbing enough water to induce swelling. From the results obtained, it was clear that the crushing strength of compacts plays an important role during disintegration. Since disintegration is also affected by the porosity of the compact structure, one must keep in mind that the 75% lactose present in the filler is forming a layer around the cellulose fibers. If the crushing strength is too high, the tablet becomes less porous and it is more difficult to absorb enough water to induce a swelling or disintegrating force which could overcome the interparticle forces and break through the lactose layer to start disintegration. Cellulose has the tendency to become gel-like and adhesive upon contact with an aqueous environment which could be detrimental to its ability to overcome the binding forces and to swell to its full capability.

Comparisons of fillers in terms of their HDI at overlapping UPS indicated faster disintegration accompanied by mechanically stronger compacts for Starlac® compared to Microcelac® (both at UPS of 22) and Cellactose® (at UPS 23). Starlac®, however, exhibited overall spontaneous disintegration at a relative fast disintegration rate without any addition of a disintegrant.

From the HDI profile it could be seen that disintegration was dependent on the crushing strength and increase of compression force as well as the filler/binders mechanisms of disintegration. Therefore, it is of great importance to be familiar with the structural properties of filler/binders to predict their tablet properties during the formulation stage.

4.4 CONCLUSION

Compression properties of filler/binders are extremely important during direct compression and are dependent on the physical powder flow properties of the materials. The modified lactose filler/binders (Lactopress®, Flowlac® and Tablettose®) unexpectedly exhibited poor compression properties, whereas the co-processed filler/binders (Starlac®, Cellactose® and Microcelac®) produced compacts with acceptable appearance and compact properties. Two lubricants (Mg-St or Pruv®) which were tested separately in formulations, were added since no compacts were produced from the single filler/binders. None of the modified lactose filler/binders, in combination with a lubricant, were able to produce an acceptable compact, since lamination occurred during compression. The co-processed filler/binders with an addition of a lubricant produced satisfactory compacts except for the lactose-cellulose (Cellactose® and Microcelac®) fillers, which exhibited no disintegration and needed a disintegrant (Ac-Di-Sol®) to induce disintegration.

There were no significant differences between the formulations containing Pruv® and Mg-St except for Cellactose®, which exhibited unexpected results regarding hardness. Cellactose® was also the only filler/binder which could not be compressed in an overlapping upper punch setting with Starlac® and Microcelac®, but was pressed at a much higher compression force. According to the results obtained, it is obvious that there is a linear relationship between hardness and friability versus compression forces. The composition of the co-processed filler/binders definitely attributed to their compression properties.

Since all the modified lactose fillers were not able to produce compacts, without lamination, no further studies, regarding the addition of an active ingredient, was done on these filler/binders. The three co-processed filler/binders, which presented with acceptable compressibility properties were chosen for further studies, where a poorly compressible drug was added in the formula.

CHAPTER 5: DRUG RELEASE PROPERTIES OF THREE CO-PROCESSED FILLER/BINDER FORMULATIONS CONTAINING PARACETAMOL

5.1 INTRODUCTION

Combination with a drug (active ingredient) and evaluation of drug-filler compacts and drug release properties from solid dosage forms are probably the best method for determining the suitability of a material as filler in these types of dosage forms and to compare various fillers in terms of these characteristics. The dissolution behavior of the drug should reveal properties present in the formulations resulting from the presence of the filler/binders that could evaluate their suitability for direct compression.

To compare different filler/binders, there are several factors which need to be taken into consideration and need to be tested and evaluated in a study. The dilution potential of filler/binders, which is an indication of how much active ingredient a filler can accommodate during direct compression is one of the important considerations during formulation using direct compression. The dilution potential is influenced by the compressibility of the active ingredient and the ability of the filler to overcome poor compaction properties of the drug. The compressibility properties of both fillers/binders and the drug (paracetamol) play a role during satisfactory tabletting where no elastic deformation takes place in the recovery phase during compression (Gohel & Jogani, 2005:78). Probably the most important factor is the ability of fillers to rapidly release the total drug dose present during dissolution.

In this section of the study, the three co-processed filler/binder, Cellactose®, Microcelac® and Starlac® were combined with the optimum paracetamol amount (as active ingredient); and tablets were prepared from each mixture at optimum compression pressures utilizing an eccentric tablet press. The physical properties of each formulation were determined and compared in terms of acceptability. Finally, drug release characteristics from each tablet formulation were determined from dissolution data, using two dissolution parameters, namely the initial dissolution rate (IDR) and the area under the dissolution curve (AUC).

A poorly recognized compressible drug, paracetamol, was used as active ingredient in all formulations. Paracetamol is known for its tendency to induce capping and lamination during direct compression.

5.2 PILOT STUDY

During a pilot study the dilution potential of Cellactose®, Microcelac® and Starlac® was determined for paracetamol as described in section 2.5.2. The aim of this experiment was to determine the maximum amount of paracetamol that could be accommodated in powder mixtures of the three filler/binders and which could be effectively tabletted at a tablet weight of approximately 400 mg (using 10 mm flat-faced punches and corresponding die). Due to the poor inherent compaction properties of paracetamol, Cellactose® and Microcelac® could accommodate 24.4% w/w of the active ingredient, and Starlac® could only accomodate 19.5% w/w paracetamol. All formulation mixtures included 0.75% w/w Mg-St (as lubricant) and 2.0% w/w Ac-Di-Sol® (as disintegrant). The composition of the three formulations is tabulated in table 5.1.

Table 5.1: *Composition of paracetamol-filler/binder formulas prepared.*

	Ingredients:	Amount (mg):
Formula 1	Starlac®	312
	Paracetamol	78
	Magnesium stearate (0.75% w/w)	3
	Ac-Di-Sol® (2% w/w)	8
Formula 2	Cellactose® 80	292
	Paracetamol	98
	Magnesium stearate (0.75% w/w)	3
	Ac-Di-Sol® (2% w/w)	8
Formula 3	Microcelac® 100	292
	Paracetamol	98
	Magnesium stearate (0.75% w/w)	3
	Ac-Di-Sol® (2% w/w)	8

Compression studies were also done at various UPS settings to determine an adequate compression force to produce acceptable tablets in terms of hardness and friability. An UPS of 20 for the Starlac® formulation, and a UPS = 22 for the Cellactose® and Microcelac® formulations were chosen.

5.3 PHYSICAL PROPERTIES OF TABLET FORMULATIONS

Tablets obtained at the predetermined UPS (on a eccentric tablet press) were analyzed for average weight, weight variation, hardness, friability and disintegration as described in

section 2.5.3. The data is presented in annexure G and the results are tabulated in table 5.2.

An obvious difference between the three formulations was that the Starlac® formulation (formula 1) could only be tabletted at an UPS of 20. Table 5.1 indicates that Starlac® could only accommodate 78 mg paracetamol compared to Microcelac® and Cellactose®, which could accommodate 97mg. Starlac is the only filler/binder which contains corn starch, whereas the other two filler/binders contain different grades of cellulose. The poor compactibility of formula 1 at higher upper punch settings could be explained by the deformation of material, which was in accordance with findings from Dressler and Wagner (2003:3), where elastic deformation increased with an increase in compression force, resulting in poor, very hard, non-disintegrating tablets.

Table 5.2: *Physical properties of paracetamol tablets (value between brackets indicate the standard deviation)*

	UPS	WV*	H*	%FR*	DT*
Formula 1	20	406.24 (9.06)	124.83 (13.16)	0.936	1.14 (0.02)
Formula 2	22	397.09 (1.79)	122.01 (8.27)	0.542	1.82 (0.02)
Formula 3	22	414.66 (0.02)	148.20 (8.32)	0.532	0.84 (0.04)

UPS* = Upper punch setting, WV* = weight variation, %FR* = friability, H* = hardness, DT* = disintegration time

According to Meggle Excipients, manufactures of all three filler/binders used in this study, Starlac® is designed to accommodate low dosage active ingredients, whereas Cellactose® and Microcelac® are manufactured to obtain formulations with a higher content of active ingredient. It is reported (Dressler & Wagner, 2003:4) that paracetamol used in direct compression dominates the tablet properties, resulting in disguising the good powder flow and compression properties of the used filler/binders. As previously mentioned both Cellactose® and Microcelac® are renowned for their primarily plastic deformation during compression and could be the reason for their ability to accommodate a higher percentage paracetamol. Paracetamol consists of large monoclinic crystals which are not easily deformed and caused resistance during compaction. This could be the main reason for the low percentage paracetamol present in the formulations.

All three formulations showed acceptable physical properties in terms of hardness and friability, with Starlac® tablets showing markedly higher friability (0.932%) compared to the other two formulations (approximately 0.5%). This could possibly be attributed to the lower

compression force (UPS = 20) used during tableting of the Starlac® powder mixture, and poorer compression characteristics of the filler as observed in the previous chapter.

The high standard deviation for crushing strength observed for all the formulas (>8%) could be caused by the presence of the lubricant (0.75% w/w magnesium stearate) which is renowned for its effect on tablet hardness during compression. Magnesium stearate has a negative effect on hardness consistency and friability during compression due to the different proportions of brittle and/or deformable materials present in the formula. All three formulations contain deformable components which affect the hardness more than brittle materials (Wang *et al.*, 2010:10).

Weight variation of the Starlac® tablets was significantly higher than both of the other two formulations (in excess of 10% compared to less than 2%). Higher variation in tablet hardness of the Starlac® formulation further indicated and confirmed the poorer compression characteristics of this filler/binder compared to both Cellactose® and Microcelac®.

All three formulations presented with excellent disintegration times (between 1 and 2 minutes), which resulted in rapid drug release from the tablets, thus presenting primary drug particles to the medium almost instantly after contact with the surrounding medium (pharmaceutical available).

From the results obtained, paracetamol delivered unexpectedly good, acceptable tablets during direct compression. No capping or lamination occurred during compression, which could be attributed to the ability of the various filler/binders to accommodate a poor compressible drug, although in a relative low concentration (less than 30% w/w). The fillers containing cellulose (Microcelac® and Cellactose®) in combination with α-lactose monohydrate proved to be able to produce tablets with a higher drug content compared to Starlac® (corn starch and α-lactose monohydrate).

5.4 DISSOLUTION STUDIES

Dissolution studies are the ultimate test to determine the suitability of a material as a filler/binder in terms of the rate and extent of drug release from a compact (tablet). Dissolution studies were performed on all three formulations according to the method described in section 2.6. Table 5.3 presents the average dissolution results from three repetitions of each formula, whilst figure 5.1 presents the data graphically.

Table 5.3: *Dissolution data of the various paracetamol-filler/binder formulations (% relative standard deviation between brackets)*

	Formula 1 (Starlac®)		Formula 2 (Cellactose®)		Formula 3 (Microcelac®)	
Time (minutes)	**Drug dissolved**		**Drug dissolved**		**Drug dissolved**	
	(mg/ml)	**(%)**	**(mg/ml)**	**(%)**	**(mg/ml)**	**(%)**
0	0	0	0	0	0	0
1	0.0259 (22.98)	29.85	0.0526 (28.26)	48.83	0.0696 (14.80)	64.54
2	0.0476 (19.15)	54.87	0.0837 (7.89)	77.64	0.0912 (8.81)	84.58
4	0.0724 (10.12)	83.51	0.0954 (3.95)	88.49	0.1006 (3.48)	93.31
8	0.0842 (2.59)	97.18	0.1017 (2.24)	94.40	0.1054 (2.62)	97.75
16	0.0881 (2.17)	101.70	0.1038 (1.74)	96.35	0.1089 (1.22)	101.06
32	0.0903 (0.97)	104.22	0.1067 (0.71)	98.97	0.1124 (1.85)	104.32
64	0.0927 (0.57)	106.94	0.1099 (1.59)	101.95	0.1189 (8.01)	110.34

The solubility of paracetamol in the phosphate buffer (pH 5.8) contributed to the high concentration drug dissolved as seen in figure 5.1. Both Microcelac® and Cellactose® formulas released more than 75% of the drug content within 2 minutes; more than 95% of the dose within 4 minutes (Microcelac®) and 8 minutes (Cellactose®) respectively. The dissolution profiles of paracetamol from all three formulations are typical for fast disintegrating tablets. The rapid disintegration contributed to the rapid contact between the drug particles and dissolution medium. It have been expected that Starlac® would present with a lower dissolution profile (figure 5.1) than the other two formulations, due the lower percentage of paracetamol present in the formula, thus releasing a lower amount of paracetamol (mg/ml). Although it consisted of a lower percentage paracetamol, it still released 100% of the drug rapidly during dissolution.

The values of two dissolution parameters (IDR and AUC) calculated from the dissolution data of each formulation are presented in table 5.4. Although all three formulations presented with a rapid initial dissolution rate (< 0.025 mg/ml/min), the Starlac® formulations performed markedly slower than the other two formulations.

Table 5.4: *The initial dissolution rate (IDR) and normalized area under the dissolution curve (AUC) of paracetamol formulas. Percentage relative standard deviation is indicated in brackets.*

	AUC (mg.min/ml)	IDR (mg/ml/min)
Formula 1	5.528 (0.06)	0.018 (9.20)
Formula 2	6.639 (1.28)	0.022 (4.95)
Formula 3	7.048 (2.33)	0.023 (4.51)

Comparison of the extent of dissolution of paracetamol from the three formulations, as indicated by the AUC, showed the following rank order: Microcelac® ≈ Cellactose® >> Starlac®. Differences in AUC were significant ($p<0.05$) between formula 1, formula 2 and 3, respectively. Although significant differences were observed between the dissolution profiles of paracetamol from the various formulations, a more discriminating dissolution medium (for example 0.1 M HCl), would have probably be more suitable to distinguish better between the effect of the various filler/binders on drug release.

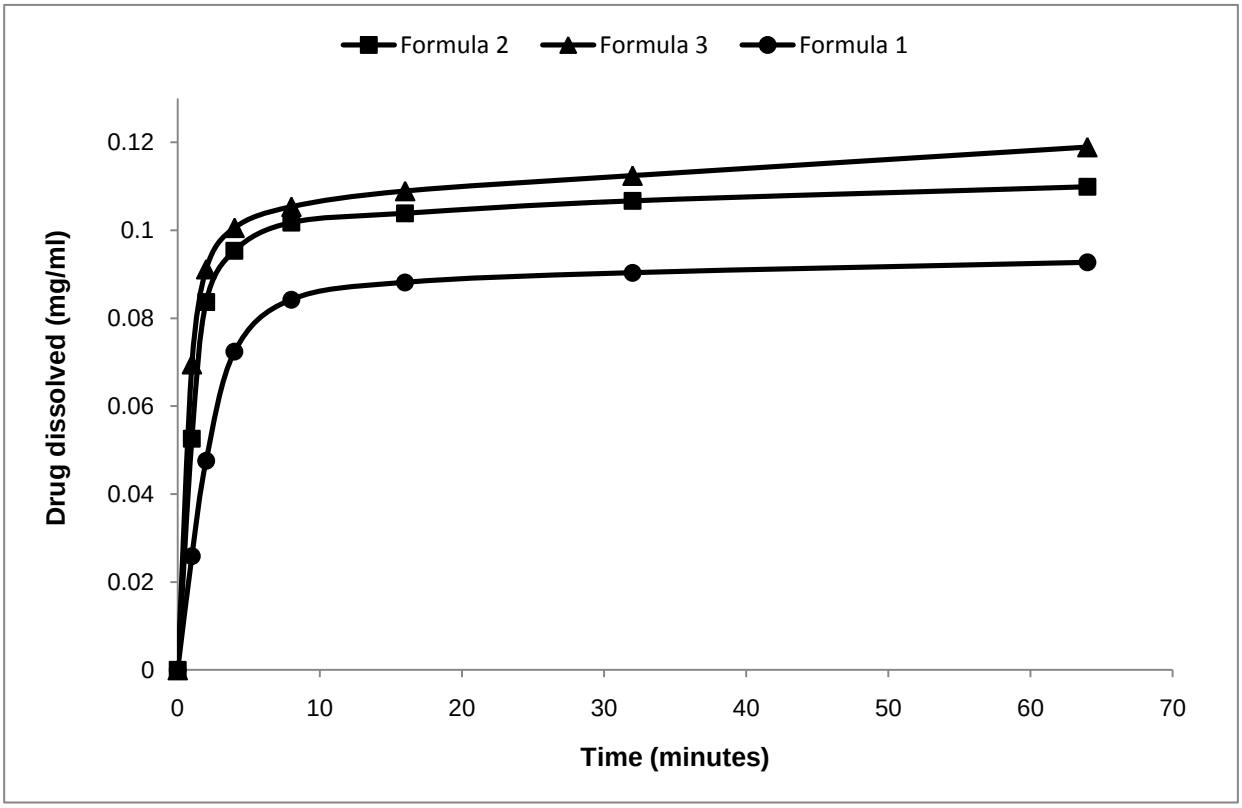


Figure 5.1: *The dissolution profiles of tablets prepared from paracetamol in combination with different co-processed filler/binders*

5.5 CONCLUSION

All three formulations containing paracetamol, surprisingly exhibited good tablet properties without any capping. During a pilot study, the percentage paracetamol a filler could

accommodate in a 400 mg tablet, was determined. Both Microcelac® and Cellactose® could accommodate 24.5% paracetamol, whereas Starlac® only accommodated 19.5%. An acceptable upper punch setting range (UPS = 20-22) was chosen for tabletting, followed by quality control tests done. All tablets exhibited disintegration below two minutes, with hardness profiles between 120 N and 148 N, and friability percentages less than 1%.

As previously mentioned, dissolution can be used to determine the effect of formulation variables (such as type of excipient, compression force, ect.) on the release of the drug from a formulation. Due to the rapid disintegration, high percentages paracetamol was released during the first four minutes. After 64 minutes, the three different tablet formulations released 100 % of the drug present in the tablet. Starlac®, however, exhibited with a lower amount of drug released from the tablet due to its lower paracetamol content (19.5%). A conclusion could be made that all three co-processed filler/binders, namely Starlac®, Cellactose® and Microcelac®, have the ability to release a high percentage poorly compressible drug (paracetamol) during dissolution.

Although it was expected that these filler/binders would accommodate at least 50% of a poorly compressible drug, it is still classified as the best lactose-based filler/binders to use during direct compression.

REFERENCE

ALDERBORN, G. 2002. Tablets and compaction, 2nd ed. (*In* Aulton, M.E., *ed.* Pharmaceutics; The science of dosage form design. London: Churchill Livingstone. p. 397-440.)

ARIDA, A.I. & AL-TABAKHA, M.M. 2008. Compaction mechanism and tablet strength of Cellactose®. Jordan Journal of Pharmaceutical Sciences, 1(1):71-82.

BARRA, J. & SOMMA, R. 1996. Influence of the physicochemical variability of magnesium stearate on its lubricant properties: possible solutions. *Drug development and Industrial pharmacy,* 22(11):1105-1120.

BRITISH PHARMACOPOEIA. 2007. London: MHRA. 3294 p.

BROADHEAD, J., ROUAN, S.K.E. & RHODES, C.T. 1992. The spary-drying of pharmaceuticals. *Drug development and industrial pharmacy.* 18(11 & 12):1169-1206.

BUYS, G.M. 2006. Formulation of a chitosan multi-unit dosage form for drug delivery to the colon. Potchefstroom: North-West University. (Ph.D.) p. 199.

CASALDERRY, M., SOUTO, C., CONCHEIRO, A., GÓMEZ-AMOZA, J.L. & MARTINEZ-PACHECO, R. 2000. A comparison of Cellactose with two ad hoc processed lactose-cellulose blends as direct compression excipients. *Chemical. Pharm. Bull.,* 48(4):398-401.

CHANG, D. & CHANG, R.K. 2007. Review of current issues in pharmaceutical excipients. Pharmaceutical Technology, 1-11. www.pharmtech.com Date of access: 17 March 2010.

DE BOER, A.H., VROMANS, H., LERK, C.F., BOLHUIS, G.K., KUSSENDRAGER, K.D. & BOSCH, H. 1986. Studies on tabletting properties of lactose. Part 2. The consolidation behavior of sieve fractions of crystalline α-lactose monohydrate. *Pharmaceutich weekblad. Scientific edition,* 8:145-150.

DRESSLER, J.A. & WAGNER, K.G. 2003. A corn starch/α-lactose monohydrate compound as a directly compressible excipient. Pharmaceutical Technology, 1-10. www.pharmtech.com Date of access: 19 April 2010.

FERRARI, F., BERTONI, M., BONFERONI, M.C., ROSSI, S., CARAMELLA, C. & NYSTRÓM, C. 1996. Investigation on bonding and disintegration properties of pharmaceutical materials. *International Journal of Pharmaceutics*, 136:71-79.

FERRERO, C., MUNOZ, N., VELASCO, M.V., MUNOZ-RUIZ, A. & JIMÉNEZ-CASTELLANOS, R. 1997. Disintegrating efficiency of croscarmellose sodium in a direct compression formulation. *International Journal of Pharmaceutics,* 147:11-21.

FREEMAN, R. 2000. The classification of powders in relation to flowability. *Freeman Technology,* 1-10. www.freemantech.co.uk Date of access: 20 July 2010.

GARR, J.S.M. & RUBINSTEIN, M.H. 1991. Compaction properties of a cellulose-lactose direct-compression excipient. *Pharmaceutical Technology International,* p. 24-27.

GELDART, D., ABDULLAH, E.C., HASSANPOUR, A., NWOKE, L.C. & WOUTERS, I. 2006. Characterization of powder flowability using measurement of angle of repose. *China Particuology,* 4:104-107.

GOHEL, M.C. & JOGANI, P.D. 2005. A review of co-processed directly compressible excipients. *Journal of Pharmaceutical Sciences,* 8(1):76-93.

GONNISSEN, Y., REMON, J.P. & VERVAET, C. 2007. Development of directly compressible powders via co-spray drying. *European journal of Pharmaceutics and Biopharmaceutics,* 67:220-226.

HARNBY, N., HAWKINS, A.E. & VANDAME, D. 1987. The use of bulk density determination as a means of typifying the flow characteristics of loosely compacted powders under the conditions of variable relative humidity. *Chemical Engineering Science*, 42(4):879-888.

HAUSCHILD, K. & PICKER, K.M. 2004. Evaluation of a new co-processed compound based on lactose and maize starch for tablet formulation. *The AAPS Journal,* 6(2), article 16:1-12.

HORN, E. 2008. The development of a composite index for pharmaceutical powders. Potchefstroom: North-West University. (M.Sc.) p. 1-185.

HWANG, R. & PECK, G.R. 2001. A systematic evaluation of the compression and tablet characteristics of various types of lactose and dibasic calcium phosphate. *Pharmaceutical technology,* p. 54-68.

ISRAELACHVILI, J. 1992. Intermolecular and Surface forces, 2nd ed. *Academic Press,* 1992:1-18.

JAIN, S. 1999. Mechanical properties of powders for compaction and tabletting: an overview. *Pharmaceutical Sciences & Technology Today,* 2(1):20-31.

JIVRAJ, M., MARTINI, L.G. & THOMSON, C.M. 2000. An overview of the different excipients useful for direct compression of tablets. *Pharmaceutical science and technology today*, 3(2):58-63.

KAERGER, J.S., EDGE, S. & PRICE, R. 2004. Influence of particle size and shape on flowability and compaction of binary mixtures of paracetamol and microcrystalline cellulose. *European Journal of Pharmaceutical Sciences,* 22:173-179.

KÁSA, P., BAJDIK, J., ZSIGMOND, Z. & PINTYE-HÓDI, K. 2009. Study of the compaction behaviour and compressibility of binary mixtures of some pharmaceutical excipients during direct compression. *Chemical Engineering and Processing*, 48:859-863.

KREMER, D.M. 2006. A numerical investigation of air flow during tablet compression. *Chemical Engineering Science*, 61:7963-7978.

KOTTKE, M.K. & RUDNIC, E.M. 2002. Tablet dosage forms. (*In* Banker, G.S. & Rhodes, C.T. *eds.* Modern Pharmaceutics. 4th ed New York : Dekker. p. 287-333.)

KUNO, Y., KOJIMA, M., NAKAGAMI, H., YONEMOCHI, E. & TERADA, K. 2008. Effect of the type of lubricant on the characteristics of orally disintegrating tablets manufactured using the phase transition of sugar alcohol. *European Journal of Pharmaceutics and Biopharmaceutics,* 69:986-992.

KUPPUSWAMMY, R., ANDERSON, S.R., AUGSBURGER, L.L. & HOAG, S.W. 2001. Estimation of capping incidence by indentation fracture tests. *The AAPS Journal,* 3(1), article 5:1-12.

LENNARTZ, P. & MIELCK, J.B. 1998. Minitabletting; improving the compactability of paracetamol powder mixtures. *International Journal of Pharmaceutics,* 173:75-85.

LI, Q., RUDOLPH, V., WEIGL, B. & EARL, A. 2004. Interparticle van der Waals force in powder flowability and compactibility. *International Journal of Pharmaceutics,* 280:77-93.

MANN, S.C, ROBERTS, R.J., ROWE, R.C., HUNTER, B.M. & REES, J.E. 1983. The effect of high speed compression at sub-atmospheric pressures on capping tendency of pharmaceutical tablets. *Journal of Pharmacy and Pharmacology*, 35:44.

MEGGLE EXCIPIENTS & TECHNOLOGY. Cellactose®. (Certificate of analysis. Copy in possession of author.)

MEGGLE EXCIPIENTS & TECHNOLOGY. Flowlac®. (Certificate of analysis. Copy in possession of author.)

MEGGLE EXCIPIENTS & TECHNOLOGY. Granulac®. (Certificate of analysis. Copy in possession of author.)

MEGGLE EXCIPIENTS & TECHNOLOGY. Microcelac®. (Certificate of analysis. Copy in possession of author.)

MEGGLE EXCIPIENTS & TECHNOLOGY. Starlac®. (Certificate of analysis. Copy in possession of author.)

MEGGLE EXCIPIENTS & TECHNOLOGY. Tablettose®. (Certificate of analysis. Copy in possession of author.)

MEGGLE, See MEGGLE EXCIPIENTS & TECHNOLOGY.

MUTASEM, M., M.R., SIMONS, F.E.R. & SIMONS, K.J. 2006. Fast-disintegrating sublingual tablets: Effect of epinephrine load on tablet characteristics. *The AAPS Journal,* 7(2):E1-E7.

NACHAEGARI, S.K. & BANSAL, A.K. 2004. Co-processed excipients for solid dosage forms. *Pharmaceutical technology,* 54-60 p, Jan.

NYSTROM, C. & KAREHILL, P.G. 1986. Studies on direct compression of tablets XVI, The use of surface area measurements for the evaluation of bonding surface area in compressed powders. *Powder Technology*, 47:201-209.

NYSTROM, C., ALDERBORN, G., DUBERG, M. & KAREHILL, P. 1993. Bonding surface area and bonding mechanism – two important factors for the understanding of powder compactibility. *Drug development and Industrial Pharmacy*, 19:2143-2196.

PAULING, L. 1960. The nature of chemical bond and the structure of molecules and crystals; An introduction to modern chemistry. Cornell University, Ithaca, NY: 1-636.

PIFFERI, G., SANTORO, P. & PEDRANI, M. 1999. Quality and functionality of excipients. *Il farmaco,* 54:1-14.

PODCZECK, F. & SHARMA, M. 1996. The influence of particle size and shape of components of binary powder mixtures on the maximum volume reduction due to packing. *International Journal of Pharmaceutics,* 137:41-47.

PRESCOTT, J.K. & BARNUM, R.A. 2000. On powder flowability. *Pharmaceutical technology*, 24(10):60-84.

RENOUX, R., DEMAZIERES, J.A., CARDOT, J.M. & AIACHE, J.M. 1996. Experimentally designed optimization of direct compression tablets. *Drug development and Industrial pharmacy,* 22(2):103-109.

SALEH, S.I. & ABOUTALEB, A. 1984. Evaluation of some water soluble lubricants for direct compression. *Labo-Pharma – Problems et Techniques*, 345:588-591.

SHAH, A.C. & MLODOZENIEC, A.R. 1977. Mechanism of surface lubrication: Influence of duration of lubricant-excipient mixing on processing characteristics of powders and properties of compressed tablets. *Journal of Pharmaceutical Sciences*, 66:1377-1382.

SHAH, R.B., TAWAKKUL, M.A. & KHAN, M.A. 2008. Comparative evaluation of flow for pharmaceutical powders and granules. *The AAPS Journal,* 9(1):250-258.

SHANGRAW, R.F. 1989. Compressed tablets by direct compression. (*In* Lieberman, A., Lachman, L. & Schwartz, J.B., *eds*. Pharmaceutical dosage forms: tablets. Vol. 1. 2nd ed. New York : Dekker. p. 195-246.)

SONNERGAARD, J.M. 2005. Quantification of the compactibility of pharmaceutical powders. *European Journal of Pharmaceutics and Biopharmaceutics,* 63:270-277.

STANIFORTH, J.N. 2002. Powder flow. 2nd ed. (*In* Aulton, M.E., *ed.* Pharmaceutics; The science of dosage form design. London: Churchill Livingstone. p. 197-210).

STANIFORTH, J.N., REES, J.E., KAYES, J.B. & PRIEST, R.C. 1981. The design of a direct compression tableting excipient. *Drug Development and Industrial Pharmacy,* 7(2):179-190.

TAKEUCHI, H., YASUJI, T., HINO, T., YAMAMOTO, H. & KAWASHIMA, Y. 1998. Spray-dried composite particles of lactose and sodium alginate for direct tabletting and controlled releasing. *International Journal of Pharmaceutics,* 174:91-100.

TAYLOR, M.K., GINSBURG, J., HICKEY, A.J. & GHEYAS, F. 2000. Composite method to quantify powder flow as a screening method in early tablet and capsule formulation development. *The AAPS Journal*, 1(3):1-11.

UNITED STATES PHARMACOPOEIAL CONVENTION. 2007. USP 30:NF 25. Rockville, Md. p. 4134.

USP, See UNITED STATES PHARMACOPOEIAL CONVENTION

VACHON, M.G. & CHULIA, D. 1999. The use of energy indices in estimating powder compaction functionality of mixtures in pharmaceutical tableting. *International Journal of Pharmaceutics*, 177:183-200.

VROMANS, H., DE BOER, A.H., BOLHUIS, G.K., LERK, C.F., KUSSENDRAGER, K.D. & BOSCH, H. 1985. Studies on tabletting properties of lactose, Part 2. Consolidation and compaction of different types of crystalline lactose. *Pharmaceutisch Weekblad Scientific edition,* 7:186-215.

WANG, J., WEN, H. & DESAI, D. 2010. Lubrication in tablet formulations. European Journal of Pharmaceutics and Biopharmaceutics, 75:1-15.

WELLS, J. 2002. Pharmaceutical preformulation: the physicochemical properties of drug substances. 2nd ed. (*In* Aulton, M.E., *ed.* Pharmaceutics; The science of dosage form design. London: Churchill Livingstone. p. 113-138).

WONG, A.C.Y. 2002. Use of angle of repose and bulk densities for powder characterization and the prediction of minimum fluidization and minimum bubbling velocities. Chemical Engineering Science, 57:2635-2640.

YU, A.B., FENG, C.L., ZOU, R.P. & YANG, R.Y. 2003. On the relationship between porosity and interparticle forces. Powder Technology, 130:70-76.

ZHANG, Y., LAW, Y. & CHAKRABARTI, S. 2003. Physical properties and compact analysis of commonly used direct compression binders. *The AAPS Journal*, 62(4):1-3.

ZUURMAN, K., VAN DER VOORT MAARSCHALK, K. & BOLHUIS, G.K. 1999. Effect of magnesium stearate on bonding and porosity expansion of tablets produced from materials with different consolidation properties. *International Journal of Pharmaceutics*, 179:107-115.