Development of a composite index for pharmaceutical powders.

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DEVELOPMENT OF A COMPOSITE INDEX FOR PHARMACEUTICAL POWDERS.

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AIM AND OBJECTIVES OF THIS STUDY

AIM

The aim of the study was to compile a composite flow index for a selection of pharmaceutical powders which could discriminate accurately between the flowability of these powders in order to aid and assist in selection of suitable components (excipients) during the formulation and manufacturing of solid oral dosage forms.

BACKGROUND

The primary prerequisites for powder mixtures / granules intended for tableting are (i) a homogeneous composition; (ii) acceptable flowability; (iii) sufficient compressibility; and (iv)anti-adhesiveness. Each of these required properties can be traced back to the physical properties of the particles of the different components in the final powder mixture / granulate. Perhaps the most important prerequisite is the flow properties of the final mixture, since this characteristic determines the uniformity of the final product in terms of drug dose, product appearance and product performance. In order to achieve this uniformity in all batches of the specific product, the components (pharmaceutical powders) must have the ability to flow freely in the various stages of handling and manufacturing. Flowability is the ability of a powder to flow under a force. The flow of a powder during manufacturing dictates the quality of the product in terms of its weight and content uniformity. Flow also affects manufacturing efficiency, because it can determine whether bins can be used or whether hand scooping will be required; to what extent the product (if any) is scrapped at the beginning or at the end of a run; and the allowable production rate of the product (Prescott *et al.*, 2000:60). It can therefore be concluded that the flowability of a powder is an essential and very important part of the manufacturing process.

Different powders used as either the active ingredient (drug) or as excipients in solid dosage forms exhibit significant differences in terms of their flowability, ranging from very, very poor to excellent. In order to determine (and classify) the flow behaviour of a powder or powder mixture/granulate, and to use this knowledge to determine the suitability of the material for inclusion into a formulation, various flow tests have been employed. These tests include angle of repose, percentage compressibility and Hausner's ratio, flow rate tests, shear cell, etc.). The various tests all have one thing in common, namely their results are affected by one or more of the different physical properties of the powder being examined. These properties include particle size, particle size distribution, shape, surface structure, density (both bulk and tapped) and packing geometry. The problem now arises that for a specific test the powder may present itself, on the basis of the result, as having adequate flowability,

whilst another test, affected by a different set of particle properties, may render the same powder inadequate in terms of flow.

To overcome this problem, Taylor *et al.* (2000:6) has introduced a composite index for powders, using the results from three of the most commonly employed flow tests, namely angle of repose, percentage compressibility and critical orifice diameter. The result was a more discriminative index for the flowability of pharmaceutical powders, which would be of much aid to the product formulator during the preformulation phase.

Careful scrutiny of the index revealed some possible flaws or shortcomings, including the fact that the weighted value of each flow test in the composite index was set equal (to 33 ⅓%) and the exclusion of a possible impotant flow property from the index, namely the flow rate of a powder.

The objective of this study, therefore, was to attempt to improve on this composite index through a variation of (i) the tests included in the composite index, and (ii) of the contribution of the various tests to the final composite index.

OJECTIVES

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

- Determination of the flowability of a selection of commonly used pharmaceutical fillers by means of the following flow tests: critical orifice diameter, percentage compressibility, angle of repose and flow rate (in the absence and presence of a glidant at ambient conditions).
- Identify (if possible) which specific set of particle properties affect the results obtained from each test.
- Use the data from the different tests and compile a new composite flow index in which either the tests included and/or the contribution of each test to the composite index is varied.
- Evaluate the new flow index in terms of accuracy in its ability to effectively discriminate between the flow properties of the powders.

ABSTRACT

The primary prerequisites for powder mixtures/granules intended for tableting is to posses the quality of (i) homogenous composition; (ii) acceptable flowability; (iii) sufficient compressibility; and (iv) anti-adhesiveness. The most important prerequisite for these powder mixture/granulates is undoubtedly the ability to flow, due to its effect on product quality, especially dose and dosage form uniformity.

A comprehensive literature study on the flowability of powders revealed that flow is affected by physical properties such as molecular- and interparticle forces, particle size and size distribution, particle shape, particle density, surface structure of the particle, and particle packing geometry. Various flow tests are available to determine powder flow, each measuring a variety of the properties mentioned above, resulting in different flow results and a subsequent variation in the classification of powders.

Particle characterization of a wide range of pharmaceutical fillers through SEM and particle size analysis, indicated considerable differences between physical properties of the various fillers, which suggested significant differences in their flow behaviour. Flow tests were conducted determining the critical orifice diameter (COD); percentage compressibility (%C); angle of repose (AoR) and flow rate (FR) of the fillers in the absence and presence of a glidant (0.25% Aerosil® 200). The results confirmed the expected differences in flow obtained from the various tests, with no one of the fillers achieving the same flow behaviour in all the tests. The difference in flow amongst the fillers for a specific test could, to a large extent, been correlated with specific physical properties of the particles within the powder bed.

COD results illustrated the influence of particle size and shape and surface structure on the flowability of these materials, with fillers with a smaller average particle size, less spherical shaped particles and uneven / rough surface structures performing poorer than their counterparts. The percentage compressibility (%C) of the materials was affected by the shape and size of the particles and the density of the materials, whilst the packing geometry also affected flow behaviour. Particles with high density and a low internal porosity tended to posses free flowing properties. Powders with a larger difference in the ratio between their respective bulk and tapped densities/volumes presented better flow results. The AoR of the fillers was affected by the cohesiveness and friction between the particles as well as the shape, surface structure and size of the particles. This method was less discriminative in terms of indicating differences in the flow of powders with comparable physical properties. A further drawback of this method was the variation in results between repetitions, which is

affected by the way the samples were handled prior to measurement. The flow rate (FR) of the fillers was predominantly affected by the density of the materials and the size, shape, and surface structure of the particles. Powders with a higher density seemed to exhibit a better flow rate, although some of the other factors affected the flow rate more when the densities were very close or identical. The following general rank order for the various fillers (as an average of their performance in all the tests) were established (with no glidant present): Cellactose® 80 > FlowLac® 100 > Prosolv® HD90 ≈ Ludipress® > Emcompress® >Avicel® PH200 > Starlac® >> Emcocel® 50M ≈ chitosan >> lactose monohydrate. Addition of a glidant failed to change the rank order significantly.

During the final stage of the study an attempt was made to modify and/or refine the composite flow index (CFI) proposed by Taylor *et al.* (2000:6) through (i) inclusion of flow rate results in its computation and/or (ii) varying the contribution (percentage) of each test to the CFI (Taylor & co-workers used equal contributions, namely 33 ⅓ %, in their calculation of the CFI). The results indicated that including the results from the flow rate test was not beneficial in terms of providing a more representative CFI (in fact it reduced the accuracy of the index). Next various weight ratios for COD, %C and AoR was used to determine the CFI of each filler, and an optimum ratio was found at 50%:40%:10% (COD:%C:AoR) resulting in the highest CFI for each powder and the widest range for the CFI (largest difference between minimum and maximum values). This ratio was found in the presence and absence of a glidant. At this ratio the CFI discriminated well between the different powders in terms of their flowability. Lastly, the flowability scale for powders as used by the USP (20007:644) for %C and AoR results was adapted and fitted on the CFI results obtained for the various powders. This scale provided an exceptional fit for the powders both in the absence and presence of a glidant) and offered an excellent means for the grouping and classifcation of powders based on their CFI.

Keywords: Powder flow, percentage compressibility, critical orifice diameter, angle of repose, flow rate, pharmaceutical fillers, composite flow index

UITTREKSEL

Die primêre voorvereistes vir poeier mengsels / granules bestem vir tabletering is: (i) 'n homogene samestelling; (ii) aanvaarbare vloei; (iii) voldoende samepersbaarheid; en (iv) anti-kleefbaarheid. Die belangrikste voorvereiste vir die poeier mengsels / granules is waarskynlik die vermoë om te kan vloei, as gevolg van die effek daarvan op produkkwaliteit, veral dosis- en doseervorm-uniformiteit.

'n Omvattende literatuur studie oor die vloeibaarheid van poeiers het getoon dat vloei beïnvloed word deur 'n wye verskeidenheid fisiese eienskappe soos: molekulêre- en interpartikulêre kragte, deeltjiegroottes en grootteverspreiding, deeltjievorm, deeltjiedigtheid, oppervlakstruktuur van die deeltjies en deeltjiepakking. Daar is verskeie vloeitoetse wat elk verskeie van die bogenoemde eienskappe gebruik om poeiervloei te meet en gevolglik kan vloeiresultate en die klassifisering van die poeiers verskil.

Karakterisering van 'n wye reeks farmaseutiese vulstowwe deur SEM en deeltjiegrootte-analise het merkbare verskille tussen die fisiese eienskappe van die stowwe aangetoon wat op betekenisvolle verskille in hul vloei kan dui. Die vulstowwe is aan vier verskillende vloeitoetse onderwerp, naamlik kritiese openingsdeursnee ("critical orifice diameter" [COD]), persentasie saampersbaarheid (%C), rushoek (AoR); vloeitempo (FR); en die vloeibaarheid sonder, en met 'n glymiddel (0.25% Aerosil® 200) is sodoende gemeet. Die verwagte verskille in vloeibaarheid tussen die verskillende poeiers is deur die resultate bevestig deurdat nie een van die poeiers dieselfde vloeigedrag getoon het vir die verskillende toetse nie. Die verskil in die vloei tussen verskillende vulstowwe vir 'n spesifieke toets korreleer tot 'n groot mate met die fisiese eienskappe van die deeltjies in die betrokke poeier.

COD-resultate het die invloed van deeltjiegrootte, -vorm en oppervlakstruktuur op die vloeibaarheid van die poeiers bevestig. Vulstowwe met 'n kleiner gemiddelde deeltjiegrootte, minder sferiese vorm en ongelyke / growwe oppervlakstruktuur vertoon swakker vloei in vergelyking met poeiers met groter, gladder en ronder deeltjies. Die %C van die poeiers is geaffekteer deur deeltjievorm en -grootte, digtheidsverskille en die pakking van die deeltjies. Deeltjies met hoë digthede en lae interne porositeit het beter vloeibaarheid vertoon. Poeiers met betekenisvolle verskille in die verhouding tussen hul waarskynlike en pakkingsdigthede het ook beter vloeiresultate getoon. Die AoR van vulstowwe is beïnvloed deur die kleefbaarheid en wrywing tussen die deeltjies asook die oppervlakstruktuur, deeltjiegrootte en -vorm. Die metode was minder akkuraat (diskriminerend) in terme van identifisering van verskille tussen poeiers met vergelykbare fisiese eienskappe. 'n Verdere nadeel van die AoR-metode is die relatiewe groot variasie tussen herhalings (hoë standaardafwykings), wat

waarskynlik beïnvloed word deur die wyse waarop die poeiermonsters hanteer is voor toetsing. Die vloeitempo (FR) van die poeiers is hoofsaaklik deur die dighteid van die poeiers, vorm, grootte en die oppervlakstruktuur van die deeltjies beïnvloed. Poeiers met hoër dighede het beter vloeitempo's getoon, alhoewel van die ander faktore 'n groter invloed gehad het in die geval van vergelykbare poeierdigthede. Die volgende rangorde vir die verskeie poeiers (as 'n gemiddeld van hul prestasie in al die toetse) is vasgestel (sonder 'n glymiddel): Cellactose® 80 > FlowLac® 100 > Prosolv® HD90 ≈ Ludipress® > Emcompress® >Avicel® PH200 > Starlac® >> Emcocel® 50M ≈ kitosaan >> laktose monohidraat. Byvoeging van die glymiddel het geen noemenswarrdige verandering in die rangorde tot gevolg gehad het nie, alhoewel dit tog die vloei van enkele poeiers verbeter het.

Tydens die laaste fase van die studie is gepoog om die saamgestelde vloei-indeks (CFI), soos ontwikkel deur Taylor *et al.* (2000:6) te verbeter deur (i) insluiting van die vloeitempo in die bepaling van die CFI en (ii) 'n verandering in die verhouding van die onderskeie toetsresultate vir 'n poeier in die berekening van die CFI (Taylor en medewerkers het gelyke gewigte, nl. 33.33%, aan elke toets toegeken). Die resultate het getoon dat insluiting van vloeitempo-resultate nie die CFI van die poeiers verbeter het nie (inteendeel swakker waardes is verkry). Verskeie verhoudings in die gewigte van COD, %C en AoR vir die berekening van die CFI is getoets om vas te stel watter verhouding 'n "optimum" CFI vir elkeen van die vulstowwe lewer, en daar is gevind dat die verhouding 50%:40%:10% (COD:%C:AoR) die beste waarde vir elke individuele poeier lewer (met identitiese resultate vir beide poeiers sonder en met 'n glymiddel), en dat hierdie verhouding ook die beste diskriminerend was ten opsigte van onderskeid tussen die vloeibaarheid van die onderskeie poeiers. Laastens is die vloeibaarheidskaal van die USP op die CFI's van die poeiers getoets en is daar gevind dat hierdie klassifikasiesisteem uiters geskik is vir toepassing om poeiers, op grond van hul CFI, te groepeer en te klassifiseer.

Trefwoorde: Poeiervloei; persentasie samepersbaarheid, rushoek; kritiese openingsdeursnee; vloeitempo; farmaseutiese vulstowwe; saamgestelde poeiervloei-indeks.

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CHAPTER 1

Significance of pharmaceutical excipients and their characteristics

1.1 Introduction

The manufacturing of pharmaceutical dosage forms is quite a complex and an interesting process. A thorough knowledge of the active ingredient and of the pharmaceutical excipients is essential to obtain the best results of the prepared dosage forms. The reason is that some patients prefer solid dosage forms like tablets and capsules to other invasive methods like injections, because of the pain and stress associated with it. Therefore, it is not remarkable that tablets account for up to 80% of all dosage forms administered to man (Jivraj *et al.*, 2000:58). Other reasons why tablets are popular are (i) the oral route represents a convenient and safe way of drug administration; (ii) compared to liquid dosage forms, tablets have general advantages in terms of the chemical and physical stability of the dosage form; (iii) the preparation procedure enables accurate dosing of the drug; (iv) tablets are convenient to handle and can be prepared in a versatile way with respect to their use and to the delivery of the drug; (v) tablets can be mass produced, with robust and quality-controlled production procedures giving an elegant preparation of consistent quality and, in relative terms low price (Alderborn, 2002:398). The research and development of pharmaceutical excipients helped and will help to improve the use of solid dosage forms even further.

In solid dosage forms, the active ingredient makes up a small percentage of the final dosage form weight. This varies according to the dosage needed and the dosage forms (tablets and capsules). For example, a 100 mg tablet can contain 2% active ingredient. The active ingredient then only constitutes 2 mg and the other 98 mg is made up of other powders (glidants, fillers, disintegrants etc.). The disintegration and dissolution of the dosage form are therefore, mostly dependent on the powders used in the formulation of the solid dosage form. It consequently affects the bioavailability of the dosage form and is especially important to manufacture the solid dosage form, from the best-suited powder.

The flow behaviour of powders is an important factor during the manufacturing of solid dosage forms. The correct filling of a die is dependent on the flow behaviour of the pharmaceutical mixture. If the flow behaviour of the mixture is poor, the incorrect amount will flow into the die and result in tablets with variations in mass (tablet weight uniformity) and the tablet will contain less of the active ingredient that is required to achieve the desired pharmacological effect. There are many pharmaceutical materials available on the market and selecting the correct one to shorten the research and development time of a solid

dosage form is a necessity and a difficult process. Formulation scientists choose and develop powders (fillers, disintegrants, etc.) according to the active ingredient's properties (sensitivity to water, other materials or light, etc.) and various other factors (flow behaviour, ease of use, manufacturing of the material and quantity availability) needed.

It is essential that an accurate assessment of the flow properties be made as early in the development process as possible so that an optimum formulation can be identified (Taylor *et al.*, 2000:2). Presott *et al.* (2000:60) found that during formulation development, the flow of a blend may affect excipient selection and may dictate whether direct compression is used or some form of granulation is required. It is clear that the early identification of inferior and/or superior materials is necessary to save time, money and most importantly, lives.

Many experiments and studies were conducted to determine and measure the flow characteristics of powders and as a result, there are numerous ways of classifying the flow behaviour, such as angle of repose, flow rate, percentage compressibility (Carr's compressibility index), Hausner's ratio, shear cell method and critical orifice diameter. The test methods utilise different characteristics of powders to classify flow. Comparisons between the powders can therefore be quite difficult, but is crucial to determine the best-suited powder for a solid dosage form.

1.2 Importance of powder flow

The definition of powder flowability is the ability of a powder to flow and powder flow can be defined as the movement of powder particles under a force (gravity or centrifugal force). Important prerequisites for a mixture intended for tabletting are (i) homogeneity and poor segregation tendencies; (ii) flowability; (iii) compression properties and compactability; and (iv) minimal friction and adhesion properties of the materials (Alderborn, 2002:402). Powders are composed of solid particles of the same or different chemical compositions (co-processed materials) having equivalent diameters less than 1000 µm. Tablets are manufactured by forcing these powder particles into close proximity to each other by powder compression. Powder compression is defined as the reduction in volume of a powder owing to the application of force (Alderborn, 2002:398). Powders can be directly compressed or wet granulated and then compressed to form tablets. Tablets are, therefore, powder mixtures of active ingredients and pharmaceutical excipients that were forced together.

A tablet press is used to manufacture these tablets. There are two types of tablet presses (single-punch press [figure 1.1] and the rotary press [figure 1.2]), but they follow the same basic concept of forcing powder particles together forming tablets. The process of tabletting can be divided into three stages, generally referred to as the compaction cycle (figure 1.3).

The first stage in the process is die filling. This process is accomplished by the gravitational flow of the powder from the hoper via the die table into the die (although presses based on centrifugal die filling are also used). The die is closed on its lower end by the lower punch. The second stage in the process is the tablet formation. The upper punch descends and enters the die and the powder is compressed until a tablet is formed. During the compression phase, the lower punch can be stationary or can move upward in the die. After the maximum applied forces are reached, the upper punch leaves the powder, i.e. the decompression phase. The last stage in the process is tablet ejection. During this phase, the lower punch rises until its tip reaches the level of the top of the die. The tablet is subsequently removed from the die and die table by a pushing device (Alderborn, 2002:399). However, if a material is cohesive and exhibits no form of flowability, it diminishes the process's ability to manufacture the tablets.

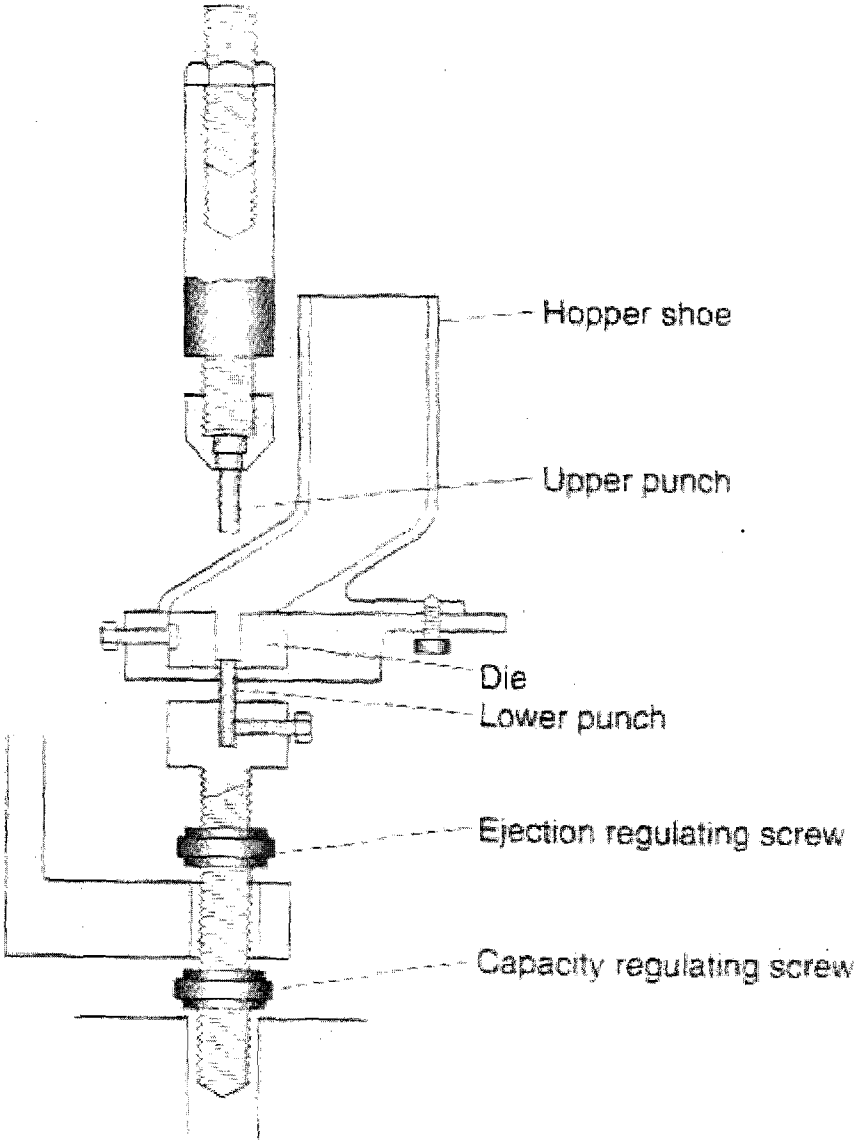


Figure 1.1: A single punch tablet press (Alderborn, 2002:400).

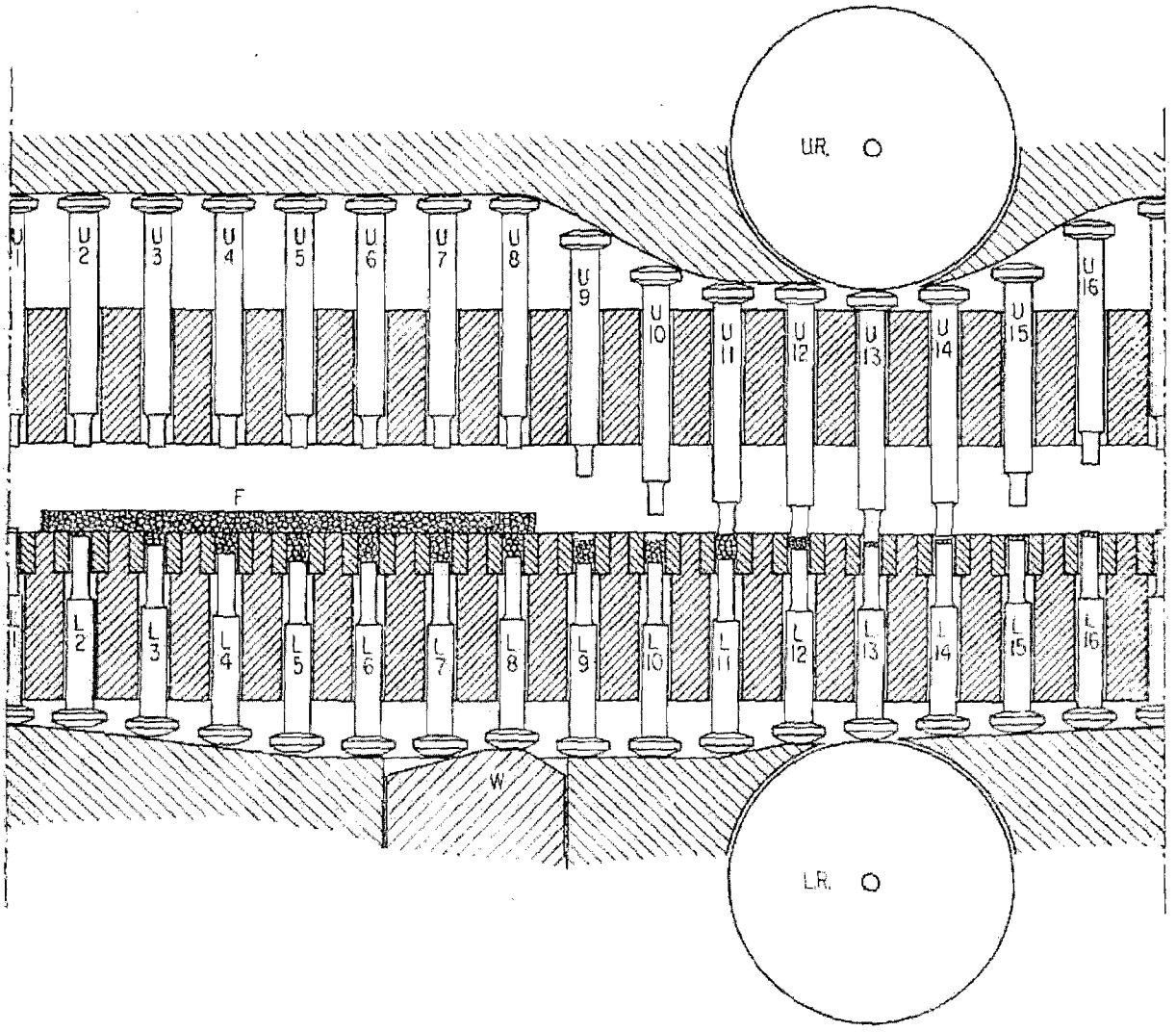


Figure 1.2: Diagram of punch tracks of a rotary tablet press. UR, upper roller; LR, lower roller; W, powder volume adjuster; F, feed frame with granules. U1 to U8, upper punches in raised positions; L1, lower punch at top position, tablet ejected; L2 to L7, lower punches dropping to lowest position and filling the die with granules to an overfill at L7; L8, lower punch raised to expel excess granules giving correct volume; U9 to U12, upper punches lowering to enter die at U12; L13 and U13, upper and lower punches pass between rollers and granules are compacted to a tablet; U14 to U16, upper punch rising to top position; L14 to L16, lower punch rising to eject tablet (Alderborn, 2002:401).

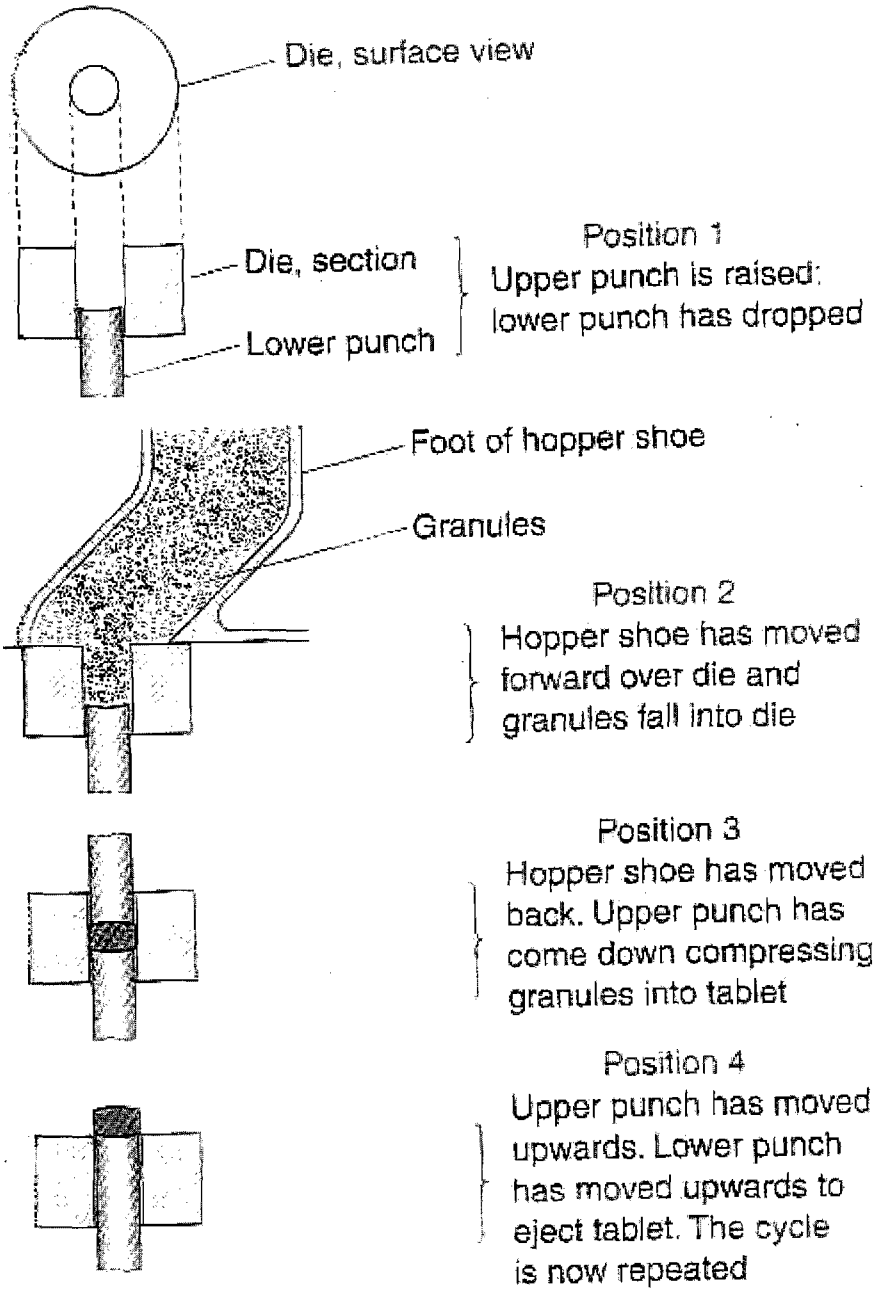


Figure 1.3: The various stages in the formation of tablets (Alderborn, 2002:399).

In tabletting applications, powder with a high degree of flowability offers several advantages: (i) a smooth downward flow of material will minimize air-pocket formation. (ii) The dosage chamber may be filled very accurately, which not only increases average weight and decreases variation in average weight coefficient but also creates even pressure during compression, thereby lessening wear on machine parts. (iii) Flowable powder increases the reproducibility of feed parameters, which results in consistent tablet hardness, friability, dissolution rates and blood levels. (iv) During compression, air is expelled well because of the powder's high degree of permeability, a quality that helps eliminate such tablet flaws as capping and splitting. (v) Finally, high production speeds may be maintained (Gioia,

1980:65). The flow behaviour of a powder is therefore important to keep the manufacturing process going and to ensure that the process does not come to a stop. To understand the flowability of pharmaceutical excipients, it is necessary to understand the different factors which affect their flow.

1.3 Characteristics of powders

The characteristics of powders affect the flow behaviour, therefore affecting the way in which it behaves while being handled and prepared for the manufacturing of the dosage forms. Some of the properties that have an effect on the flow behaviour are molecular- and interparticle forces, particle size, particle shape, particle density, surface structure of the particle and particle packing geometry. Other factors that might affect the flow behaviour are environmental factors (humidity and temperature) in which the powders are stored or in the production area.

1.4 Effect of powder properties on powder flow

1.4.1 Molecular forces and interparticle forces

Particles of powders have molecular and interparticle forces like most other materials. During handling operations, powder particles come in contact with various surfaces and become charged by the process known as tribo-electrification (Bailey, 1984:72). The molecular and interparticle forces inhibit as well as aid the flow behaviour of powders. Intermolecular forces including van der Waals forces, local chemical bonds, electrostatic charges, bridging forces and surface liquid capillary attractions mainly cause interparticle adhesion. These forces are strongly affected by the surface properties such as texture, surface chemistry, adsorption layers, and contact area. For larger particles, gravity and inertia are generally greater than the interparticle adhesion force, hence they normally flow easily. For fine particles (less than 10 μm), the interparticle adhesion force is appreciable relative to gravity. Therefore, they tend to adhere to one another and are problematic to handle (Li *et al.*, 2004:78).

The hoppers and feeders of tablet presses are typically made from metals like stainless steel or other metal alloys. Metals are good conductors of charge. Charged particles experience attractive forces to metallic surfaces and may adhere firmly to these surfaces especially if powder resistivity is high (Bailey, 1984:84). When powder mixtures are poured into a hopper, and the powder particles are allowed to flow, it can cause friction between the particles which can lead to the particles becoming electrically charged. This can cause the particles to be strongly attracted to one another and to the surface of the hopper. The adherence of particles to one another and/or to the surfaces of hoppers and bins negatively

affect the flow behaviour of powders, slowing down the manufacturing process. Although molecular and interparticle forces are relatively small, it they still affect the flow of powders.

1.4.2 Particle properties

1.4.2.1 Particle size

A powder is made up of many particles. The particles in a powder are not always of the same size and can therefore have many different particle sizes. By sieving the powder, powder fractions may be obtained that are of the same size. The size of a particle will affect the way the particle behaves during powder flow. The smaller or more fine the particle size of a powder, the more it tends to stick to other particles and to sides of hoppers and bins. This is due to the attractive forces between the particles. During powder flow the particles move closer together which causes stronger attractions between the particles which render the powder to be more cohesive. The smaller the particle the smaller the distance between the particles. Interparticle forces are therefore stronger and particles are attracted more strongly to one another. These powders exhibit poor flowability due to the cohesion force arising mainly from van der Waals attraction (Yang *et al.*, 2005:21). The origin of van der Waals forces is a molecular interaction due to various polarisation mechanisms. Polarisation of atoms and molecules in materials are inherent to all materials; there are little dependence upon the externally imposed conditions. Because of their relatively short interaction range, the overall magnitude of van der Waals forces on a particle can be highly sensitive to the microscopic surface structures (Feng *et al.*, 2003:65).

The opposite is true of larger particles. The distances between the larger particles are larger because of their relative size and the interparticle forces are therefore weaker, as the attractive forces are more distant between the particles. Bagster *et al.* (1985:16) found that large particles alone (say 4 mm) have greater strength than finer particles (say 1 mm) of the same substance, perhaps due to structural influence, while much finer particles (<500 µm) exhibit an increase in strength probably due to the cohesive properties of fine particles. Today it is well known that particles smaller than 100 µm exhibit strong interparticle attractive forces. Larger particles, therefore, flow more easily and freely than the smaller or fine particles because of their size.

1.4.2.2 Particle shape

The powder characteristic of particle shape is one of the important factors that affect the flow behaviour of powders. Powders are not all manufactured in the same way and therefore they have different properties. The particle shape is a derived property of the manufacturing process. Depending on the shape of the particle, the powder will either flow freely or poorly.

Powder particles exhibit different shapes. The following defines some commonly used descriptors of particle shape: acicular, columnar, flake, plate, lath and equant (British Pharmacopoeia [B.P.], 2007:A408); and spherical, non-spherical, needle, splinter and fibrous (figure 1.4 and 1.5).

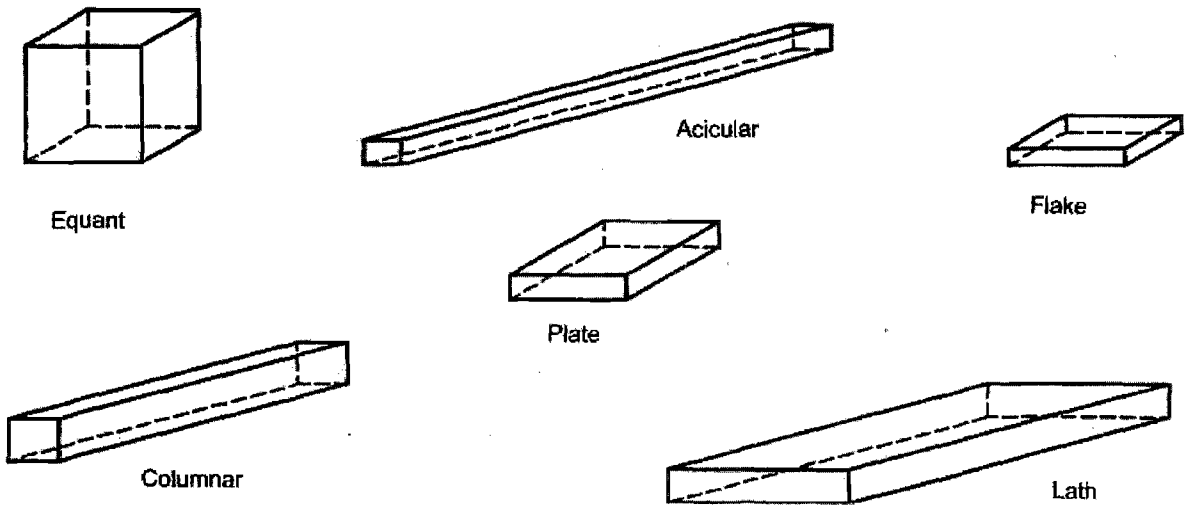
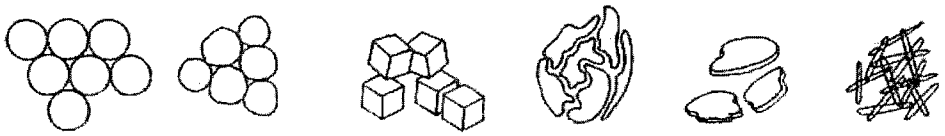


Figure 1.4: Commonly used descriptions of particle shapes (B.P., 2007:A409).



(1) (2) (3) (4) (5) (6)

Figure 1.5: The general shapes of particles: (1) spherical; (2) oblong; (3) cubed; (4) irregular (5) flake; and (6) fibrous (Lantz *et al.*, 1990:40).

Particles with different shapes behave differently during the flow of the powder. Spherical particles will flow the best where as non-spherical particles will flow more poorly. There is friction between the particles in a powder bed. This causes the powder to flow poorly. Large particles are often already freely flowing without a glidant, and therefore the addition of a glidant will not lead to major improvement, if any, of powder flow. While the friction properties depend more on the asymmetry or elongation of the particles, powder flow depends more on the geometric shape. For unlubricated powders, the flow factor increases from needle shape, cubic, angular to spherical particles. However, at an optimal glidant concentration needle shaped particles can provide similar flow properties to spherical particles, because the surface structure of such particles is less than that of angular shaped particles (Podczeck *et al*, 1996b:194).

1.4.2.3 Particle surface

Another property of powders that affects its flow is the surface structure. The surface structure of the particle is not only in contact with the other particles of the powder, but also with other excipients and to the walls of the bins and hoppers. Smooth surfaced particles will flow more easily and freely than rough surfaced particles, because the rough surfaces grind and budge against one another which causes friction. These particles will, therefore, not flow freely. The surfaces of most powders contain a unique distribution of peaks and valleys depending on the structure, or the type of processing used (Narayan *et al.,* 2003:26). One of the ways to observe the surface structure is by scanning electron microscopy (SEM). SEM provides qualitative information about the variations on the surface structure within a 2D image (Narayan *et al.,* 2002:26). These photomicrographs provide information on the particles surface structure as well as possible particle-particle interactions.

1.4.2.4 Particle density

The density of a powders is its mass divided by the volume it occupies. This density is known as the bulk density of the powder. Abdullah and Geldart (1999:151) also referred to bulk density as the mass of a powder that can be packed into specific volume which includes the spaces between particles as well as the volumes of the particles themselves.

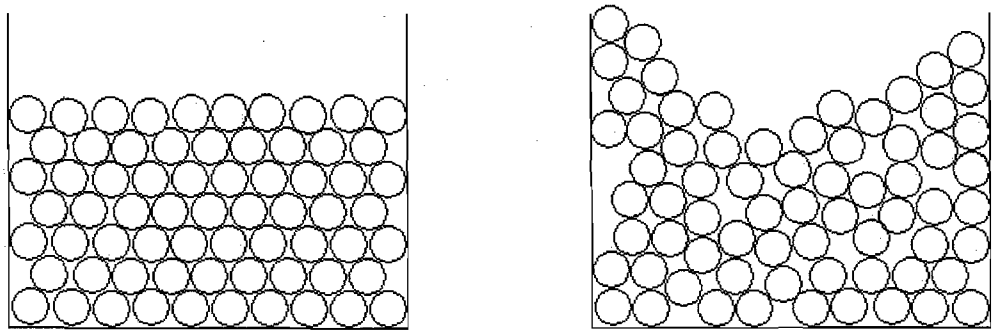
The aerated bulk density (*random loose packing*) of a powder is determined by allowing the dispersed powder to settle in a container under the influence of gravity. A powder with a strong structural strength will resist collapse when dispersed in a container and will have a low bulk density, while a structurally weak powder will collapse easily and have a high bulk density (Harnby *et al.*, 1987:881). High friction between the particles results in a low apparent bulk density. With decreasing friction, the bulk density increases. Aerated bulk density of a powder changes when the powder is handled during transport and processing. Tapped density (*random dense packing*) is obtained by tapping or vibrating the container holding the aerated sample. The structure of a cohesive powder will collapse significantly on tapping while the weak (uncohesive) or free flowing powder has little scope for further consolidation. The powder particles are forced to jump and to lose contact with each other for a moment while tapping. When there is reduced friction between the particles, the particles rearrange and thus tapping results in improved packing conditions (Adullah *et al.*, 1999:151). It is clear that the volume of a cohesive powder will change considerably when compared to a free flowing powder. The volume of the free flowing powder will change slightly if at all.

Mohammadi *et al.*, (1997:1) stated that for large particles the weight of the particle will be large compared to the structural strength of the powder and individual particles will be movable, which will ensure a free flow bulk characteristic, and a high-aerated bulk density within the container. For smaller particles, the weight of the particle is comparable to, or smaller, than the structural forces within the bulk powder and individual particles lose their mobility. This results in a cohesive bulk powder and small-aerated bulk density within the container.

1.4.2.5 Packing geometry

The packing of powders is an issue of great concern to industry, because the packing structure directly influences powder compaction and powder flow, which must be controlled during tablet manufacture in order to produce a high quality product (Fu *et al.*, 2006:134). Podczeck *et al.* (1996c:41) stated that the packing properties of powders are very important in the production of solid dosage forms such as tablets or capsules. For example, in capsule filling it is desirable to be able to fill powders or granules into capsules of smaller sizes such as size 1 (0.50 ml), 2 (0.37 ml) or 3 (0.30 ml), even if the required fill weight of the formulation is rather large. To attain this volume the powder's tapped density must be able to change. Low compression of the powder into the capsule is used to achieve this (Podczeck *et al.*, 1996a:101). It is, therefore, important to understand the particle packing of powders and what effect it has on the flow of a powder.

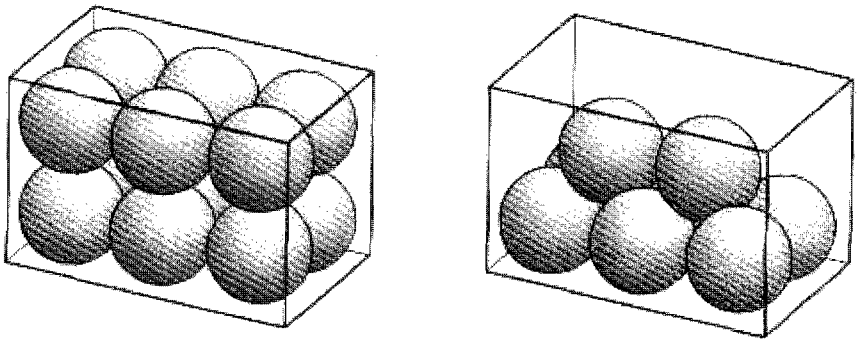
There are two types of packing, namely ordered and random (figure 1.6). Ordered packing occurs where the particles occupy specific sites with respect to each other such that long-range order exists as in a crystal structure. On the other hand, random packing is the packing of particles without order and can be subdivided into two types, based on the procedure used in assembling the packing, namely, random dense packing and random loose packing. Random dense packing is defined as random packing where the particles have been agitated to attain the closest packing possible without introducing long-range order of deformation, and is equivalent to tapped bulk density (Abdullah *et al.*, 1999:151).



(1) (2)

Figure 1.6: (1) Ordered packing and (2) random packing of spherical particles.

Powder beds of uniform sized spheres can assume either one of two ideal packing arrangements: (i) closest or rhombohedral, and (ii) most open, loosest, or cubic packing (see figure 1.7). The theoretic porosity of a powder consisting of uniform spheres in a rhombohedral packing is 26% and 48% in a cubic packing. The particles in real powders are neither spherical in shape nor uniform in size (Martin *et al.*, 1993:443).



(1) (2)

Figure 1.7: Different geometric packings of spherical particles (1) cubic packing and (2) rhombohedral packing (Staniforth, 2002:201).

The packing of powders is affected by particle size, particle shape, surface structure of the particle, density of the powder and handling of the powder. The more densely packed the particles are, the more difficult it will be for the powder to flow freely. Therefore, more force or alterations to the powder mixture will be needed to obtain acceptable powder flow.

The properties of particles (particle size, shape and surface structure area of a particle, density and packing geometry) of a powder all contribute to the behaviour of the powder

during powder flow. All of these properties have to be taken into account when studying powder flow.

1.5 Other factors affecting powder flow

Other factors which affect the flow behaviour of powders are humidity and temperature. Temperature has an indirect effect on powder flow whereas humidity more directly affects the flow of a powder.

Powders are stored in silos and bins before being used in the manufacturing process. When the storage temperature is at a level where it changes the physical properties of the material, these changes could affect the flow behaviour of the powder.

Air at a given temperature is capable of taking up water vapour until saturated (at 100% relative humidity). It is a simple solution of water in air that follows the rules of most solutions – such as increased solubility with increasing temperature, a maximum solubility at a particular temperature (saturation) and precipitation of the solute on cooling (condensation). This relationship shows that the relative humidity of air is dependent not only on the amount of moisture in the air, but also on its temperature, as the amount of water required to saturate air itself is dependent on temperature (Aulton, 2002:381). Therefore, the higher the temperature (i.e. water vapour can only be taken up into the air until saturation), the higher the moisture content and thus the higher the relative humidity. The moisture content of a powder affects the way the powder behaves during flow. As the relative humidity of the surrounding air is increased, powders tend to absorb water; liquid bridges may form between powder particles which result in an increase in powder cohesion and reduced flow. On the other hand, as relative humidity decreases, the powder tends to desorb water, and liquid bridges will disappear (Teunou *et al.*, 1999:109).

Faqih *et al.* (2007:344) and Teunou *et al.* (1999:115) found that an increase in the relative humidity, decreased the flowability of the powders tested, but the flow behaviour was dependent on the type of powder used. The time a powder is stored at certain conditions can also affect the flow behaviour of the powder. Iqbal *et al.* (2006:278) demonstrated that the storage time under certain conditions affected the friction of the powders tested, which caused a change in the flow properties of the powder during use.

It can be concluded that a thorough knowledge of the micromeretrics of powders as well as other factors are needed to properly understand the effect on the flow behaviour of the powder.

1.6 Measuring of powder flow

The measurement of the flowability of powders is very important to the formulation scientist. He must choose the best-suited powder for the solid dosage form, and must, therefore, be able to compare the different powders. A way of comparing the different powders with one another is by measuring and testing the powder's flow. There are many methods of determining and measuring the flowability of a powder (i.e. angle of repose, Carr's compressibility index, Hausner's ratio, flow rate through an orifice, shear cell, critical orifice diameter) and variations to these methods. Sinka *et al.* (2004:28) adds that a vast amount of research was undertook to develop experimental techniques suitable for characterising the flow properties of powders. All of these flow tests are affected by different properties of particles.

1.6.1. Angle of repose

The angle of repose is one of the most commonly used methods to evaluate and compare the flow of powders. Angle of repose is a characteristic related to inter-particulate friction or resistance to movement between particles (United States Pharmacopoeial Convention [USP], 2007:644), and is dependent on the friction between the particles in a powder bed. The test is preformed by discharging an amount of powder through a funnel from a constant height onto a smooth surface resulting in a powder cone. The surface of the structure plays an important role in the accuracy of the results. It is important to choose the correct surface for this experiment. The surface must not be too smooth nor too rough. When the surface is too smooth or too rough, the heap will not form accurately. To overcome this problem the USP (2007:644) suggested that a base of poured powder is formed on which the heap will form. The cone forms by particles stacking on top of one another. The particles stack until the approach angle of the subsequent particles joining the stack is large enough to overcome friction, and they slip and roll over each other until the gravitational forces balance the interparticle forces thus forming a powder cone (Staniforth, 2002:200).

The angle of repose is the angle between the horizontal base and the slope of the powder cone. The angle of repose can be determined by measuring the height of the heap of powder and horizontal base of the powder and then determining the angle using the tangent equation (figure 1.8). Many different methods are used to determine the angle of repose. The fixed height-, fixed base-, tilting table-, rotating cylinder-, ledge-, crater- and platform methods are used (Staniforth, 2002:206).

Table 1.1: *Flow properties and corresponding angles of repose (USP, 2007:644)*

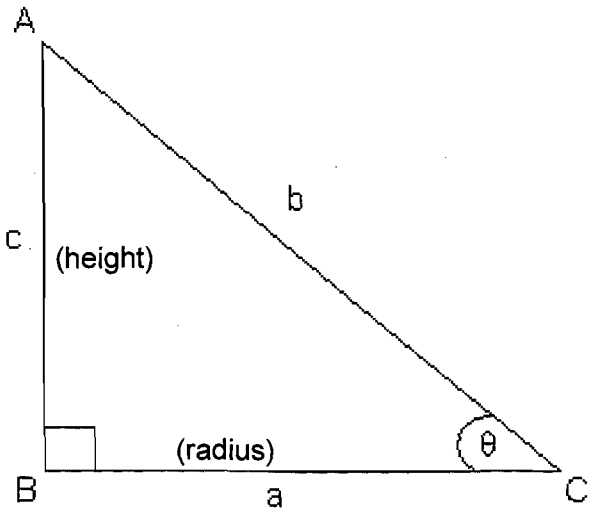


Figure 1.8: Triangle to illustrate tangent equation.

The angle C (θ) is determined by using equation 1.1:

$$\text{Tan } \theta = \frac{\text{opposite side (c)}}{\text{adjacent side (a)}} = \frac{\text{height of the cone (mm)}}{\text{radius of the cone (mm)}} \qquad \text{[Eq. 1.1]}$$

The angle of repose is similarly calculated to the tangent of the triangle. The height of the powder cone is equivalent to opposite side of the triangle (c) and the radius of the powder cone is equivalent to the adjacent side (a).

The recommended procedure according to the USP (2007:644) is to form a fixed layer of powder particles with a retaining lip. The base should be free of vibration. Care should be taken to prevent vibration as the funnel is moved. The funnel height should be maintained approximately 2 - 4 cm from the top of the powder pile as it is being formed in order to minimize the impact of falling powder on the tip of the cone or heap. Care should also be taken that there is no breeze, which can affect the way the powder cone is formed. The smaller the angle of repose, the better the flow of the powder. As a general guide, the powders with angles of repose greater than 50° have unsatisfactory flow properties, whereas minimum angles close to 25° correspond to very good flow properties (Staniforth, 2002:207). See table 1.1 for the flow properties according to angle of repose as defined by the USP.

Table 1.1: *Flow properties and corresponding angles of repose (USP, 2007:644)*

Flow property	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

1.6.2. Carr's compressiblitly index (Percentage compressiblitly)

The first methods used to determine and attach a measurement to the flow of a powder were Carr's compressibility index (percentage compressibility) and Hausner's ratio. Carr compared interparticle cohesive properties with angle of repose measurements and the effects of packing geometry of solids with bulk and tap density measurements. He found that the density of a powder depends on the particle packing and that density changes as the powder consolidates (Taylor *et al.*, 2000:1). The Hausner ratio also used the changes in density to classify the flow of a powder. The change in the bulk density measured as the ratio between the tapped and the aerated bulk density is known as the Hausner ratio. It is an indication of the incremental, volumetric, structural and/or increasing external forces (Harnby *et al.*, 1987:881).

There are some variations in the methods used to determine Carr's compressibility index. A certain mass of powder is poured into a graduated cylinder and the aerated volume is noted. The cylinder is then tapped and the final tapped volume is taken. Flowability of the powder is calculated from these results. The recommended procedure according to the official pharmacopoeias is to measure the unsettled apparent volume and the final tapped volume of the powder after tapping the material until no further volume changes occur. A 250 ml graduated cylinder is used and a mass of 100 g is recommended (USP, 2007:645). The bulk density of the powder (ρ_b) is determined by using equation 1.2.

$$\rho_b = \frac{\text{Weight of 100 ml of material (g)}}{\text{Bulk powder volume (ml)}} \qquad \text{[Eq. 1.2]}$$

Tapped density (ρ_t) of the powder is determined by using equation 1.3.

$$\rho_t = \frac{\text{Weight of 100 ml of material (g)}}{\text{Tapped powder volume (ml)}} \quad \text{[Eq. 1.3]}$$

The percentage compressibility is calculated using equation 1.4.

$$\% \text{ Compressibilty} = \left[1 - \frac{\rho_b}{\rho_t}\right] \times 100 \quad \text{[Eq. 1.4]}$$

Hausner's ratio is determined by substituting the bulk density (ρ_b) and tapped density (ρ_t) (calculated from equation 1.2 and 1.3 respectively) of the powder in equation 1.5.

$$\text{Hausner ratio} = \frac{\rho_{\text{tapped}}}{\rho_{\text{bulk}}} \quad \text{[Eq. 1.5]}$$

Considerations that have to be taken into account is the diameter of the cylinder used, number of times the powder is tapped to achieve the tapped density, the mass of material used in the test and rotation of the sample during tapping. Instead of using the apparent bulk and tapped density of the powder, the bulk- and tapped volume can be used in the equations. The smaller the compressibility index and Hausner ratio, the better the powder flow (table 1.2).

Table 1.2: *Scale of flowability (USP, 2007:645)*

Compressibility index (percent)	Flow character	Hausner ratio
1 – 10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very poor	1.46 – 1.59
> 38	Very, very poor	>1.60

1.6.3. Flow rate

The flow rate of a powder through an orifice is one of the most uncomplicated and simplest methods to determine the flowability of a powder. Gravitational flow of granular particles is encountered most commonly with powder handling and storage, and during tablet preparation. The discharge of particles from hoppers generates flow, which behaves like a viscous liquid in laminar flow (Khanam *et al.*, 2005:30). This behaviour of powder, led to the development of the flow rate method. The flow rate of a powder is determined by measuring the time it takes for a mass of powder to flow from a hopper or feeder through a well-defined orifice under the force of gravity. There are two variations used to measure the flow of the powder, namely the hopper flow rate and the recording flow meter.

A recording flow meter is similar to the hopper flow rate in which the powder is allowed to flow freely from a hopper but the powder falls onto a balance. The balance is connected to a recording device or computer. A recording device or computer captures the mass of powder that fell onto the balance according to a certain time setting. Interval at which the mass of powder is measured is mostly every second, but can also be minutes. The flow rate of the powder can then be determined. Either the mass flow rate or volume flow rate can be determined. The considerations that have to be taken into account is the diameter and shape of the orifice, the type of container material (metal, glass, plastic) and the diameter and height of the powder bed (USP 2007:646).

The recommended procedure in the USP (2007:646) is for powders that have some capacity for flow. It is not useful for cohesive materials. If the height of the powder bed is much greater than the diameter of the orifice, the flow rate is then virtually independent of the powder head. This configuration results in a flow rate being determined by the movement of the powder over powder rather than powder moving along the wall of the container. The orifice should be circular and the cylinder should be free of vibration. Use of a hopper as a container may be appropriate and representative of flow in a production situation. It is not advisable to use a funnel, particularly one with a stem, because the flow rate will be determined by the size and length of the stem as well as the friction between the stem and the powder. A truncated cone may be more appropriate, but flow will be influenced by the powder wall friction coefficient. For the opening in the cylinder, use a flat bottom plate with the option to vary orifice diameter to provide maximum flexibility and to better ensure a powder-over-powder flow pattern. Rate measurements can be either discrete or continuous. Continuous measurement using an electronic balance can more effectively detect momentary flow rate variations. There is no scale or index available because flow rate is critically dependent on the method used to measure it (USP 2007:646).

1.6.4. Critical orifice diameter

Critical orifice diameter is a method that employs a cylinder with a series of interchangeable base plate discs that have different diameter orifices. In order to carry out measurements of critical orifice diameter, the powder is poured into the cylinder. The shutter is removed and the powder is allowed to flow. The critical orifice diameter is the size of the smallest orifice in a base plate disc through which the powder in a cylinder will discharge (Taylor *et al.*, 2000:2). Gioia (1980:66) used this method to determine and compare the flowability of powders. There are many variations on this method. It is a direct measure of powder cohesiveness and arch strength. Two types of flow are generally obtained namely funnel flow and mass flow (see figure 1.9). Funnel flow is defined by Presott *et al.* (2000:64) as an active flow channel that forms above an outlet with non-flowing at the periphery; and mass flow is where all of the powder is in motion.

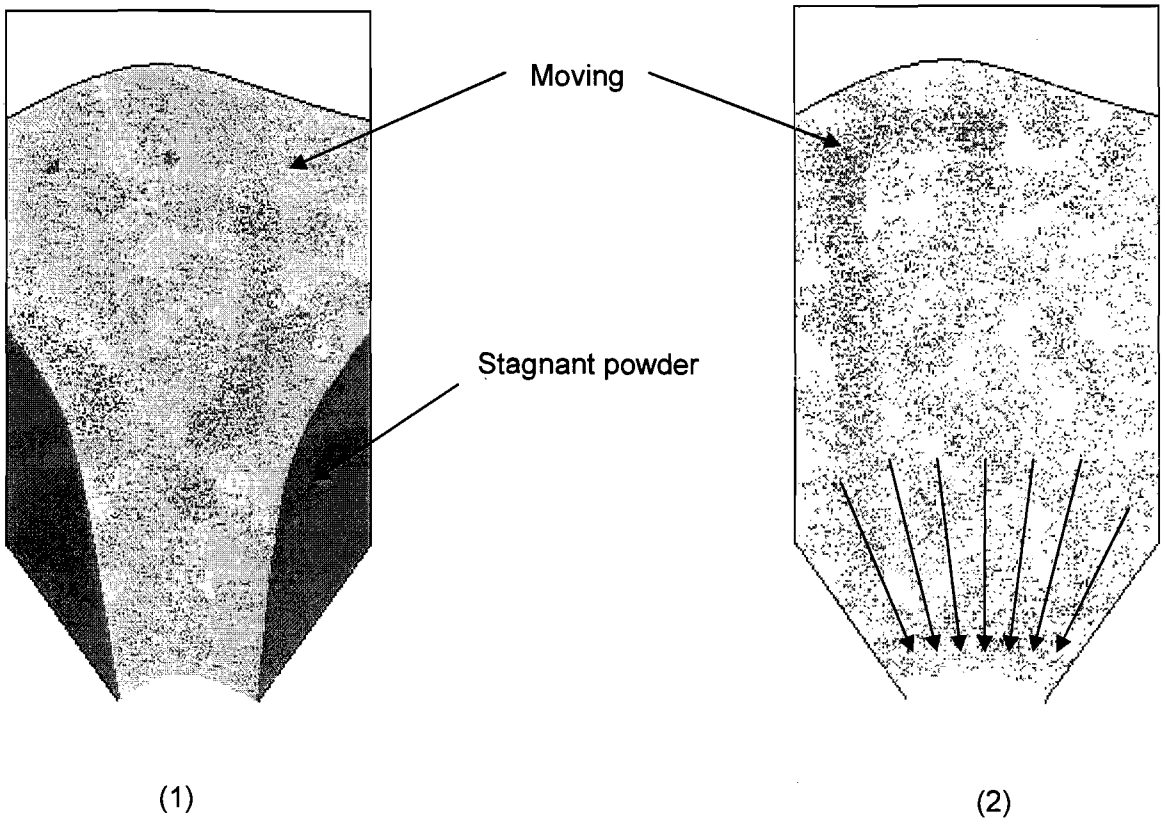


Figure 1.9: (1) Funnel flow and (2) mass flow (Prescott *et al.* 2000:64).

There is no index available for critical orifice diameter to distinguish between excellent, good, average and poor flowing powders. It is therefore up to the formulation scientist to determine a scale which ranks powders in terms of flow. It's generally accepted that free flowing powders will flow through the smallest critical orifice diameter, while more cohesive powders

will flow through larger critical orifice diameters. Critical orifice diameter is used more regularly because of its efficient and accurate measurement of powder flowability.

1.6.5. Conclusion

The different flow tests utilise various properties of powders to obtain results. By perhaps incorporating the various flow tests into one composite index, better and more "true" results of the flow of powders might be obtained.

1.7 Comparing powders and powder flow

Powders are compared with respect to constituents, sizes and shapes and are then classified according to those properties. Powders are also classified and compared, by its intended use (as a filler, glidant, disintegration etc.). It has been difficult to compare powders and their powder flow with one another because the methods to determine powder flow uses different properties to define powder flow. As a result a formulation scientist will have difficulty in comparing a powder that was tested with the angle of repose method with the flow rate method. The different methods used to classify the powder flow of the different powders, each tests different properties of the powder, even though all of the properties contribute and affect the flow of the powder.

Good flow properties are critical to the successful development of any pharmaceutical tablet or capsule formulation. It is essential that an accurate assessment of flow properties be made as early in the development process as possible so that an optimum formulation can be quickly identified. Costly, time-consuming studies of poor candidates can then be avoided. Although most of these simple tests are related to the flow of dry materials, through bins, hoppers, and feeders, and are especially relevant to the formulation scientist, individual powder flow tests will challenge only one or two components of the complex phenomenon known as flow (Taylor *et al.*, 2000:2). Therefore, a composite index for the flow of powders will be the best way to compare the different powders and to classify them accordingly.

1.8 Composite flow index

An index is defined as a guide to list objects or materials according to their features or properties in order to simplify comparisons between them. Carr's index (Carr, 1965:163) is an example of an index for pharmaceutical excipients which aid in classifying them in terms of their flowability. To classify and compare pharmaceutical excipients using an index, they must have common properties which would make a classification possible.

Using various flow tests described in the previous sections, individually to compare and classify powders may, however, present some problems due to the fact that the various tests could present conflicting results, i.e. a certain powder may indicate a certain level of flowability according to the results of a specific test, but a total different flow level according to the results obtained from another test. One of the reasons for these conflicting observations from the results of the different flow tests may be the fact that the various test results depend on different properties of a powder. For instance, the results of the test for angle of repose depend primarily on particle properties such as size, size distribution and surface structure, whilst the test for critical orifice diameter is more dependent on particle shape and density.

Taylor *et al.* (2000:6) came up with the idea that a composite index, which is constructed from the results of the various flow tests, might better characterise powder flow and present a more accurate parameter to compare and classify various pharmaceutical powders. Their basic approach in constructing such a composite flow index (CFI) was to use the results from three commonly employed flow tests, namely the angle of repose, percentage compressibility (Carr's index) and the critical orifice diameter and to transform these results to a new value, the CFI.

Taylor and co-workers (2000:6) assigned an arbitrary value of one-third (33 ⅓%) to each of the three test methods, and by using the lower and upper limits of the data obtained for each test method they derived mathematical equations to transform the data obtained for each excipient with each method. By using the lower and upper limits for each method as indicated in table 1.3 (presented graphically in figure 1.10) they derived equations 1.6 – 1.8 for transformation of the results of the various excipients used in their study.

Table 1.3: *Lower and upper limits used for each test method in setting up for data transformation according to Taylor et al. (2000:6).*

Test	Y-values	Corresponding X-values (lower & upper limit)	Slope (m) and y-axis intercept (c)	
			m	c
Angle of repose	0	75	-0.667	50.000
	33.3	25		
Percentage compressibility	0	55	-0.667	36.667
	33.3	5		
Critical orifice diameter	0	34	-1.111	37.778
	33.3	4		

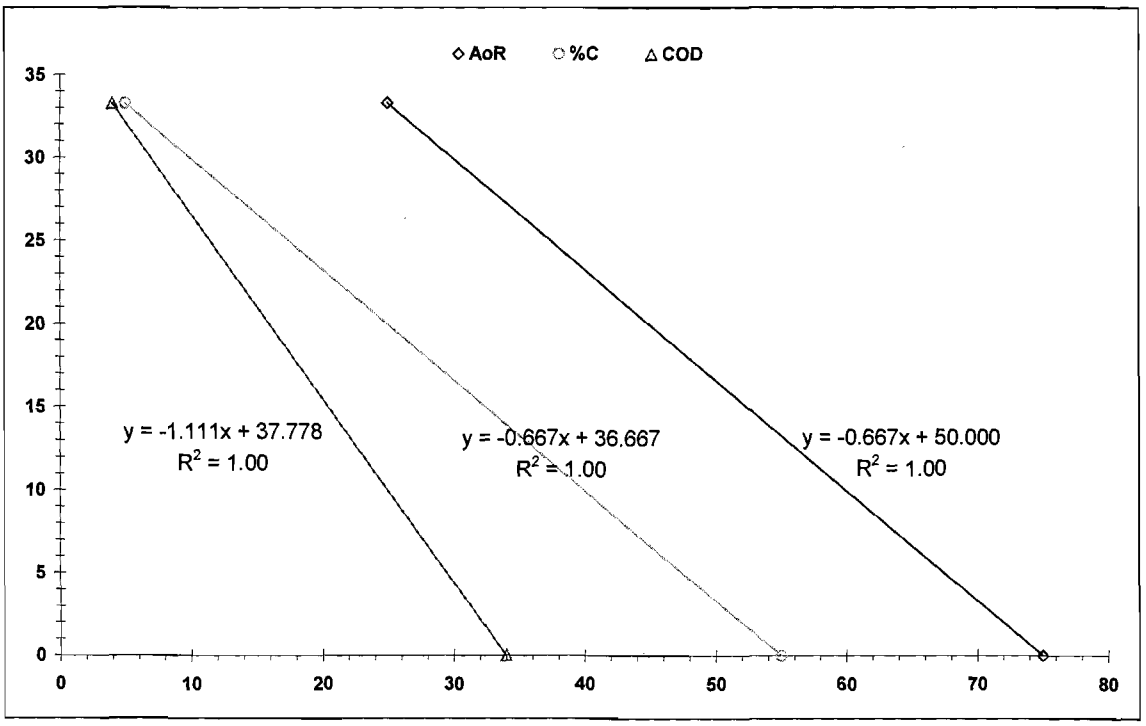


Figure 1.10: Graphic representation of the data used by Taylor *et al.* (2000:6) to generate equations for data transformation.

Angle of repose: -0.667*(results for AoR) + 50.000 [Eq. 1.6]

Percentage compressibility: -0.667*(results for % C) + 36.667 [Eq. 1.7]

Critical orifice diameter -1.778*(results for COD) + 37.778 [Eq. 1.8]

The results from Taylor *et al.* (2000:5) clearly showed the advantages of using a composite index to assess and evaluate powder flowability compared to the result from a single test. The major advantage of this index is the fact that it is a better discriminating parameter to compare the flow of powders, which significantly differ in terms of physical properties and chemical composition, i.e. it better discriminates between powders with clearly different flow properties and it accommodates most of the different physical properties of powder particles which are known to affect their flowability.

Shortcomings in Taylor's index are the equal weight (percentage) assigned to each test method (i.e. 33 ⅓%) and the fact that an important factor namely flow rate, does not figure in this index. It was, therefore, the aim of this study to explore the use of the different contributions of the various flow tests and to determine the effect of including the flow rate as another factor in the composite index.

CHAPTER 2

Materials and Methods

2.1 Introduction

The materials used in this study are frequently used as directly compressible and wet granulated fillers/binders to manufacture tablets. The materials exhibit different characteristics and physical properties. The noticeable differences in the materials are the particle shape, particle size, surface of the particles, the molecular- and interparticle forces and densities.

This chapter focuses on the discussion of the universal properties of the different fillers used in this study and the various methods utilised to determine and compare the specific flow properties. The criteria used to select the flowability methods were (i) applicability of the method to obtain the required information, (ii) repeatability of the method, (iii) efficiency of the method, (iv) ease of use (v) time efficiency and (vi) availability of the apparatus. These selection criteria ensure that these methods are easily utilised in the pharmaceutical industry and at academic institutions without the added burden of large capital expenditure.

2.2 Materials

Table 2.1 presents the various materials used in this study with references to composition, batch number, manufacturer and supplier. All of the materials were of analytical grade and were used as supplied.

Table 2.1: *Information of the various raw materials used in the study.*

Material	Composition	Batch number	Manufacturer
Avicel® PH-200	Microcrystalline cellulose	M939C	FMC International, Wallingstown, Little Island, Cork, Ireland
Cellactose® 80	Lactose monohydrate and cellulose	27973	Meggle GmbH & Co., Wasserburg, Germany
Chitosan	Chitosan hydrochloride	30912	Warren Chemical Ltd. Durban, South Africa
Emcocel® 50M	Microcrystalline cellulose	5S2672	Penwest Pharmaceutical Co., Mendell, United Kingdom
Emcompress®	Calcium phosphate, dibasic dihydrate	C06D	Penwest Pharmaceutical Co., Mendell, United Kingdom
FlowLac® 100	Spraydried Lactose, anhydrous and monohydrate	04492	Meggle GmbH & Co., Wasserburg, Germany
Lactose, monohydrate	Lactose monohydrate	620042	Frieslandfoods Domo, Zwolle, Holland
Ludipress®	Lactose, povidone and crospovidone	25-0194	BASF, Ludwigshafen, Germany
Prosolv SMCC® HD90	Silicified microcrystalline cellulose	K9S0055	Penwest Pharmaceutical Co., Surrey, England
Starlac®	Lactose monohydrate and corn starch	001362	Meggle GmbH & Co., Wasserburg, Germany
Aerosil® 200	Colloidal silicon dioxide	1016102009	Degussa, Parsippany, New Jersey, United States of America

2.3 Scanning electron microscopy (SEM)

Powder fractions were affixed on double-sided conductive carbon tape to a sampling tray and dusted with an inert gas. Fractions were consequently sputter-coated with a mixture of gold/palladium (80:20) to form a layer of approximately 28 nm on the surface of the samples. An Eiko® ion coater (model IB-2, Eiko Engineering, Japan) was used in all coating procedures and operated under a vacuum higher than 0.06 Torr. The fractions were studied using a GAUNTA FEI SEM microscope (Eindhoven, The Netherlands).

2.4 Discussion of the various materials utilised

In this section the various materials used in the study was briefly described in terms of their applications, composition, method of manufacture, and physical properties. Especially considering the physical properties of nominal mean particle size, particle size distribution, and bulk and tapped densities. See table 2.2 for the various physical properties of the powders.

2.4.1. Microcrystalline cellulose-based materials

It is manufactured by controlled hydrolysis with dilute mineral acid solutions of α-cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad size distribution. It is widely used as a filler/binder in oral tablet and capsule formulations in both direct compression and wet granulation processes. It also exhibits some lubrication and disintegration properties.

2.4.1.1 Avicel® PH200

Avicel® PH200 contains microcrystalline cellulose. It is purified, partially depolymerised cellulose that occurs as a stable, white, odourless, tasteless, crystalline powder composed of porous particles. Avicel® PH200 is a large particle sized microcrystalline cellulose material. It is insoluble in water (Weller, 2003:108).

2.4.1.2 Emcocel® 50M

The major constituent in Emcocel® 50M is microcrystalline cellulose. It differs from other microcrystalline cellulose based materials in the method of manufacture, by being a partly depolymerised cellulose prepared from α-cellulose by treatment with mineral acid as well as in particle shape and size. It is also insoluble in water (Weller, 2003:108).

2.4.1.3 Prosolv SMCC® HD90

Prosolv SMCC® HD90 contains microcrystalline cellulose (98%) and colloidal silicon dioxide (2%). It is a white powder. Silicified microcrystalline cellulose is manufactured by co-drying a suspension of microcrystalline cellulose particles and colloidal silicon dioxide. The colloidal silicon dioxide appears physically bound onto the surface and inside the silicified microcrystalline cellulose particles. It has improved compaction properties compared to conventional microcrystalline cellulose. Prosolv SMCC® HD90 is used as filler in capsules and in direct compression and wet-granulation of tablets and is insoluble in water (Moreton, 2003b:115).

2.4.2. Lactose-based materials

Lactose is a natural disaccharide consisting of galactose and glucose and is present in the milk of most mammals. Commercially, lactose is produced from the whey of cows' milk; whey being the residual liquid of the milk following cheese and casein production. Cows' milk contains 4.4–5.2% lactose; lactose constitutes 38% of the total solid content of milk. α-Lactose monohydrate is prepared by crystallisation from supersaturated solutions below 93.5 °C. Various crystalline shapes form and are dependent on the method of precipitation and crystallisation. Direct compression grades of α-lactose monohydrate are prepared by granulation/agglomeration and spray-drying.

2.4.2.1 Cellactose® 80

The major constituents in Cellactose® 80 are lactose monohydrate (75%) and cellulose powder (25%). The spray-dried compound is a white or almost white and odourless powder, partially soluble in water. It is mostly used as a filler/binder for directly compressed tablets. It has the best combined qualities and properties of lactose monohydrate and powdered cellulose (MEGGLE).

2.4.2.2 FlowLac® 100

The major constituent in FlowLac® 100 is spray-dried lactose monohydrate. The lactose monohydrate occurs as white to off-white crystalline particles or powder. Odourless and slightly sweet tasting. It is freely but slowly soluble in water. Spray-dried direct compression grades of lactose monohydrate are generally composed of 80% to 90% specially prepared pure α-lactose monohydrate along with 10% to 20% amorphous lactose. It is manufactured by atomising a suspension of α-lactose monohydrate crystals in a lactose solution and drying it in a spray drier. Approximately 10–20% of the total amount of lactose is in solution and the remaining 80–90% is present in the crystalline form. The spray-drying process predominantly produces spherical particles (MEGGLE).

Spray-dried lactose is widely used as a filler/binder, and flow aid in direct compression tableting. The physical properties of spray-dried lactose produced from alchoholic media are directly affected by the ethanol-to-water ratio in the feed solution. Lactose spray-dried from pure ethanol was shown to be 100% crystalline, whereas lactose spray-dried from pure water was 100% amorphous. The surface area of the spray-dried lactose increases as function of the amorphous content. Spray-dried lactose exhibits good flow properties (Kibbe *et al.*, 2003:323).

2.4.2.3 Lactose monohydrate

Lactose monohydrate is a white to off-white crystalline particle or powder. In its solid state lactose appears as various isomeric forms, depending on the crystallisation and drying conditions, i.e. α-lactose monohydrate, β-lactose anhydrous and α-lactose anhydrous. The stable forms of lactose are α-lactose monohydrate, β-lactose anhydrous and α-lactose anhydrous. It is odourless and slightly sweet tasting. It is soluble in water Kibbe *et al.*, 2003:323).

Lactose is widely used as a binding agent, tablet binder, tablet and capsule diluent and diluent for dry powder inhalers. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics (Kibbe *et al.*, 2003:323).

2.4.2.4 Ludipress®

The major constituents in Ludipress® are lactose monohydrate (93%), Kollidon® 30 (3.5%) and Kollidon® CL (3.5%). White and odourless powder and soluble in water. Mostly used as a filler/binder for directly-compressed tablets. See section 2.4.2.3 for more information on lactose monohydrate (BASF:2003).

2.4.2.5 Starlac®

The major constituents in Starlac® are lactose monohydrate (85%) and corn starch (15%). It is a spray-dried white or almost white and odourless powder, partly soluble in cold water. See section 2.4.2.3 for more information on lactose monohydrate. It is mostly used as a filler/binder for directly compressed tablets (MEGGLE).

2.4.3. Other materials

Materials containing different materials as primary constituent.

2.4.3.1 Chitosan

The major constituent in chitosan is chitosan hydrochloride. Chitosan is an odourless white or creamy-white powder or flakes. It is sparingly soluble in water. Fiber formation is common during precipitation and the chitosan may look "cottonlike". It is a stable material at room temperature, although it is hygroscopic after drying (Jones *et al.*, 2003:132).

It is manufactured by chemically treating the shells of crustaceans such as shrimps and crabs. The basic manufacturing process involves the removal of proteins by treatment with alkali and other minerals such as calcium carbonate and calcium phosphate and then by treatment with acid. Before these treatments, the shells are ground to make them more accessible. The shells are initially deproteinised by treatment with an aqueous sodium hydroxide (3–5% solution). The resulting product is neutralized and calcium is removed by treatment with an aqueous hydrochloric acid (3–5% solution) at room temperature to precipitate chitin. Chitin is dried so that it can be stored as a stable intermediate for deacetylation to chitosan at a later stage. *N*-deacetylation of chitin is achieved by treatment with an aqueous sodium hydroxide 40–45% solution at elevated temperature (110 °C), and the precipitate is washed with water. The crude sample is dissolved in acetic acid (2%) and the insoluble material is removed. Resulting clear supernatant solution is neutralized with aqueous sodium hydroxide solution to give a purified white precipitate of chitosan. The product can then be further purified and ground to a fine uniform powder or granules (Jones *et al.*, 2003:132).

Animals from which chitosan is derived must fulfill the requirements for the health of animals suitable for human consumption to the satisfaction of the competent authority. The method of production must consider inactivation or removal of any contamination by viruses or other infectious agents. It can be processed into drug delivery systems using several techniques including spray-drying, coacervation, direct compression and conventional processes (Jones *et al.*, 2003:132).

It is used as a coating agent, disintegrant, film-forming agent, muco-adhesive, tablet binder and viscosity increasing agent. Commercially it is available in several types and grades that vary in molecular weight from 10 000 – 1000 000, and vary in degree of deacetylation and viscosity (Jones *et al.*, 2003:132).

2.4.3.2 Emcompress®

Emcompress® contains dibasic calcium phosphate dihydrate. It is a white, odourless, tasteless powder or crystalline solid. Insoluble in water and a non-hygroscopic, relatively stable material. Calcium phosphate is manufactured by reacting very pure phosphoric acid

with calcium hydroxide, obtained from limestone, in aqueous suspension followed by drying at a temperature that will allow the correct hydration state to be achieved. After drying, a coarse-grade material is obtained by means of a classification unit; the fine particle-size material is obtained by milling. Two main particle-size grades are mostly used as tablets and capsule diluents. The milled material is used in wet-granulated, roller-compacted or slugged formulations while the coarse-grade material is used in direct-compression formulations (Moreton, 2003a:74).

2.4.3.3 *Aerosil® 200*

The major constituent of Aerosil® 200 is colloidal anhydrous silica. It is a light, bluish-white coloured, odourless, tasteless, non-gritty amorphous powder. Soluble in hot solutions of alkali hydroxide. It is prepared by the vapour hydrolysis of chlorosilanes, such as silicon tetrachloride, at 1800 °C using a hydrogen-oxygen flame. Several grades of colloidal silicon dioxide are available, which are produced by modifying the manufacturing process. The modifications do not affect the silica content, specific gravity, refractive index, colour or amorphous state. It affects the particle size, surface areas and densities. Its small particle size and large distribution give it desirable flow characteristics to improve the flow properties of dry powders for tabletting. It is mostly added as a glidant to tablet formulations (Morefield *et al.*, 2003).

Table 2.2: *Information on the various physical properties of the materials used in the study.*

Materials	Nominal particle size (µm)	Particle size distribution	Bulk density ($g.cm^{-3}$)	Tapped density ($g.cm^{-3}$)	True density ($g.cm^{-3}$)
Avicel® PH-200[1]	180	20 – 200 µm	0.337	0.478	1.512–1.668
Cellactose® 80[2]	n/a	≤ 20% < 32 µm 35 – 65 % < 160 µm ≥ 80% < 200 µm	0.380	0.500	1.534
Chitosan[1]	n/a	< 30 µm	n/a	n/a	1.35 - 1.40
Emcocel® 50M[1]	91	20 – 200 µm	0.29	0.35	1.512–1.668
Emcompress®[1]	180	130 – 180 µm	0.915	1.17	2.389
FlowLac® 100[1]	n/a	≤ 10%< 32 µm < 25 – 40 % <100 µm ≥ 80%.< 200 µm	0.62	0.73	1.545
Lactose monohydrate[1]	n/a	> 80% < 75 µm > 98% < 150 µm	0.61	0.84	1.545
Ludipress®[2]	n/a	max 15% < 63 µm 40 – 60 % < 200 µm min 90% < 400 µm	0.62	0.73	1.545
Prosolv SMCC® HD90[1]	110	20 – 200 µm	0.31	0.39	1.58
Starlac®[2]	n/a	≤ 15%< 32 µm, 35 – 65 % < 160 µm, ≥ 80% < 250 µm	0.57	0.69	1.535
Aerosil® 200[1]	n/a	7-16 nm	0.029 – 0.042	0.05	n/a

[1]Handbook of pharmaceutical excipients, 4th ed, The Pharmaceutical Press.

[2]Certificates of analysis in possession of author.

n/a – not available in literature

2.5 Methods

The next section describes the different methods utilised to determine the flow characteristics of the various materials and are divided into two sections, namely (2.5.1.) the preparation and treatment of the various materials before testing and (2.5.2.) the methods utilised to determine the flow properties of the various materials and the calculations of the various flow factors from the results.

2.5.1 Preparation of the materials for testing and experimental conditions

The various powders' particle size and particle size distribution were determined, because of the effect that these characteristics have on the flowability. Given that flow properties of materials are affected by environmental conditions, especially humidity, (effect of moisture in the atmosphere which in turn is directly affected by temperature), experiments were carried out in a temperature controlled room in which the humidity could be controlled.

2.5.1.1 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.

A volume of 100 ml of ethanol was used as dispersant for most of the materials except Aerosil® 200. The dispersant used for it was distilled water. Prior to every measurement background measurements were taken. After completion of the background measurement a sufficient quantity of the raw material was added to render an obscuration of 10-20% whereafter the particle size measurement was made. Two measurements 20 seconds apart consisting of 12000 sweeps each were taken. Samples were analysed in duplicate.

2.5.1.2 Pre-treatment of materials

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 5 hours. The oven was pre-heated for 30 minutes to the required temperature. After the set drying time, the powders were removed, and moved to the climate-controlled area, left to cool for 5 hours and then carefully poured into glass containers, after which the openings were covered with Parafilm®, and the lids were screwed on tightly.

2.5.1.3 Experimental Conditions

All the flow experiments were conducted in a controlled environment, fitted with an air-conditioner (regulates the temperature) and humidifier (regulates the relative humidity). The experiments were conducted at ambient conditions (see Table 2.3). All of the materials were also stored at these conditions after pre-treatment.

Table 2.3: *Conditions of the controlled environment.*

	Conditions
Temperature (°C)	25±1 °C
Relative Humidity (%)	40 – 60%

2.5.1.3 Mixtures containing a glidant

Part of this study was to determine the effect of a glidant on the flow properties of the different powders. Mixtures of each powder and 0.25% (w/w) Aerosil® 200 were prepared in a Turbula®-mixer for 10 minutes at 69 rpm. The mixtures were carefully poured into glass containers, after which the openings were covered with Parafilm®, and the lids were screwed on tightly and stored at the experimental conditions until testing.

2.5.2 Flow tests

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

2.5.2.1 Critical orifice diameter (COD)

The apparatus used for the critical orifice diameter is the same one used in the determination of angle of repose. This apparatus was designed by Buys (2006:40). The apparatus consists of a set of brass discs between 5 and 10 mm thick that was stacked on top of each other. The largest brass disc opening is 32 mm and the smallest is 1.5 mm. The angle between the opening and the orifice of each disc was machined to a set angle. There is also no static powder because of the absence of a cylinder floor and base plate. A cylinder was fitted at the top of the funnel to create a holding chamber for the measured powder fraction. Brass discs were chosen to minimise the effect of static electricity between the powder and the cylinder (see figure 2.1).

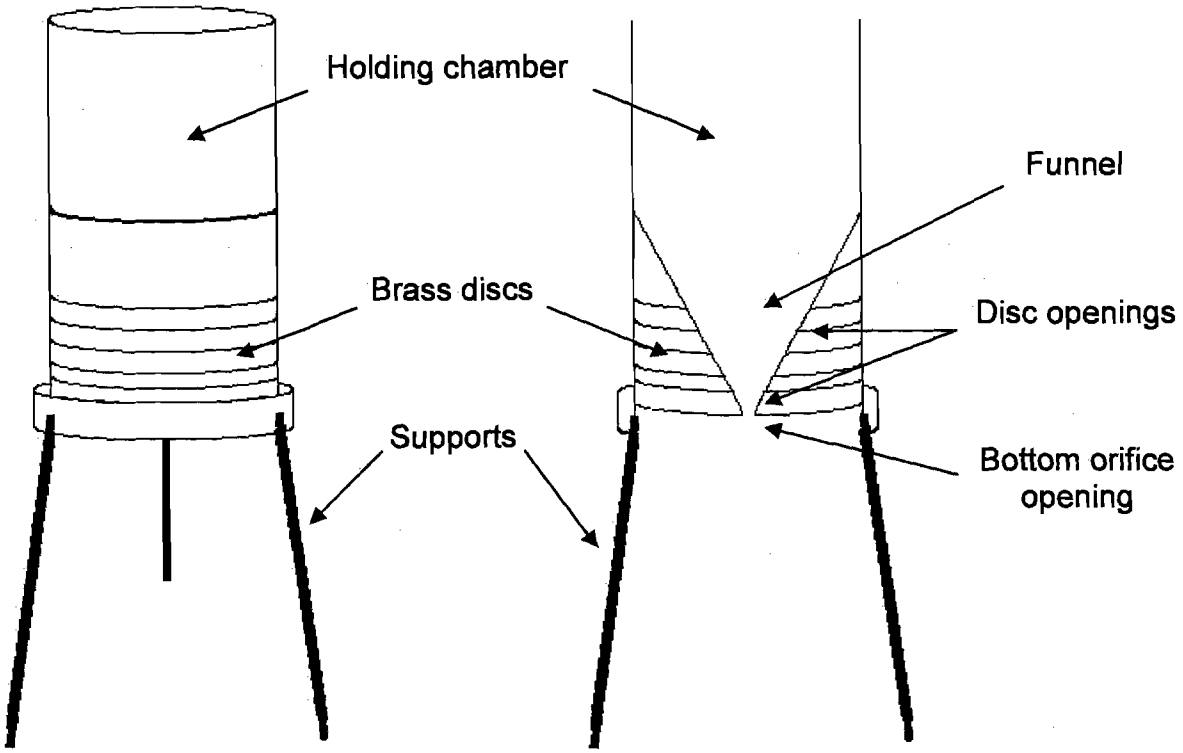


Figure 2.1: Diagram of apparatus used in determining the critical orifice diameter (COD) and angle of repose (AoR).

Critical orifice diameter is the smallest opening (diameter) through which a powder will flow freely without assistance or interference. A set volume of powder (100 ml) was loaded into the holding chamber while the bottom orifice was kept shut. Opening the orifice allowed the powder to flow through the orifice (if possible). Interchangeable brass discs allow the orifice diameter (available range of 1 to 32 mm) to be changed. The smallest orifice diameter through which the powder flowed freely was noted as the critical orifice diameter of that specific powder. The experiment was repeated in triplicate for each powder and the average COD and the standard deviation were calculated.

2.5.2.2 Angle of repose (AoR)

The same apparatus used for determining the critical orifice diameter was used (see figure 2.1). An amount of powder (100 g) was allowed to flow freely from the apparatus (bottom orifice was equal to two larger sizes than the COD) onto a piece of paper (see figure 2.2) placed on a smooth piece of glass over a distance of 15 cm. The cone formed was photographed (Canon digital camera, Powershot A700) and reference lines were drawn (see figure 2.3). Angle of repose was determined (equation 1.1) from the height and diameter of the cone as described by Wong (2002:2636). Experiment was done in triplicate with all the powders. The average AoR and the standard deviation were calculated.

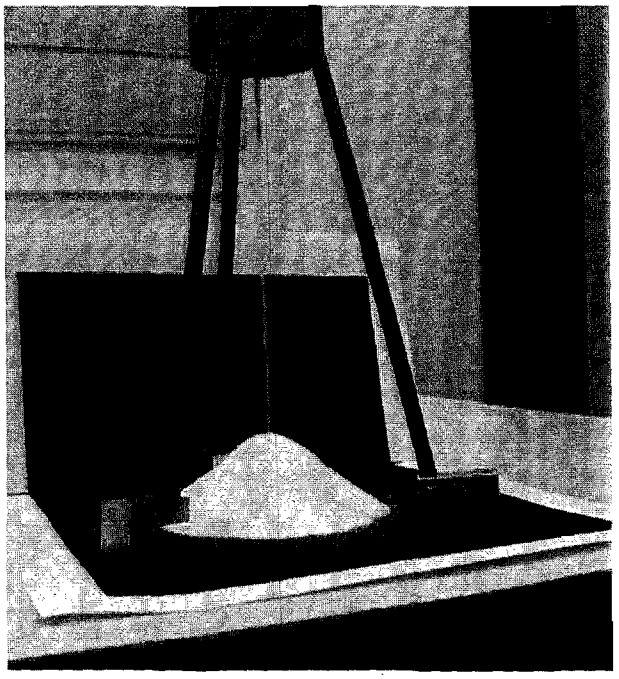


Figure 2.2: Formation of a powder cone by the critical orifice apparatus to determine the angle of repose (AoR).

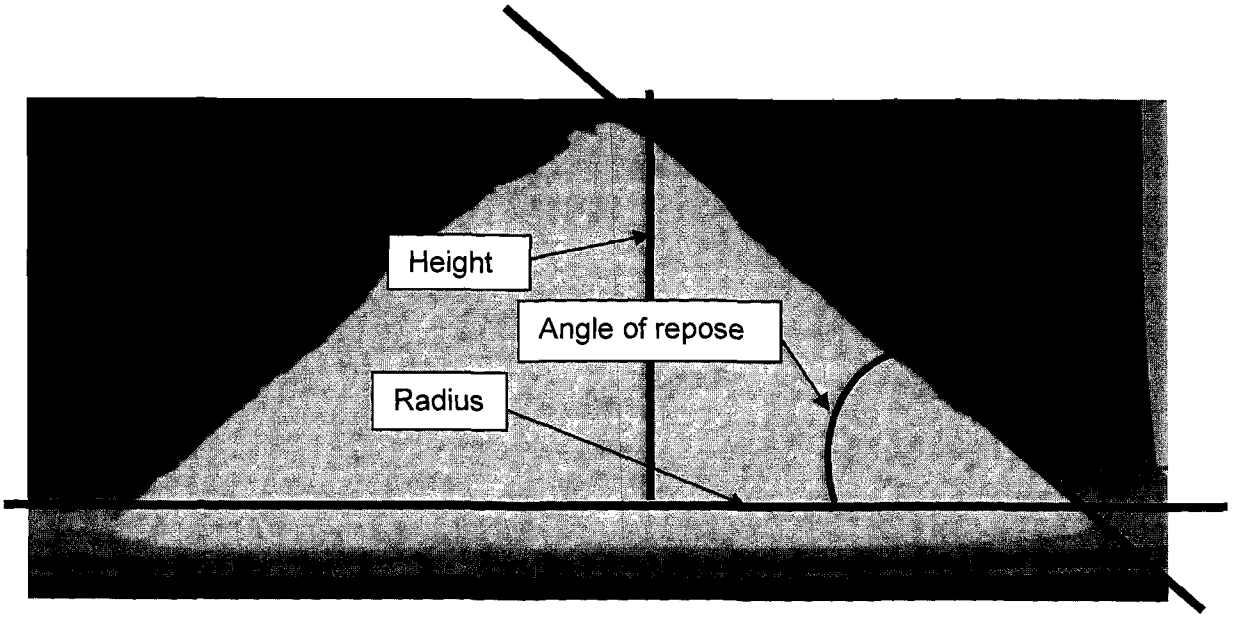


Figure 2.3: Reference lines drawn on a photograph to determine the height and radius of the powder cone.

2.5.2.3 Flow rate (FR)

The same apparatus used to determine the critical orifice diameter and angle of repose was used to establish the flow rate of each powder (setup shown in figure 2.4). An amount of powder (100 ml) was loaded into the holding chamber and the shutter at the bottom of the apparatus opened. Powder flowed into a tared beaker on the analytical balance (Mettler Toledo balance, model PB303-S). The amount of powder released per time unit (seconds)

was recorded using a computer program (Mettler Toledo Balancelink, Version 3.01). The experiment was repeated in triplicate, for each powder; and the average FR ($g.sec^{-1}$) and standard deviation were calculated.

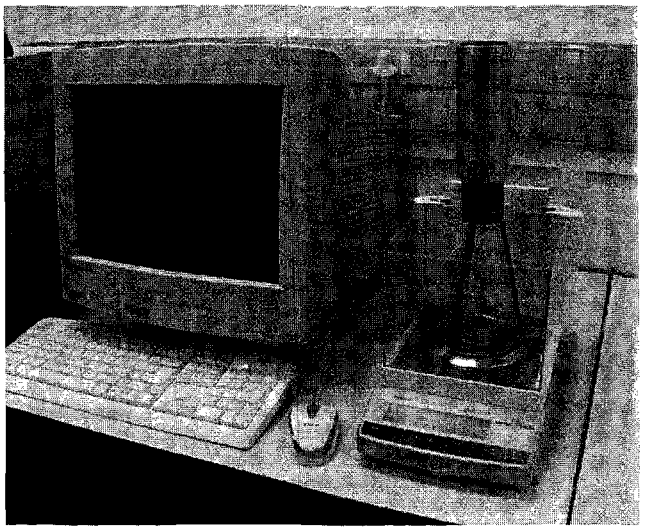


Figure 2.4: Experimental setup for flow rate experiments.

2.5.2.4 Percentage compressibility (%C)

The percentage compressibility (also known as Carr's Index) is calculated from the bulk and tapped density of a powder. A volume of powder (100 ml) was gently poured into a tared graduated cylinder and the weight recorded on an analytical balance (Mettler Toledo balance, model PB303-S). Bulk density (ρ_b) was determined using equation 1.2. Tapped density of each powder was determined by vibrating the graduated cylinder containing the powder (100 ml) to constant volume on a Fritsch analysette (type 30.502) at an amplitude of 7. The tapped density (ρ_t) was determined by using equation 1.3. Both densities of each powder were determined 6 times and the average bulk and tapped densities and standard deviation calculated. The percentage compressibility of each powder was calculated by using its respective bulk and tapped density in equation 1.4.

2.5.3 Data treatment and statistical evaluation of the experimental data

The data calculations were done using the Microsoft® Office Excel® XP package for Windows® XP (Microsoft Corporation, Seattle, Washington, USA). Statistical analysis was performed with STATISTICA® 6.1 (StatSoft®, Inc., 2003). A 95% confidence level ($P<0.05$) was considered satisfactory for indicating significant differences. The mean values of the various parameters determined, i.e., flow rate, percentage compressibility and angle of repose were compared for significant differences using one-way or two-way analysis of variance (ANOVA) for single factor and two factor comparisons respectively.

CHAPTER 3

Flow properties and parameters of different pharmaceutical fillers

3.1 Introduction

The flow properties of fillers are important in the manufacturing operations of solid dosage forms because of their high concentration in the final dosage form. Knowledge about the flow properties of individual tablet components and tablet powder mixtures in the early stages of preformulation and formulation enables the formulator to determine potential problems which might lead to poor tablet characteristics, such as poor compression characteristics, variation in tablet weight and hardness and reduced efficiency of certain tablet excipients due to poor distribution within the tablet structure. Tablet properties are determined by a combination of (i) powder characteristics, such as particle size, size distribution, shape, packing density and surface properties and (ii) operating conditions, such as moisture, temperature, static charge, aeration, or history of applied stress (Sinka *et al.*, 2004:27). Poor flow properties of powder mixtures or components not only affect the physical properties of the product, but may also influence certain pharmaceutical processes during manufacturing, especially mixing (i.e. the blending of the different tablet components to produce a homogenous mixture). The best solid dosage forms (tablets) are obtained by understanding and adjusting these properties, thereby attaining the best flow.

The various methods to determine the flow properties have been discussed in chapter 1. A selection of these methods has been applied to a number of pharmaceutical powders commonly used in tablet formulations (particularly direct compressible formulations) as described in chapter 2. Each of these methods is affected by specific particle properties, which may differ from method to method. Particle shape and size, surface structure of the particles and particle density are major factors affecting the behaviour of particles, especially their flow.

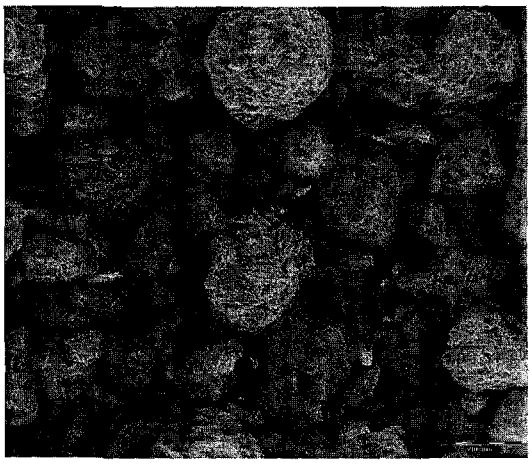
This chapter presents the results from the various flow tests. Discussions and comparisons of the flow properties of the various materials are presented, and special attention was paid to establish which powder property / properties affected the results of each flow parameter and why, i.e. do the results from the flow tests relate to the properties that affect them?

3.2 Particle morphology studies

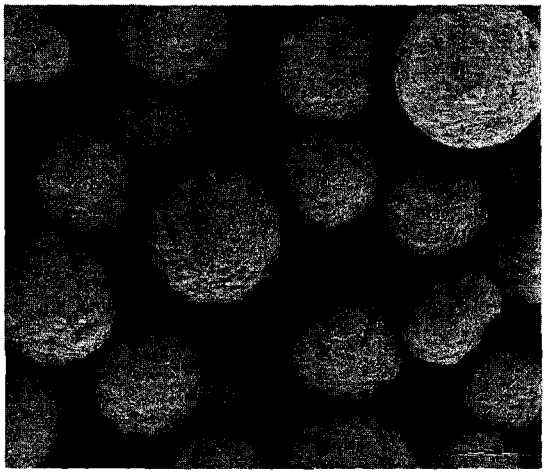
Scanning electron microscopy (SEM) and particle size analysis were used to study the morphology of the different powders evaluated in this study. SEM photomicrographs

provides an excellent method to study the particle shape and structural properties of powders, whilst particle size analysis provides important information concerning the mean particle size and particle size distribution within the powder. Knowledge of these physical properties of powders enables the formulator to explain observed behavioural differences between powders especially in terms of powder flowability.

SEM photomicrographs of each powder were taken as described in section 2.3, whilst particle size analysis were done employing an laser diffraction as described in section 2.5.1.1. The SEM photomicrographs are presented in figure 3.1. (a – j) and the particle size data in table 3.1. The results from these studies will primarily be used to explain the observed differences and similarities in the flow results of the powders obtained from the various flow tests which follow in section 3.4.



(a) Avicel® PH200 (200X)



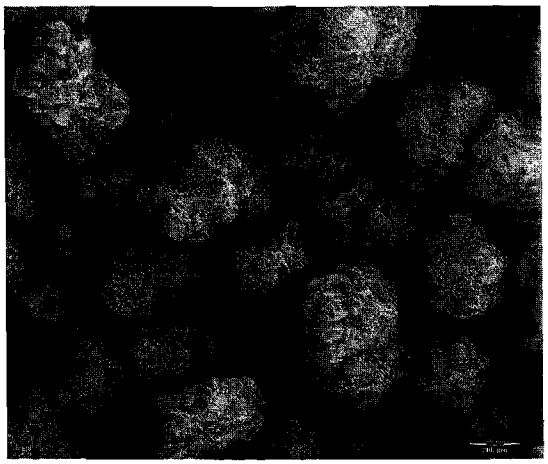
(b) Cellactose® 80 (200X)



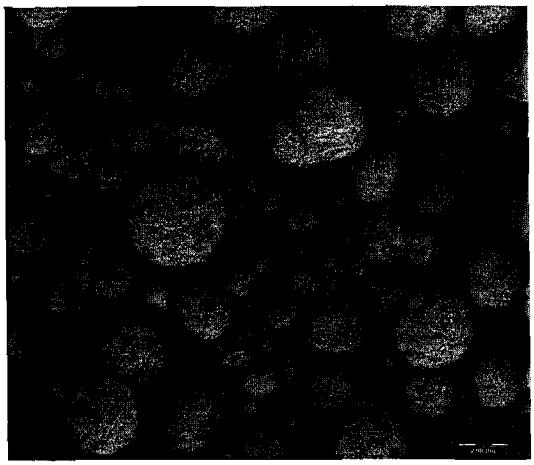
(c) Chitosan (200X)



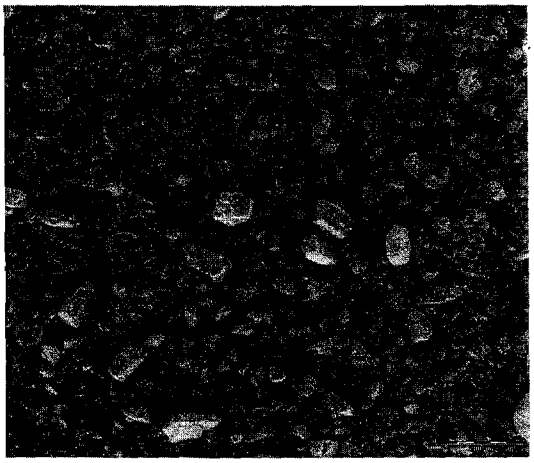
(d) Emcocel® 50M (200X)



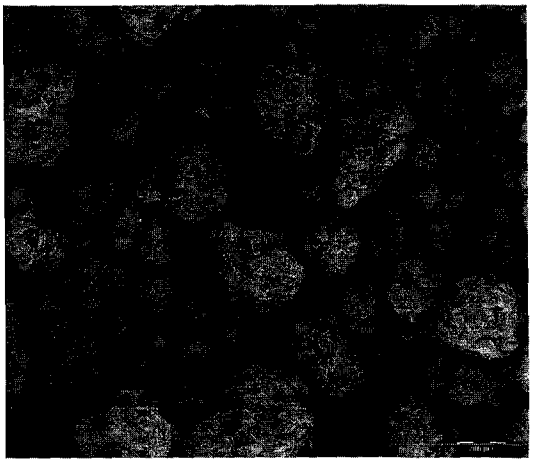
(e) Emcompress® (200X)



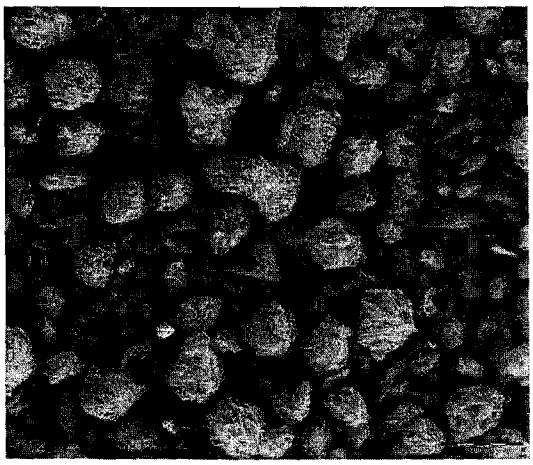
(f) FlowLac® 100 (200X)



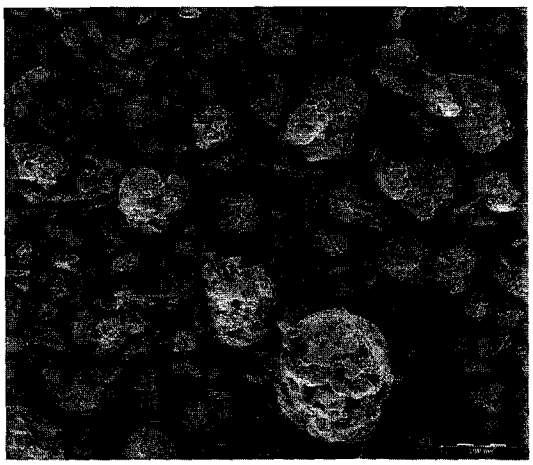
g) Lactose monohydrate (200X)



(h) Ludipress® (200X)



(i) Prosolv SMCC® HD90 (200X)



(j) Starlac® (200X)

Figure 3.1: Photomicrographs of the various fillers employed in the study. The enlargement factor is indicated in brackets.

The observed differences in the shape and surface structure (figure 3.1) and particle size and size distribution (table 3.1) of the various fillers predict major differences in the flowability

of the compounds. The following would be expected in terms of the theory concerning the effect of particle properties on the flowability of a powder bed:

- Spherical particles should exhibit optimal flow due to minimum contact between particles which reduces frictional forces. The more particles deviate from spherical the greater the expected reduction in flowability.
- Larger particles normally show better flow properties compared to smaller particles since more frictional forces are present between the latter. Particles smaller than 100 µm are considered to be cohesive, whilst particles in excess of 250 µm are normally free flowing.
- A small amount (±10 – 15%) of small particles (20 – 50 µm) in a powder bed with a larger average particle size (>150 µm) may be advantageous to powder flow, since the smaller particles may adhere to the surfaces of the larger particles thus smoothing out the surface structure with a resultant improvement in flowability. An increase in the percentage of smaller particles may, however, reduce powder flow due to movement of the smaller particles between the larger particles which would increase particle contact and also frictional forces with a resultant decrease in flowability of the powder bed.
- Particles with a smooth surface structure flow better than particles of uneven (rough) surface, since the latter may cause interlocking which reduces flow.
- "Heavy" powders (high mass to volume) should exhibit superior flow compared to "light" powders due to the effect of gravitational forces.
- The effects of the various physical properties of powders (shape, surface, structure, size, size distribution, density, etc.) are interrelated when considering their effect on powder 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)
Aerosil® 200	14.05	34.77	79.49	48.5
Avicel® PH200	70.78	186.03	357.79	202.66
Cellactose® 80	86.22	169.2	291.87	179.58
Chitosan	72.19	163.71	305.8	177.49
Emcocel® 50M	22.8	71.37	167.3	85.77
Emcompress®	12.4	192.78	356.1	195.88
FlowLac® 100	70.96	137.73	244.03	148.6
Lactose monohydrate	7.11	33.3	99.45	45.91
Ludipress®	20.775	97.18	226.74	132.26
Prosolv SMCC® HD90	46.62	111.67	212.56	122.12
Starlac®	122.06	217.8	374.18	234.29

Based on the available knowledge of the effect of the physical properties of particles on the flow of the powder bed, the following rank order for the various fillers was predicited in terms of their flowability: Cellactose® 80 > FlowLac® 100 ≈ Avicel® PH200> Emcompress® Ludipress® > Prosolv SMCC® HD90 >> Emcocel® 50 M ≥ chitosan ≥ lactose monohydrate.

In the following sections this rank order and the correlation between theory principles and practice will be tested and evaluated.

3.3 Reproducibility of individual flow tests (Repeatability)

The percentage relative deviation (%RSD) of the results of each of the flow tests (in triplicate) was determined to obtain an indication of the reproducibility of each method. The results were as follow: critical orifice diameter (0.00%), percentage compressibility (4.04%), flow rate (6.35%) and angle of repose (6.59%). The results indicate that the reproducibility of critical orifice diameter and percentage compressibility tests were noticeably higher compared to that of the tests for angle of repose and flow rate.

3.4 Flow test results

The following section presents and discusses the results from the various flow tests performed on the different materials used in this study.

3.4.1 Critical orifice diameter (COD)

The critical orifice diameters of the various materials were determined at ambient conditions, and in the absence and presence of 0.25% w/w Aerosil® 200. The flow rate index shown in table 3.2 was used to classify the flow characteristics of the various materials based on their respective critical orifice diameter. The measurements were determined as described in section 2.5.2.1 and the results are presented in table 3.3 with the data tabulated in Annexure B.

Table 3.2: 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

Table 3.3: *The critical orifice diameter (mm) (COD of the different pharmaceutical fillers in the absence and presence of 0.25% w/w Aerosil® 200 at ambient conditions).*

Material	No glidant	0.25% Aerosil® 200
Avicel® PH200	2	2
Cellactose® 80	2	1.5
Chitosan	11	3
Emcocel® 50M	32	24
Emcompress®	3	3
FlowLac® 100	3	1.5
Lactose monohydrate	32	28
Ludipress®	3	2
Prosolv SMCC® HD90	3	2
Starlac®	3	2

The ranking of the critical orifice diameter results is presented in figure 3.2. In the absence of a glidant, most of the powders flowed through a critical orifice diameter of 2 – 3 mm (figure 3.2). Only chitosan, Emcocel® 50M and lactose monohydrate presented with large critical orifice diameters (>11 mm). Cellactose® 80 and Avicel® PH200 exhibited excellent flowability (COD = 2 mm) according to the ranking index of flowability (table 3.2). This could be attributed to the spherical shape of the particles (figure 3.1[b] and [a]) and to their relatively large average particle size of (±180 μm and ±203 μm respectively). Spherical and larger particles are known to possess less interparticle friction due to less contact between particles. The excellent flow of FlowLac® 100, Ludipress®, Starlac®, Prosolv SMCC® HD90 and Emcompress® (COD = 3 mm) could be ascribed to their (i) larger mean particle size and/or (ii) spherical shape. Starlac® and FlowLac® 100 (as well as Cellactose® 80) are all manufactured through the process of spray-drying (section 2.4.2), which is known for the production of spherical particles, which exhibit optimal flow properties (Podczeck *et al.*, 1996b:194). Considering the rough surface structure of Starlac® (figure 3[j]) compared to the smooth-surfaced FlowLac® 100 (figure 3[f]), poorer flow would be expected due to possible interparticle friction, but the larger mean particle size of this material (>234 μm) possibly counteracted this effect. Ludipress® showed unexpected excellent flow considering the

smaller mean particle size (±132 μm) and the relative rough surface structure (figure 3[h]) of the particles. The flow of Emcompress® can be ascribed to its spherical particle shape (figure 3.1[e]) and the large mean particle size (±196 μm). Large particles are generally free flowing because of the relatively small contact areas between particles, which reduce interparticle friction and attraction forces. The excellent flow of Prosolv SMCC® HD90 could be ascribed to its' larger particle size (table 3.1) and spherical shaped particles (figure 3.1[i]). Although the smaller mean particle size of ±122 μm of Prosolv SMCC® HD90 would suggest poorer flow compared to the particle sizes of other microcrystalline cellulose based materials (see table 3.1 for average particle sizes of Avicel® PH200 and Emcocel® 50M), its flow is improved by the presence of 2% colloidal silicon dioxide (section 2.4.1.3), which acts as glidant.

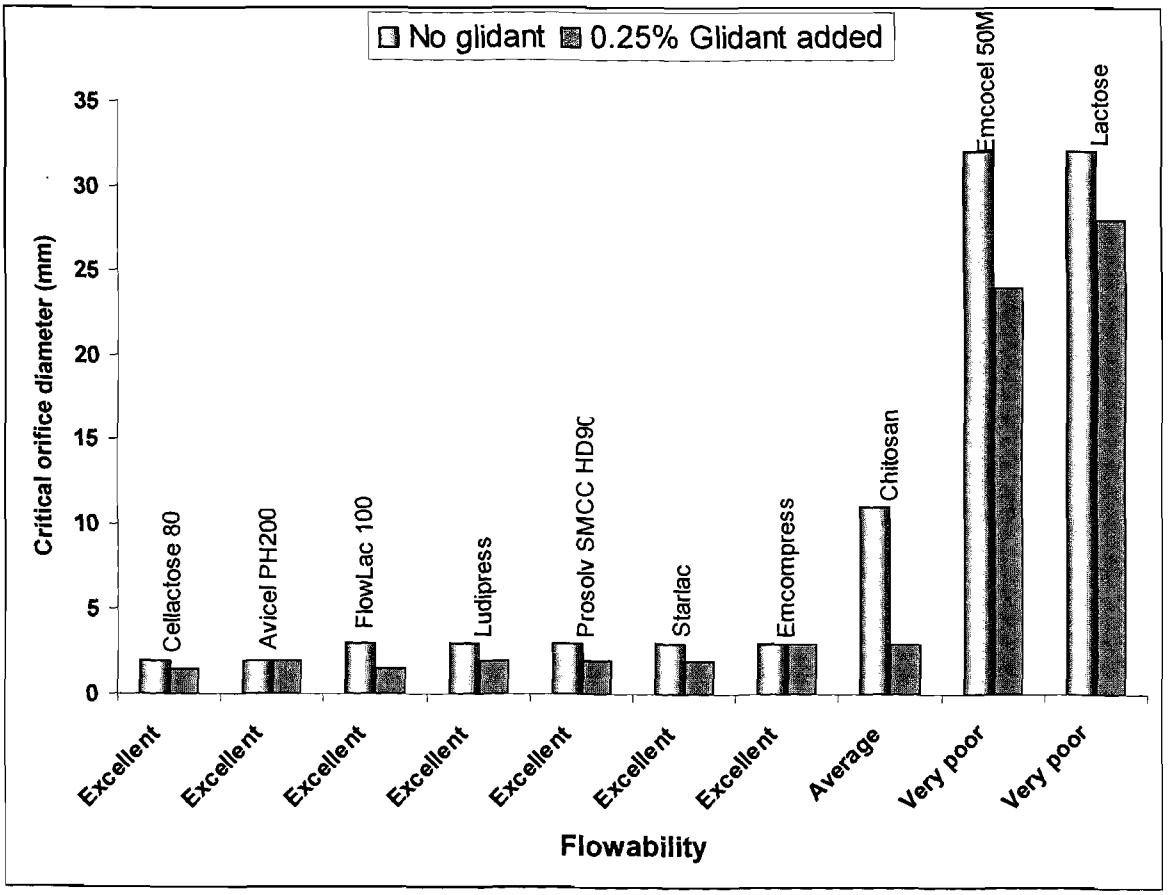


Figure 3.2: Flow characterization of different pharmaceutical fillers in the presence and absence of a glidant (0.25% Aerosil® 200) according to critical orifice diameter.

Chitosan, Emcocel® 50M and lactose monohydrate displayed the poorest flow of all the materials. The poor flow of chitosan could be attributed to the flake-like particles (figure 3.1[c]), which were not conducive to proper flow. The particles might have glided over one another due to the particle shape and not flow properly. The poor flow of Emcocel® 50M may be attributed to the small particle size of the material, ±86 μm (table 3.1), and the irregular

shaped particles (figure 3.1[d]). It is commonly acknowledged that small particles (especially below 100 µm) exhibit poor flow due to higher interparticle attractive forces, whilst a fibrous shape also reduces flow due to possible interlocking between particles. Lactose monohydrate exhibited the poorest flow (COD = 32 mm) compared to the other materials. This extremely poor flow may be attributed to the small mean particles size, ±46 µm (table 3.1 and figure 3.1[g], which is common in materials with an average particle size ≤100 µm.

The addition of a glidant (0.25% w/w Aerosil® 200) seemed only to improve the flow of the fillers with inherent poor flow properties. The flow of Cellactose®, FlowLac® 100, Ludipress®, Prosolv SMCC® HD90 and Starlac® only slightly improved with the addition of the glidant (COD decreased to one unit lower), whilst the flow of Avicel® PH200 and Emcompress® exhibited no improvement in flow (figure 3.2). The absence of a noticeable effect on the flow of these materials could only be explained in terms of the fact that the materials have probably already reached their optimal flowability or the possibility that the apparatus was not sensitive enough to produce a higher accuracy.

Chitosan exhibited an improvement in flow upon the addition of the glidant with a reduction in the critical orifice diameter from 11 mm to 3 mm. Its flow category improved from average to excellent (table 3.2). This is probably due to the glidant attaching to the surfaces of the flake-like particles (figure 3.1[c]) and reducing cohesiveness. Emcocel® 50M reacted positively to the addition of a glidant with a reduction in the critical orifice diameter from 32 mm to 24 mm. Lactose monohydrate showed an improvement in flow with the addition of the glidant with a decrease in the COD from 32 to 28 mm, but its flow remained very poor. Since the glidant improves flow through smoothing the surface structure of the base material (i.e. adhesion of small glidant particles, 7-16 µm, to the surface of the base material, thus filling the crevices on the surface, which reduce interparticle friction), it required a relative large particle size to be affective. The adhesion of the glidant to the lactose particles was probably impaired by the small particle size of the lactose (±45 µm) thus negating its anti-friction effect.

3.4.1.1 Conclusion

The results obtained for the COD of the fillers illustrated the influence of particle size, shape and surface structure on the flowability of these materials. There was a difference in flow between the smaller and larger particle sized powders. These results correlate with the findings of Staniforth (2002:200), who suggested that the larger the particle size (only to the extent where large particle size results in poor flow due to particle shape) and more uniform particle shape, the better the flowability of the material. The effect of the glidant was unexpectedly poor in terms of improvement of powder flow for fillers exhibiting acceptable flow, but its positive effect on powders with poor flow was confirmed. The glidant coated the

surface of the particles and thus lowered the molecular and interparticle forces between particles.

3.4.2 Percentage compressibility (%C)

The percentage compressibility (%C) is an indirect method to assess the flowability of powders which utilises interparticle cohesive properties. According to Harnby *et al.* (1987:881) powders with a strong structural strength will resist collapse when dispersed in a container resulting in a low bulk density (i.e. low mass to volume ratio), whilst a structurally weak powder will collapse easily exhibiting a high bulk density. The extent of volume reduction in a powder bed during transport and handling (simulated by tapping) of the powder, is an indication of the cohesiveness of the powder and frictional forces between individual particles in the bed. Therefore, monitoring change in the density of a powder bed during tapping (vibration) could be related to the extent of powder cohesion and frictional forces, thus, indicating the flowability of the powder.

The scale presented in table 3.4 was used to characterize the flow of the fillers. The percentage compressibility of the various materials was determined at ambient conditions in the absence and presence of 0.25% w/w Aerosil® 200 (a glidant) as described in section 2.5.2.4 and the results are presented in table 3.5. The data is recorded in Annexure C.

Table 3.4: Flow categories for powders in terms of percentage compressibility according to the USP (2007:645).

Flow Character	Compressibility Index (%)
Excellent	<10
Good	11 – 15
Fair	16 – 20
Passable	21 – 25
Poor	26 – 31
Very poor	32 – 37
Very, very poor	>38

Table 3.5: The percentage compressibility (%C) of the different pharmaceutical fillers in the absence and presence of 0.25% w/w Aerosil®200 at ambient conditions.

Material	No glidant	0.25% Aerosil® 200
Avicel® PH200	20.50 ± 0.55	16.50 ± 1.38
Cellactose® 80	14.67 ± 0.52	10.67 ± 0.82
Chitosan	36.33 ± 0.82	36.00 ± 0.63
Emcocel® 50M	31.67 ± 1.03	27.83 ± 0.75
Emcompress®	18.17 ± 0.75	15.17 ± 0.41
FlowLac® 100	15.00 ± 0.00	10.50 ± 0.55
Lactose monohydrate	40.17 ± 0.41	43.17 ± 0.41
Ludipress®	19.83 ± 0.41	12.67 ± 0.52
Prosolv SMCC® HD90	15.00 ± 0.63	17.00 ± 0.00
Starlac®	24.00 ± 0.89	15.17 ± 0.75

The %C-value reflects the relative difference between the bulk and tapped volume of a powder bed, i.e. $\frac{V_b - V}{V_b}$, (or the relative difference between the tapped en bulk density), and the value of %C is inversely proportional to the flowability of a powder (table 3.4). Therefore, the greater the relative difference between bulk and tapped volume (or tapped and bulk density), the higher the %C and the poorer the flowability (figure 3.3).

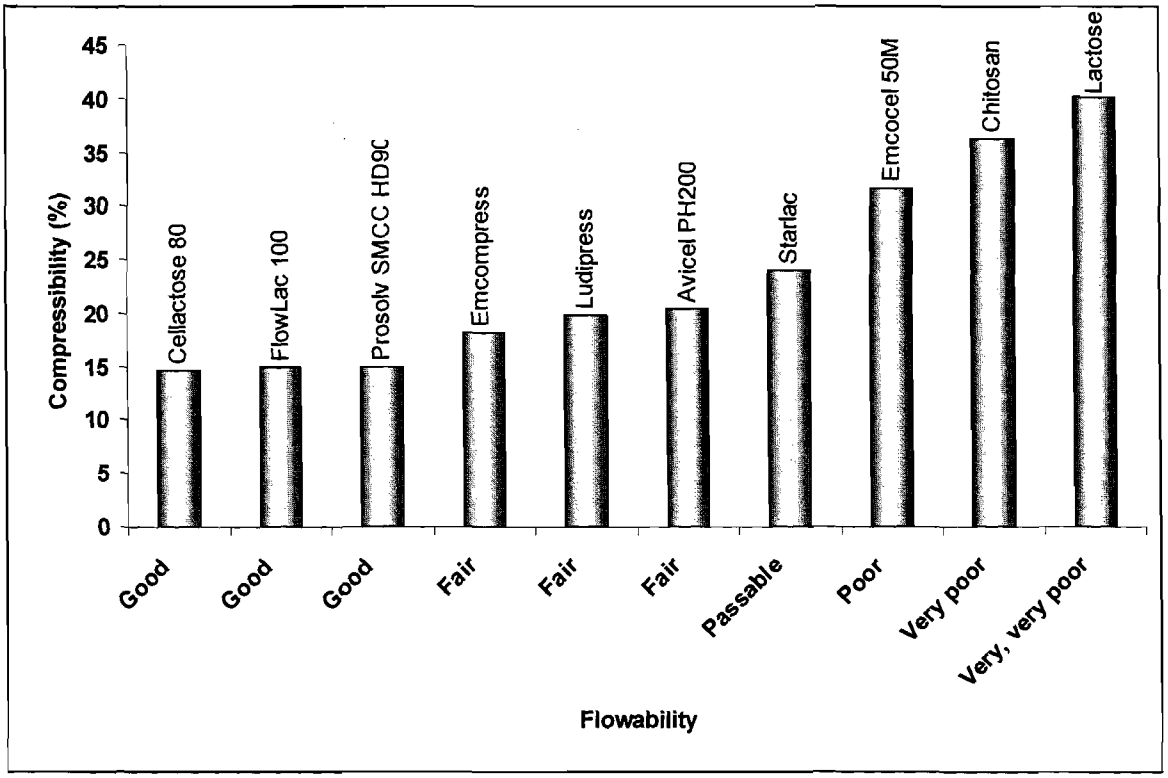


Figure 3.3: Flow characterization of different pharmaceutical fillers according to percentage compressibility.

The results for the percentage compressibility studies fitted the explanation provided in the literature why this parameter could be used as an indicator for powder flow (Harnby *et al.*, 1987:881 and Abdullah *et al.*, 1999:151). The superior flow of Cellactose® 80 and FlowLac® 100 could be attributed to their spherical shape which reduced friction between particles allowing them to move independently from one another and obtain dense packing when dispersed in a container. Tapping had little effect on the rearrangement of the particles which was reflected in only a slight change in the powder volume (<15%). Prosolv SMCC® HD90 seemed to be the odd one out in this group of fillers which produced good flow, since its surface structure was obviously less smooth and its shape less spherical than the other two (figure 3.1). Its comparable %C (±15%) could, however, be attributed to the presence of 2% silicone dioxide (a glidant), which was incorporated in the material during the manufacturing process.

The fillers exhibiting fair to passable flow, namely Emcompress®, Ludipress®, Avicel® PH200 and Starlac® (with %C in the range of 18-25%) all have relative large mean particle sizes in the range of 132 – 235 μm (see table 3.1) with a spherical particle shape. Their poorer flow, compared to Cellactose® 80 and FlowLac® 100 could be attributed to their rougher surface structure (figure 3.1[b] and [f] respectively). A rough surface structure enhanced frictional

forces due to possible interlocking which prevented particles to move individually, thus, impeding the natural flow of individual particles within the powder bed.

The poor flow of Emcocel® 50M and lactose monohydrate (%C >30%) could be related to their unfavourable particle shape (figure 3.1[d] [g] respectively) and relative small average particle size (45 – 85 μm). The significant reduction in the volume of the powder bed upon tapping (in excess of 55%) is typical of cohesive powders where frictional forces prevent individual movement of particles. The particles are forced to "jump" and to lose contact with each other for a moment during tapping. When there is reduced friction between the particles, they rearrange with improved packing, which coincided with a reduction in the volume of the powder bed (Abdullah *et al.*, 1999:151). The appearance of chitosan in this group, despite its relative large average particle size (±177 μm) could be ascribed to the particle shape (flat, flake-like shaped) which obviously were not conducive to natural flow. Once again, a large reduction in the volume of the chitosan powder bed (64%) upon tapping suggested strong cohesiveness amongst particles which retarded its flow.

The linearity between the bulk volume reduction and %C upon tapping of materials with significant different physical properties (figure 3.4) confirmed the applicability of volume changes during consolidation of powders (as a result of handling, transport or pharmaceutical processes) for predictions on the percentage compressibility (and the flowability) of powders.

The effect of the presence of a glidant (0.25% w/w Aerosil® 200) on the percentage compressibility of the fillers is demonstrated in figure 3.5. Glidants act as flow enhancers due to their ability to adsorb onto the surfaces of larger particles and smooth-out the uneven or rough surfaces of the particles, thereby reducing friction and possible interlocking. This effect should reduce the pour volume (bulk) of the powder due to optimal packing and lessen the volume reduction during tapping.

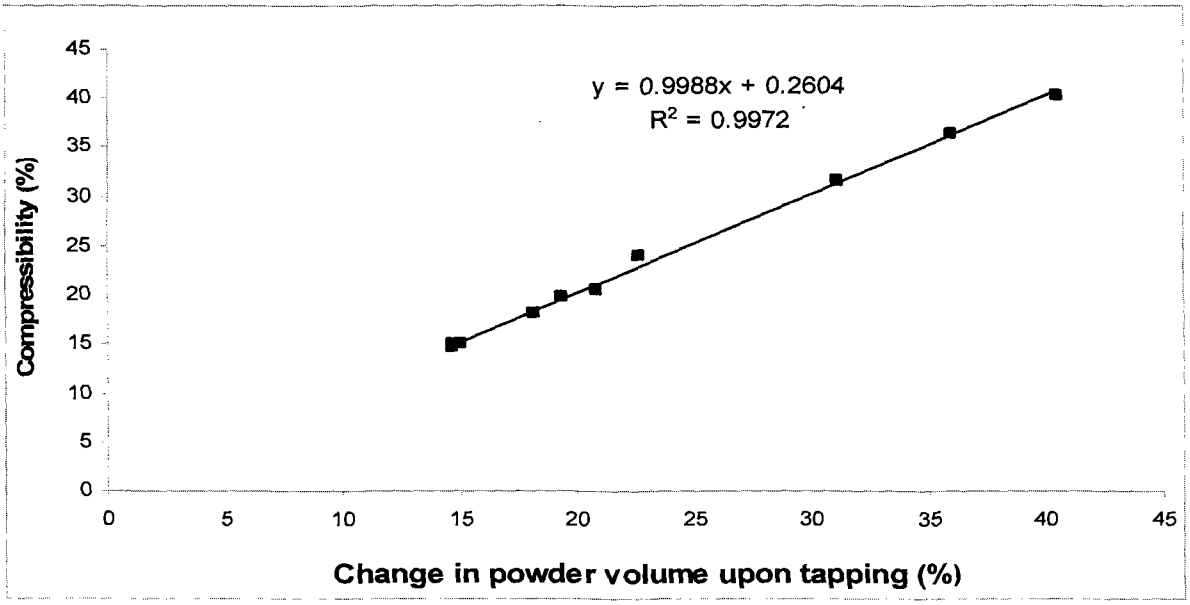


Figure 3.4: Relationships between %C and percentage change in bulk volume upon tapping for several pharmaceutical tablet fillers.

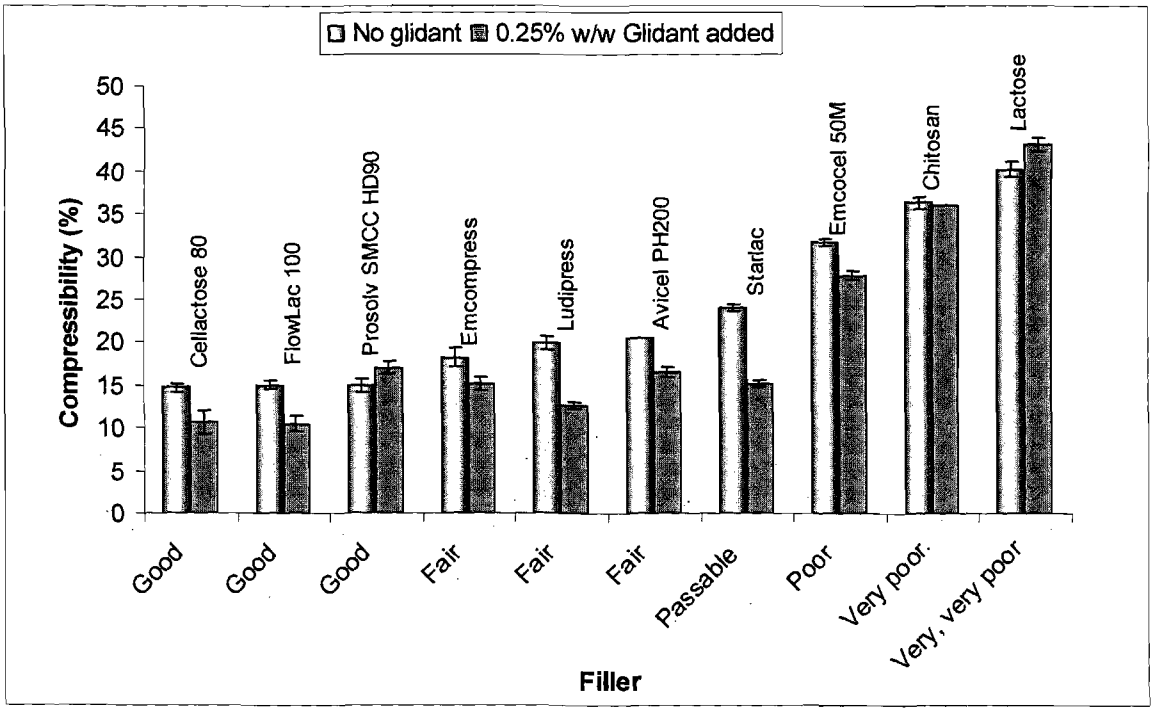


Figure 3.5: Effect of the addition of a glidant (0.25% w/w Aerosil® 200) on the percentage compressibility of the fillers.

The addition of the glidant significantly improved the %C of most of the fillers ($p<0.05$), except for Prosolv SMCC® HD90 and lactose monohydrate (which %C worsened), whilst chitosan showed no response (table 3.5). The percentage improvement in %C ranged from 12% for Emcocel® 50M to 38% for Starlac® (with an average increase of 25±9.65% for all the materials exhibiting an improvement in %C). The results obtained for Prosolv SMCC® HD90

(which is a co-processed compound containing 2% silicon dioxide) suggested that excess glidant (above the optimal) increase, rather than decrease, frictional forces which retarded the flowability of the material. The decrease in flow properties with the addition of the glidant observed for lactose confirmed that glidants need larger particles and a suitable surface structure to adhere to. Comparison of the average particle size of Aerosil® 200 (±48 μm) and lactose (±45 μm) clearly indicate that this was not the case.

An interesting observation from the effect of the glidant on powder flow was that, despite the fact that it improved the flow of most of the fillers used in this study, the improvement did not change the flow category of any of the compounds, i.e. the increase in flowability was not significant enough to change (improve) the flow category of any of the fillers (compare figure 3.5 with the flow categories in table 3.4).

Statistical analysis of the data (Turkeys test) showed significant differences (at a 95% confidence level, i.e. $p<0.05$) between the %C of the majority of the fillers within the two groups, that is between the fillers without a glidant and between the fillers containing 0.25% Aerosil® 200 (table 3.6). This high percentage of observed significant differences (in approximately 90% of the cases) between the various fillers within a group confirmed the accuracy and sensitivity of the parameter to distinguish between the flow properties of different materials, which rank it as a very reliable method to predict the flow properties of powders.

Table 3.6: Results of Turkey's statistical test for the indication of significant differences (indicated by ✓) in the percentage compressibility between the various fillers within the two groups (i.e. without and with a glidant) at a 95% confidence level ($p<0.05$).

	Avicel® PH200	Cellactose® 80	Chitosan	Emcocel® 50M	Emcompress®	FlowLac® 100	Lactose monohydrate	Ludipress®	Prosolv SMCC® HD90	Starlac®	Avicel® PH200	Cellactose® 80	Chitosan	Emcocel® 50M	Emcompress®	FlowLac® 100	Lactose monohydrate	Ludipress®	Prosolv SMCC® HD90	Starlac®
	No glidant present										**0.25% w/w Aerosil® 200 added as glidant**									
Avicel® PH200		✓	✓	✓	✓	✓	✓	NSD	✓	✓		✓	✓	✓	NSD	✓	✓	✓	NSD	NSD
Cellactose® 80	✓		✓	✓	✓	NSD	✓	✓	NSD	✓	✓		✓	✓	✓	NSD	✓	✓	✓	✓
Chitosan	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓
Emcocel® 50M	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Emcompress®	✓	✓	✓	✓		✓		✓	✓	✓	NSD	✓	✓	✓		✓	✓	✓	✓	NSD
FlowLac® 100	✓	NSD	✓	✓	✓		✓	✓	NSD	✓	✓	NSD	✓	✓	✓		✓	✓	✓	✓
Lactose monohydrate	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Ludipress®	NSD	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
Prosolv SMCC® HD90	✓	NSD	✓	✓	✓	NSD	✓	✓		✓	NSD	✓	✓	✓	✓	✓	✓	✓		✓
Starlac®	✓	✓	✓	✓	✓	✓	✓	✓	✓		NSD	✓	✓	✓	NSD	✓	✓	✓	✓	

✓ = significant differences

NSD = no significant differences

3.4.2 Conclusion

The percentage compressibility of the materials evaluated were affected by the particle shape, size and the density of the materials. The way the particles pack also affected the density. Elongated or flat particles tend to pack, albeit loosely, to give powders with high porosity. Particles with high density and a low internal porosity tend to posses free flowing properties. This could be offset by surface roughness, which lead to poor flow characteristics due to friction and cohesiveness (Martin *et al.* 1993:447). Addition of the glidant improved the flowability of most powders to a varying degree. The powder which presented with the best improvement with the addition of the glidant was Ludipress®.

3.4.3 Angle of repose (AoR)

The angle of repose is another one of the indirect methods used to quantify powder flowability. It has been labelled 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. Its acceptance as approved method for determining powder flow, however, has been substantiated by its inclusion in official pharmacopoeia, foe 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).

The angle of repose for the various fillers were determined at ambient conditions in the absence and presence of 0.25% w/w Aerosil® 200 as described in section 2.5.2.2. Table 3.7 presents the classification of powder according to its angle of repose as defined by the USP (2007:644). The results are presented in table 3.8 with the data tabulated in Annexure D.

Table 3.7: Flow properties and corresponding angles of repose (USP, 2007: 644).

Flow property	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

Table 3.8: The angle of repose (degrees) (AOR) of the different pharmaceutical fillers in the absence and presence of 0.25% w/w Aerosil®200 at ambient conditions.

Material	No glidant	0.25% Aerosil® 200
Avicel® PH200	34.87 ± 0.99	34.87 ± 0.54
Cellactose® 80	32.51 ± 0.94	30.36 ± 0.71
Chitosan	45.14 ± 2.21	44.46 ± 0.93
Emcocel® 50M	37.30 ± 4.83	34.64 ± 1.78
Emcompress®	38.30 ± 1.35	35.90 ± 0.49
FlowLac® 100	32.41 ± 3.20	30.64 ± 0.40
Lactose monohydrate	55.39 ± 7.85	26.80 ± 3.81
Ludipress®	34.44 ± 2.09	34.60 ± 2.39
Prosolv SMCC® HD90	33.63 ± 1.45	34.88 ± 0.27
Starlac®	36.18 ± 2.07	36.15 ± 0.23

The results obtained for the AoR proved that this method failed to discriminate between the flow properties of the various powders (Table 3.9). Within the group of fillers without a glidant present, significant differences ($p<0.05$) could only be established in 24% of the cases, whilst within the group where a glidant was added significant differences could be observed in 42% of the cases. In comparison with the results from the percentage compressibility test, where significant differences in flow could be observed in more than 90% of the cases (in both groups), the AoR test was markedly less sensitive to observe

differences between different powders. Comparison of the results of AoR to that of %C (figure 3.6) clearly indicate that AoR is more sensitive towards differences in powders presenting poor to average flow (>41°), than towards powders which exhibit fair to excellent flow (i.e. in the range of 25 - 40°). One of the reasons for its failure to discriminate between the flow properties of powders may be the relative high standard deviation observed between repetitions (in some cases as high as ±8° SD).

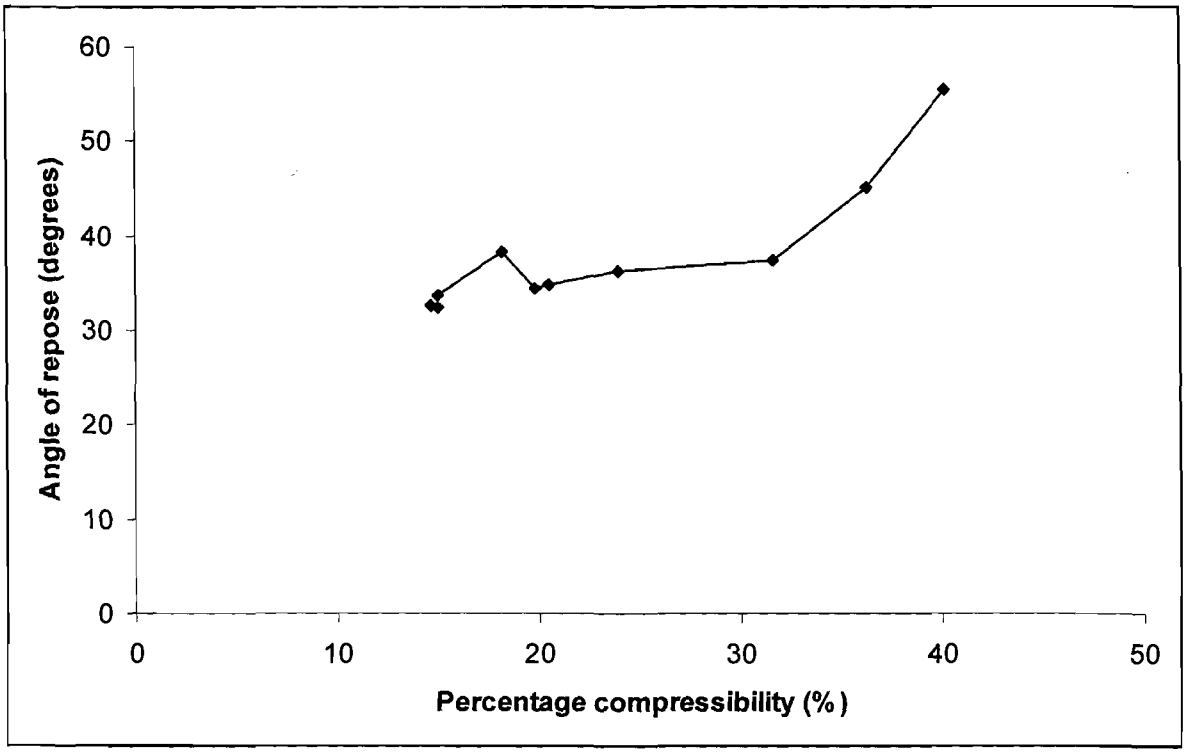


Figure 3.6: Relationship between the angle of repose versus percentage compressibility of the various powders.

Table 3.9: Results of Turkey's statistical test for the indication of significant differences (indicated by ✓) in the angle of repose between the various fillers within the two groups (i.e. without and with a glidant) at a 95% confidence level ($p<0.05$).

	Avicel® PH200	Cellactose® 80	Chitosan	Emcocel® 50M	Emcompress®	FlowLac® 100	Lactose monohydrate	Ludipress®	Prosolv SMCC® HD90	Starlac®	Avicel® PH200	Cellactose® 80	Chitosan	Emcocel® 50M	Emcompress®	FlowLac® 100	Lactose monohydrate	Ludipress®	Prosolv SMCC® HD90	Starlac®
	No glidant present										**0.25% w/w Aerosil® 200 added as glidant**									
Avicel® PH200		NSD	✓	NSD	NSD	NSD	✓	NSD	NSD	NSD		NSD	✓	NSD	NSD	NSD	✓	NSD	NSD	NSD
Cellactose® 80	NSD		✓	NSD	NSD	NSD	✓	NSD	NSD	NSD	NSD		✓	NSD	✓	NSD	NSD	NSD	NSD	✓
Chitosan	✓	✓		NSD	NSD	✓	✓	NSD	NSD	NSD	✓	✓		✓	✓	✓	✓	✓	✓	✓
Emcocel® 50M	NSD	NSD	NSD		NSD	NSD	✓	NSD	NSD	NSD	NSD	NSD	✓		NSD	NSD	✓	NSD	NSD	NSD
Emcompress®	NSD	NSD	NSD	NSD		NSD	✓	NSD	NSD	NSD	NSD	✓	✓	NSD		✓	✓	NSD	NSD	NSD
FlowLac® 100	NSD	NSD	✓	NSD	NSD		✓	NSD	NSD	NSD	NSD	NSD	✓	NSD	✓		NSD	NSD	NSD	✓
Lactose monohydrate	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	NSD	✓	✓	✓	NSD		✓	✓	✓
Ludipress®	NSD	NSD	✓	NSD	NSD	NSD	✓		NSD	NSD	NSD	NSD	✓	NSD	NSD	NSD	✓		NSD	NSD
Prosolv SMCC® HD90	NSD	NSD	✓	NSD	NSD	NSD	✓	NSD		NSD	NSD	NSD	✓	NSD	NSD	NSD	NSD	✓		NSD
Starlac®	NSD	NSD	NSD	NSD	NSD	NSD	✓	NSD	NSD		NSD	✓	✓	NSD	NSD	✓	✓	NSD	NSD	

✓ = significant differences
NSD = no significant differences

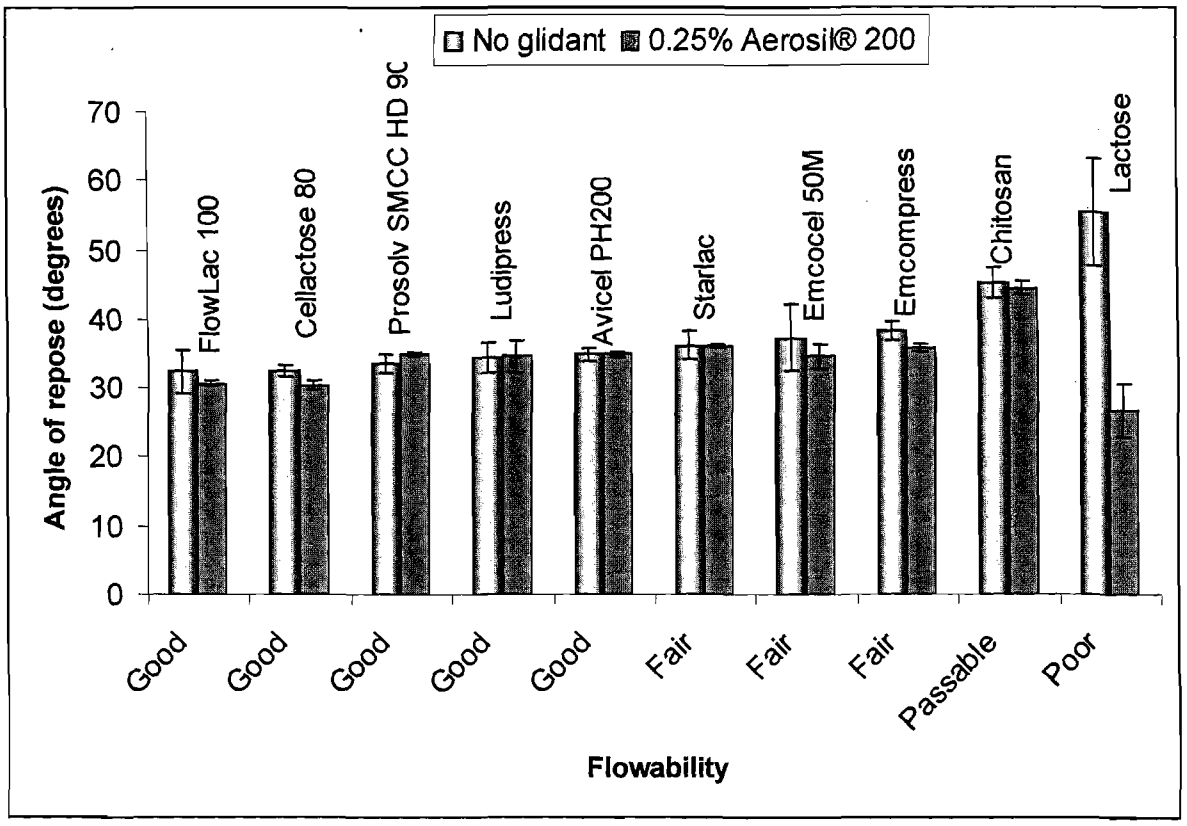


Figure 3.7: Flow characterization of different pharmaceutical fillers in the presence and absence of glidant (0.25% Aerosil® 200) according to angle of repose.

The following rank order could be established for the fillers without a glidant present: FlowLac® 100 ≈ Cellactose® 80 ≈ Prosolv SMCC® HD90 ≈ Ludipress® ≈ Avicel® PH200 ≈ Starlac® ≈ Emcocell® (no significant differences) >> chitosan (significantly poorer) >> lactose monohydrate (significantly poorer) (figure 3.7). The fillers presenting good to fair flow all possessed relative large particle sizes in excess of 120 μm (table 3.1) and spherically shaped particles (figure 3.1). It is commonly known that large, spherical shaped particles flow better because of the relatively large interparticle distances resulting in a decrease in attractive and friction forces. During formation of the powder cone beneath the funnel, the particles readily flowed over each other and down the sides of the cone since the gravitational forces exceeded the interparticle attractive forces, which led to a reduction in the height-diameter ratio of the cone. The acceptable flow of Prosolv SMCC® HD90, despite its relative smaller average particle size (compared to the other fillers in the group) could be attributed to the presence of 2% colloidal silicon dioxide, which acted as a glidant (reducing friction).

Somewhat unexpectedly, Emcocel® 50M appeared in the group of fillers exhibiting fair to good flow, despite its relative small average particle size (±85 μm) and fibrous shape (figure3.1[d]), both properties which are not conducive to good flow. No explanation for this unexpected good flow could be found.

Lactose monohydrate exhibited the poorest flow (figure 3.7) and according to the USP classification (table 3.7) its flow could be described as very, very poor. Small particles (average particle size of lactose monohydrate was ±46 μm) tend to be more cohesive since their relatively small size allowed for closer contact between the particles, therefore being more affected by the interparticle attractive forces. Stacking of the particles, due to friction, resulted in an increase in the cone height-diameter ratio with a corresponding high angle of repose for the material (>55°).

Despite the relative large average particle size of chitosan (±177 μm) the material displayed rather poor flow (passable according to the USP classification in table 3.7). Its flow behaviour might be ascribed to the unfavourable particle shape of the material (figure 3.1[c]). The flake-like particles glide, rather than flow, across each other and "stacking" continued until the approach angle of the falling particle overcame the cohesive forces, and only then did the particles start to slide down the side of the powder cone.

The addition of 0.25% w/w Aerosil® 200 as a glidant significantly improved ($p<0.05$) the flowability of only three of the fillers, namely lactose monohydrate, Cellactose® 80 and Emcompress® (table 3.7). Of more importance, however, was the increase in the number of significant differences which were observed in the flowability between specific fillers; before the addition of the glidant there were only 13 significant differences in the flow of the fillers (out of a total of 45 comparisons). Most of these differences were between the materials exhibiting fair/good flow and the materials with poorer flow (lactose and chitosan with AoR >40°). Very few significant differences were present between materials exhibiting good and fair flow (i.e. AoR <40°). Upon addition of the glidant, significant difference were observed in the group of fillers exhibiting fair to good flow (which was not apparent in the absence of the glidant), for example between Starlac® and Cellactose® 80; Cellactose® 80 and Emcompress®; FlowLac® 100 and Emcompress®; and Starlac® and FlowLac® 100. This illustrated the ability of a glidant to further improve powder flow of powders already having suitable flow properties, and to further discriminate between the flow behaviour of powders with acceptable flow.

As was the case with %C and COD, the flow of Prosolv SMCC® HD90 decreased somewhat upon the additional addition of a glidant (since it already contained 2% silicone dioxide), which emphasized the fact that for every material an optimum exists for the glidant to exercise a positive effect.

3.4.3.1 Conclusion

The angle of repose of the fillers was affected by the cohesiveness and friction between the particles as well as the shape, surface structure and size of the particles. This method in

comparison to the COD and %C tests is less discriminative in terms of indicating differences in the flow of powders with comparable physical properties, but more in the obvious dissimilarity in flow properties. A further drawback of this method is the variation in results between repetitions (indicated by a larger standard deviation compared to the other two methods) which is affected by the way the samples were handled prior to measurement.

3.4.4 Flow rate (FR)

Flow rate is affected by particle and process related effects. Particle-related effects are affected by particle size, shape and density; and process related effects are orifice diameter, hopper width, head size (height of the powder bed) and hopper wall angle (Staniforth 2002:204). All of the process related effects were kept identical and the materials evaluated presented the full range of flow characteristics available, i.e. from free flowing to cohesive materials. Flow rate is useful for materials that have some capacity to flow, but is not useful for cohesive materials. Selecting an orifice diameter was difficult because selecting an inappropriate orifice diameter may result in a false measurement of the flow rate due to funnel flow (Staniforth, 2002:205). A mass flow rate was therefore preferred, and an orifice diameter of 15 mm was chosen, which was roughly midway between the smallest and largest diameter through which all the powder flowed (as determined in section 3.4.1:- critical orifice diameter).

Since no official index or scale is available to classify materials according to their flow rate, the ranking presented in table 3.10 was designed to produce a system to evaluate and compare the flow rate of the fillers evaluated in this study.

Table 3.10: Ranking index used to classify flow according to the flow rate.

Flow description	Flow rate ($g.sec^{-1}$)
Excellent (free flowing)	>20
Good (no glidant needed)	>10 - 20
Average	>5 - 10
Poor (glidant required)	2 - 5
Very poor (extremely cohesive with little or no natural flow)	<2

The flow rate of the various materials was determined at ambient conditions in the absence and presence of 0.25% w/w Aerosil® 200 as described in section 2.5.2.2; and the results are presented in table 3.11 with the data tabulated in Annexure E.

Table 3.11: The flow rate ($g.sec^{-1}$) (FR) of the different pharmaceutical fillers in the absence and presence of 0.25% w/w Aerosil® 200 at ambient conditions.

Material	No glidant	0.25% Aerosil® 200
Avicel® PH200	7.14 ± 0.71	8.31 ± 0.11
Cellactose® 80	11.48 ± 0.11	12.33 ± 3.32
Chitosan	4.23 ± 0.37	5.12 ± 1.01
Emcocel® 50M	00.00 ± 0.00	00.00 ± 0.00
Emcompress®	22.58 ± 0.21	21.63 ± 2.61
FlowLac® 100	12.03 ± 1.28	16.39 ± 0.03
Lactose monohydrate	00.00 ± 0.00	00.00 ± 0.00
Ludipress®	14.34 ± 0.14	14.84 ± 0.08
Prosolv SMCC® HD90	8.55 ± 1.41	7.45 ± 0.03
Starlac®	8.14 ± 0.06	6.11 ± 1.37

In the absence of a glidant, the fillers exhibited the following rank order in terms of flow rate: Emcompress® >> Ludipress® >> Cellactose® 80 ≈ FlowLac® 100>> Starlac® ≈ Prosolv SMCC® HD90 ≈ Avicel® >> chitosan >> Emcocel® 50M ≈ lactose monohydrate (>> indicating significant differences at a 95% confidence level with $p<0.05$). No relationship could,

however, be established between particle size, shape and surface structure, and flow rate, except in the cases of chitosan (flake-like particles), Emcocel® 50M (±85 μm) and lactose monohydrate (±46 μm) where unfavourable particle shape and small particle sizes unquestionably had a negative effect on particle flow in general and specific flow rate. From the results of the COD of these three materials (section 3.4.1) it was expected that chitosan would just flow through the chosen orifice (COD = 11 mm), and Emcocel® 50M and lactose would not flow through (COD = 32 mm).

Emcompress® exhibited excellent flow (table 3.11) which might be attributed to the material's relatively high density (table 2.2) as well as other contributing factors, namely the spherical particles (figure 3.1[e]) and its particle size distribution (table 3.1). It had the highest density of all the materials which caused the powder to flow faster and the smaller particles attached to the larger particles and smoothed the surface structure which resulted in less interparticle friction and resulted in the best flow rate.

The comparable flow rate of Avicel® PH200 (7.14 $g.s^{-1}$) and Prosolv SMCC® HD90 (8.55 $g.sec^{-1}$), despite the particle size difference (±202 μm and ±122 μm respectively), could be attributed to the presence of a glidant in Prosolv SMCC ® HD90, which reduced friction and enhanced particle flowability.

Figure 3.8 provides a comparison between the flow rate of the fillers with and without the glidant. The addition of the glidant (0.25% Aerosil® 200) significantly improved the flow rate of Ludipress®, FlowLac® 100 and Avicel® PH200, whilst the flow rate of none of the other fillers were significantly affected by the presence of the glidant. The common factor in the materials positively affected by the addition of a glidant seemed to be a rough / uneven surface structure and relative large particle sizes (>132 – 234 μm), which could accommodate adsorption of the smaller glidant particles onto their surfaces thereby smoothing the roughness and reducing frictional forces. The flow rate of Flowlac® 100 benefited most by the addition of the glidant resulting in an increase from approximately 12 to over 16 $g.sec^{-1}$ (an increase of ±36%)

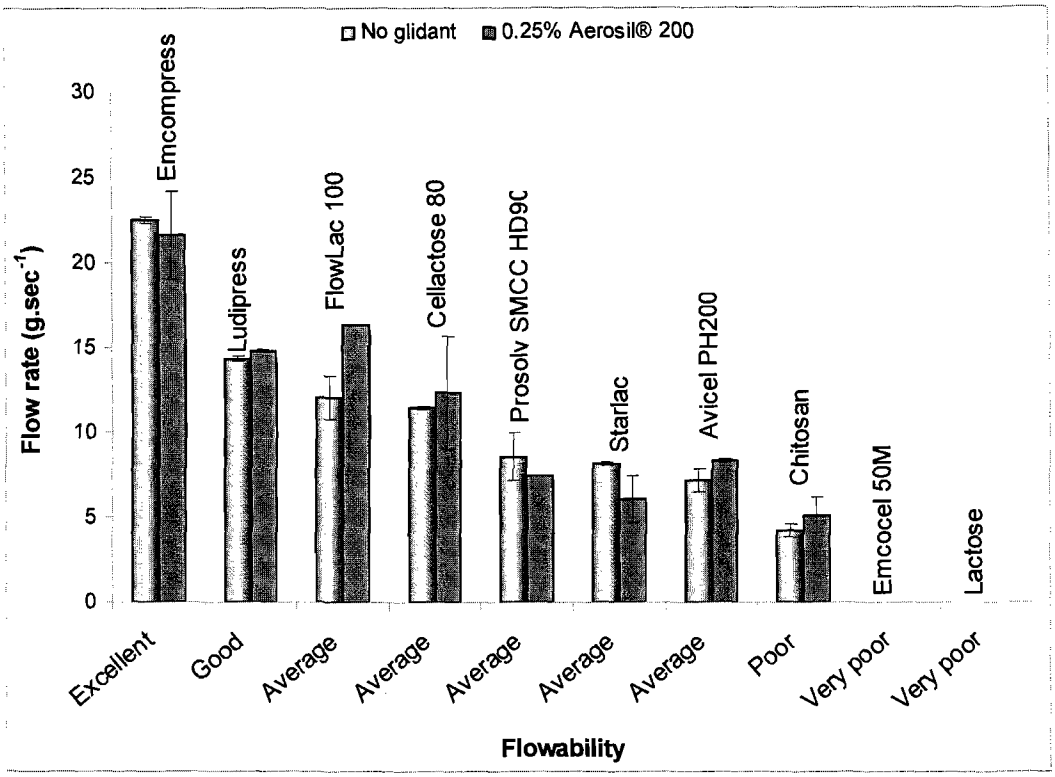


Figure 3.8: Flow characterization of different pharmaceutical fillers in the presence and absence of glidant (0.25% Aerosil® 200) according to flow rate.

3.4.4.1 Conclusion

The flow rate of the fillers was predominantly affected by the density of the materials and the size, shape and surface structure of the particles. Powders with a higher density seemed to exhibit a better flow rate, although some of the other factors affected the flow rate more when the densities was very close to one another or identical. Small particles (<100 µm) have poorer flow in comparison with larger particles and the flow rate tests illustrated it. Flow rate is a good indicator of the flowability of materials. The only problem with this method is that the material must have the ability to flow. If a material is very cohesive and exhibits no flow, then this method would not be recommended. Most of the materials exhibited better flow with the addition of the glidant, even though it was not significant in most cases.

3.5 Conclusion

From the results obtained from various flow tests performed on the different fillers, it can be concluded that not one of the various powders achieved the outright best result in all of the four flow tests (see table 3.12). The results clearly indicated that flow results and flow classification (based on the test results) for a specific material may vary depending on the *method used to determine the flow rate.*

Table 3.12: *Ranking of the different fillers based on the results of each flow test.*

Materials	No glidant					Addition of 0.25% w/w Aerosil® 200				
	COD	%C	AoR	FR	Average ranking	COD	%C	AoR	FR	Average ranking
Avicel® PH200	1	6	5	7	4.75 (6th)	3	6	5	5	4.75 (4th)
Emcocell® 50M	9	8	7	9	8.25 (8th)	9	8	6	9	8.00 (9th)
Emcompress®	3	4	8	1	4.00 (5th)	7	4	8	1	5.00 (5th)
Prosolv SMCC® HD90	3	2	3	5	3.25 (3rd)	3	7	7	6	5.75 (6th)
Cellactose® 80	1	1	1	4	1.75 (1st)	1	2	2	4	2.25 (2nd)
FlowLac® 100	3	2	2	3	2.50 (2nd)	1	1	3	2	1.75 (1st)
Lactose monohydrate	9	10	10	9	9.50 (10th)	10	10	1	9	7.50 (8th)
Ludipress®	3	5	4	2	3.50 (4th)	3	3	4	3	3.25 (3rd)
Starlac®	3	7	6	6	5.50 (7th)	3	5	9	7	6.00 (7th)
Chitosan	8	9	9	8	8.50 (9th)	7	9	10	8	8.50 (10th)

The reasons for these differences in the outcome of the tests could primarily be found in the fact that different physical properties of powders (particle size and shape, surface structure, density of the powder etc.) affected their flowability, and that the different tests measured different powder properties. Each flow test challenged only two or more components that contributed to the flowability of the powder. Taylor *et al.* (2000:10) stated that AoR provided an indirect measurement of the shape, size, porosity, cohesion, fluidity, surface structure and bulk properties of the materials and that percent compressibility indicated the uniformity in size and shape, deformability, surface structure, cohesion and moisture content. He further added that critical orifice diameter was a direct measure of powder cohesion and arch strength. Flow rate seemed to be affected by a wide range of different physical powder properties, such as density, surface structure, particle shape and size.

Comparisons and classifications of powders (in terms of their flowability) based on the results from a single flow test may result in a "false" or misleading evaluation of their flowability, followed by incorrect selection of the most suitable material during product formulation, which could jeopardise the quality of the final product. If the results obtained from a specific flow test is biased towards a specific property of the filler being tested (perhaps due to the dynamics of the test conditions), whilst for another material this particular property is not favourable, but it possesses other physical properties that favour suitable flow, the latter material may be at a significant disadvantage in terms of being selected based on the outcome of the test. For instance, it is well known and accepted that larger particles flow better than smaller particles; but it is also acknowledged that particles with a smooth surface structure flow better than particles with a rough / uneven surface, and that flowability diminishes the more the shape of a particle deviates from a spherical shape. The question now arises: how would one compare the flow of non-spherical, smooth-surfaced particles with a relative large particle size with that of smaller, spherical particles, using a method which favours particle size more than particle shape or surface structure? At this stage no mention has even been made about other particle properties i.e. powder density, the structural strength of the particles, deformability, particle size distribution, etc.

Careful consideration of the results obtained from the various flow tests and relating the results to specific powder or particle properties, clearly emphasized that no single test can be used to judge, compare and classify powders with different physical properties. It remains, however, unquestionable that a sound knowledge and understanding of the flow properties of pharmaceutical powders (and the factors affecting it) are essential to establish a much needed basis in which to compare and evaluate powders.

Taylor *et al.* (2000:6) presented a quite simple solution to this problem through integration of the results obtained from different flow tests into a composite index. This allowed for each of the various factors / properties, affecting powder flow, to contribute to a more "true" representative result of the flowability of a powder. This will allow formulation scientists to better select the correct / suitable pharmaceutical excipients for inclusion in solid dosage form formulations.

CHAPTER 4

Compilation of a reliable composite index for pharmaceutical powders

4.1 Introduction

Taylor *et al.* (2002:1-11) was the first to compile a composite flow index for pharmaceutical powders which include the results of three different flow tests, namely angle of repose, critical orifice diameter and percentage compressibility. The results from their study clearly indicated the advantage of a composite flow index to evaluate and compare powder flowability instead of using only one test result, since it presented a parameter which better discriminated between the flow of materials with markedly different flow properties and it accommodated most of the various powder properties which are known to affect powder flow.

Three possible shortcomings were identified from the work of Taylor and co-workers, namely:

- omission of an important flow factor, the flow rate of a powder, from the composite index;
- assigning an equal weight (contribution) for each test score in the composite index; and
- using a rather inaccurate flow classification scale, with only three divisions (good, average and poor) to rank the powders.

The aim of this section of the study, therefore, was to determine:

- if inclusion of the flow rate of powders would contribute significantly to the accuracy of the composite flow index;
- whether assigning different weights to the test scores included in determining the CFI would increase the accuracy of the results in terms of better distinguishing between powders with different flow properties; and
- if the use of a more comprehensive (accurate) flow scale (classification) would improve the ability to better separate powders from one another in terms of their flow properties.

Table 4.1 presents the flow scale used by Taylor *et al.* (2000:6) based on the CFI of the powders they tested, and the modified scale suggested in this study (based on the scale used by the USP, 2007:644). The major disadvantage of Taylor's flow scale is that it does not allow for differentiation between powders with CFI's ranging from 0 - 60 and from 70 - 100, whilst both groups definitely include powders with significantly different flow properties.

Table 4.1: Flow scale used by Taylor et al. (2000:6) and the scale proposed in this study based on the classification of the USP (2007:644).

Scale used by Taylor & co-workers		Suggested scale	
Flow description	**CFI**	**Flow description**	**CFI**
Good	>70	Excellent	>85
Average	>60-70	Good	>75 - 85
Poor	<60	Fair	>60 - 75
		Passable	>45 - 60
		Poor	>30 - 45
		Very poor	>15 - 30
		Very, very poor	≤15

4.2 Equations derived to determine the composite flow index

Taylor *et al.* (2000:6) used linear equations to transform the test results of each material for each of the 3 flow tests to a value between 0 and 33 ⅓%; the latter being the maximum contribution of each test to the composite flow index (see section 1.8). The transformed results for each material obtained from each test were then summed to yield the composite flow index for that specific material (equation 4.1). The composite flow index (CFI) is the sum of the transformed data for each test included in the composite index:

$$CFI = y_1 + y_2 + \ldots\ldots\ldots + y_n. \qquad \text{[Eq. 4.1]}$$

Where:

y_1 to y_n are the transformed scores for test 1 to test n.

The linear equations ($y = mx + c$) used for data transformation of the test scores for the different tests performed in this study were obtained from figure 4.1 for the scenario where all 4 tests were included in the CFI, each with an equal weight of 25%:

- Critical orifice diameter value (y_1) = -0.7576*(test score for COD) + 25.758 [Eq. 4.2]
- Angle of repose value (y_2) = -0.5556*(test score for AOR) + 33.333 [Eq. 4.3]
- Percentage compressibility value (y_3) = -0..625*(test score for %C) + 28.125 [Eq. 4.4]

- Flow rate value (y_4) = +0.25*(test score for FR) + 0 [Eq. 4.5]

The lines in figure 4.1 were obtained as follows:

- *Firstly, for each test the range was determined within which the result / score for each material would fall and the minimum and maximum values were noted (x-values).* The range, minimum and maximum value of each test are presented in table 4.2;
- Secondly the number of tests included and the weight (percentage) of each test in the composite flow index was set;
- Thirdly, two sets of x;y-coordinates were set up (x_1;y_1) and (x_2:y_2);
- Finally, x;y-coordinates were plotted and the linear equation for each line was determined (figure 4.1).

Table 4.2: *Minimum and maximum values and x;y coordinates used for determining transformation equations to calculate the composite flow index in which each of the four tests have an equal weight (i.e. 25%).*

Test	Minimum	Maximum	$x_1;y_1$ coordinates	$x_2;y_2$ coordinates
Angle of repose (°)	15	60	60;0	15;25
Critical orifice diameter (mm)	1	34	34;0	1;25
Percentage compressibility (%)	5	45	45;0	5;25
Flow rate ($g.sec^{-1}$)	0	25	0;0	25;25

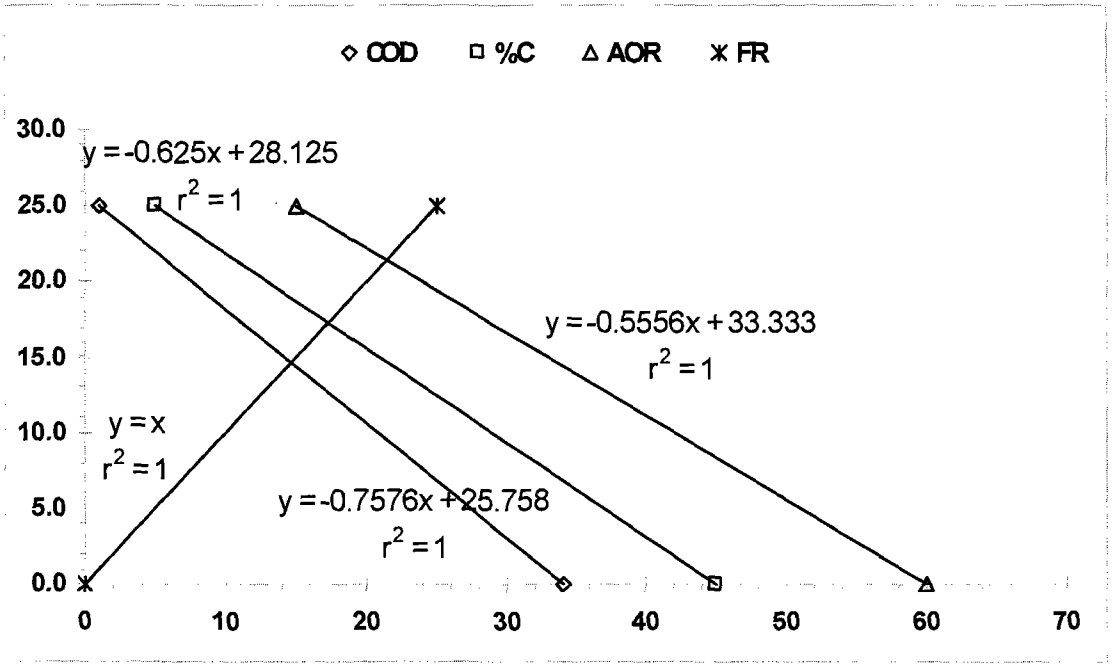


Figure 4.1: Plots of the x;y-coordinates for each individual flow tests where all four test scores were included and each test score contributed 25% to the CFI.

Two factors determine the constants (the slope and the y-axis intercept) in the linear equations used for data transformation of the individual test, namely the (i) percentage contribution of each test to the composite index, and (ii) the range of the scores obtained for each test (estimated minimum and maximum values which defined the range within which the test scores for each specific test fell). Since the range for each test remained a constant in this study, it implied that a change in the contribution of each test to the CFI (resulting from a change in the number of tests included in the CFI), would automatically lead to a change in the slope (m) and the intercept (c) of the various lines, thus changing the equations used for data transformation (eq. 4.2 – 4.5). Table 4.3 presents the values for the slopes (m) and y-axis intercepts for a range of different weights for each of the various flow tests used for data transformations to determine CFI's.

Table 4.3: *Slopes (m) and y-axis intercepts (c) used for data transformations of scores for different weight contributions of a test in the CFI.*

Weight (%)	Flow test							
	COD		%C		AoR		FR	
	m	c	m	c	m	c	m	c
10	-0.30	10.30	-0.25	11.25	-0.22	13.33	0.4	0.00
20	-0.60	20.60	-0.5	22.5	-0.44	26.66	0.8	0.00
30	-0.90	30.90	-0.75	33.75	-0.66	40	1.2	0.00
40	-1.21	41.21	-1	45	-0.88	53.33	1.6	0.00
50	-1.51	51.51	-1.25	56.25	-1.11	66.66	2	0.00

4.3 *Inclusion of the results of only 3 flow tests (equally weighted at 33.33%) versus the inclusion of the results of all 4 flow tests (equally weighted at 25% each) in determining the CFI*

Table 4.4 presents CFI of the various fillers for the scenarios where the tests score of all four flow tests were included (column 2); and where the test score of one of the tests were excluded (columns 3-5). Equations 4.2 – 4.5 were used to transform the individual test scores which were then summed (eq. 4.1). The tests scores for each filler (without a glidant added) are presented in table 3.3 on page 42 (COD), table 3.5 on page 46 (%C), table 3.8 on page 53 (AoR) and table 3.11 on page 59 (FR).

Table 4.4: *Composites flow indexes for the different fillers (without a glidant) with a change in the number of tests included*

	Composite flow index (CFI)				
	All 4 tests included	**FR excluded**	**COD excluded**	**%C excluded**	**AOR excluded**
Weight	**25% each**	**Weight of each test included = 33.33%**			
Avicel® PH200	60.7	71.4	48.5	60.5	62.2
Cellactose® 80	70.0	78.1	61.0	68.1	72.9
Chitosan	35.3	41.5	23.8	39.9	36.0
Emcocel® 50M	22.5	29.9	27.9	18.8	13.1
Emcompress®	74.9	69.7	68.5	77.5	83.7
Flowlac® 100	69.6	76.8	61.4	67.8	72.3
Lactose	7.1	9.5	7.4	5.4	6.0
Ludipress®	67.8	71.2	59.0	69.4	71.4
Prosolv® HD90	65.4	75.8	55.9	62.2	67.7
Starlac®	58.0	66.5	45.9	59.8	59.6

The calculation of the CFI for each filler, when the score of the flow rate was excluded and the weight of the remaining three tests were set equal, i.e. at 33 ⅓% (values in column 3 of table 4.4), corresponds with the method used by Taylor *et al.* (2000:6) and will be used as a baseline for further comparisons.

Inclusion of the score for the flow rate test markedly reduced the CFI for almost all the fillers, except for Emcocel® 50M and Emcompress® (see figure 4.2). Excluding either one of the other tests had the same effect, varying only in the magnitude of the change. These results indicated that inclusion of the flow rate in the CFI or excluding any one of the other tests condensed the values and reduced the ability to discriminate between the different fillers. For example, it grouped together (on Taylor's flow scale) fillers like Avicel® PH200 and Prosolv SMCC® HD90 (fillers with noticeable superior flow) with Emcocel® 50M and lactose (fillers with inferior flow properties).

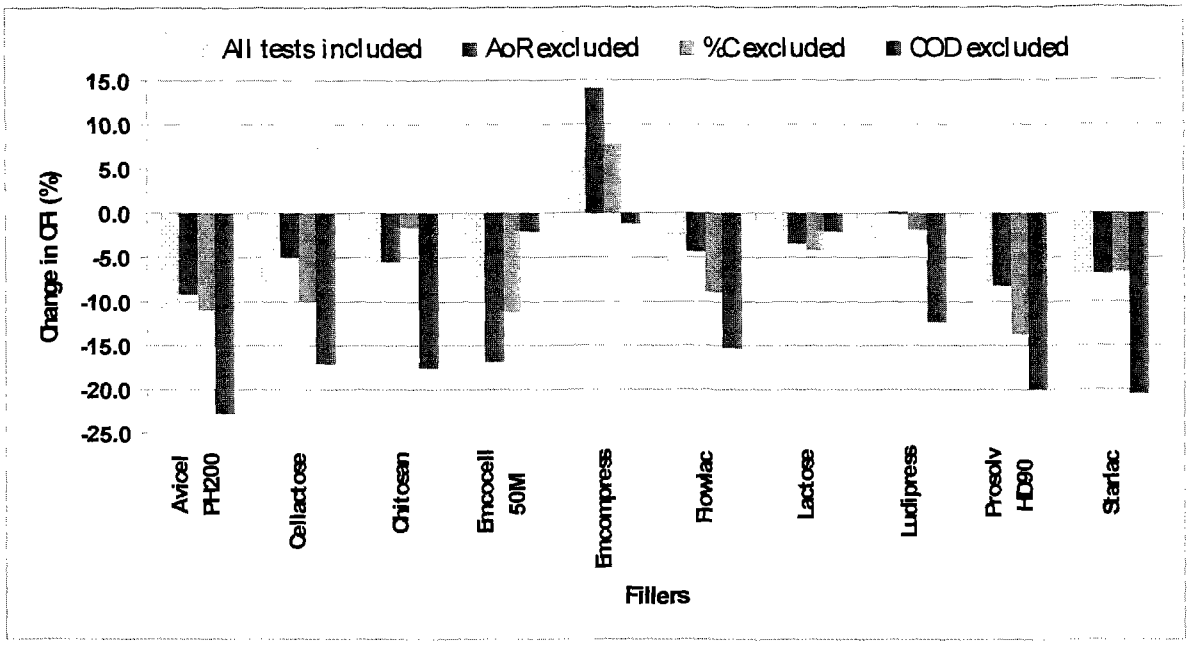


Figure 4.2: Effect of changing the composition of the composite flow index. The CFI where COD, AoR and %C were included with an equal weight of 33.33% were use as baseline (data from table 4.3).

The difference in the effect on the CFI of Emcompress® (an increase in the CFI when including FR or excluding the test scores of either AoR or %C) could be attributed to the unexpected high flow rate of this material (>22 $g.sec^{-1}$) compared to the other fillers (FR ranging between 4 and 15 $g.sec^{-1}$). Inclusion of the FR benefited the CFI of this filler significantly due to its high flow rate.

The most significant decrease in the CFI of almost all fillers was observed when the tests scores of the COD were excluded from the CFI, which indicated the importance of this test for the prediction of powder flow. The following rank order for the reduction in CFI with a change in its composition could be established: ***Excluding COD*** (13% change) **>** ***excluding %C*** (7.6% change) ≈ ***including FR*** (6.9% change) **>** ***excluding AoR*** (5.7% change). The same tendency was observed with the addition of a glidant (0.25% w/w Aerosil® 200), with the following rank order: ***Excluding COD*** (15% change) **>** ***excluding AoR*** (9% change) ≈ ***excluding %C*** (8.9% change) **>** ***including FR*** (8.1% change).

Upon consideration of the results obtained for the CFI, (with the inclusion of all 4 tests scores) it was obvious that the addition of the flow rate was detrimental, rather than beneficial, in terms of providing a more representative composite flow index. It reduced the CFI-values obtained for each individual filler and condensed the range between lowest and highest values. The scores for this test will, therefore, be omitted in the following section in

which the effect of varying the contribution (weight percentage) of the remaining three test scores on the CFI is determined.

Figure 4.3 illustrates the relation between each flow test and the CFI. The results indicated that the best correlation with CFI was obtained by %C (r^2 = 0.9012) followed by COD (r^2 = 0.8919. Both AoR and FR showed poor correlation with CFI having correlation coefficients of 0.7697 and 0.7317 respectively.

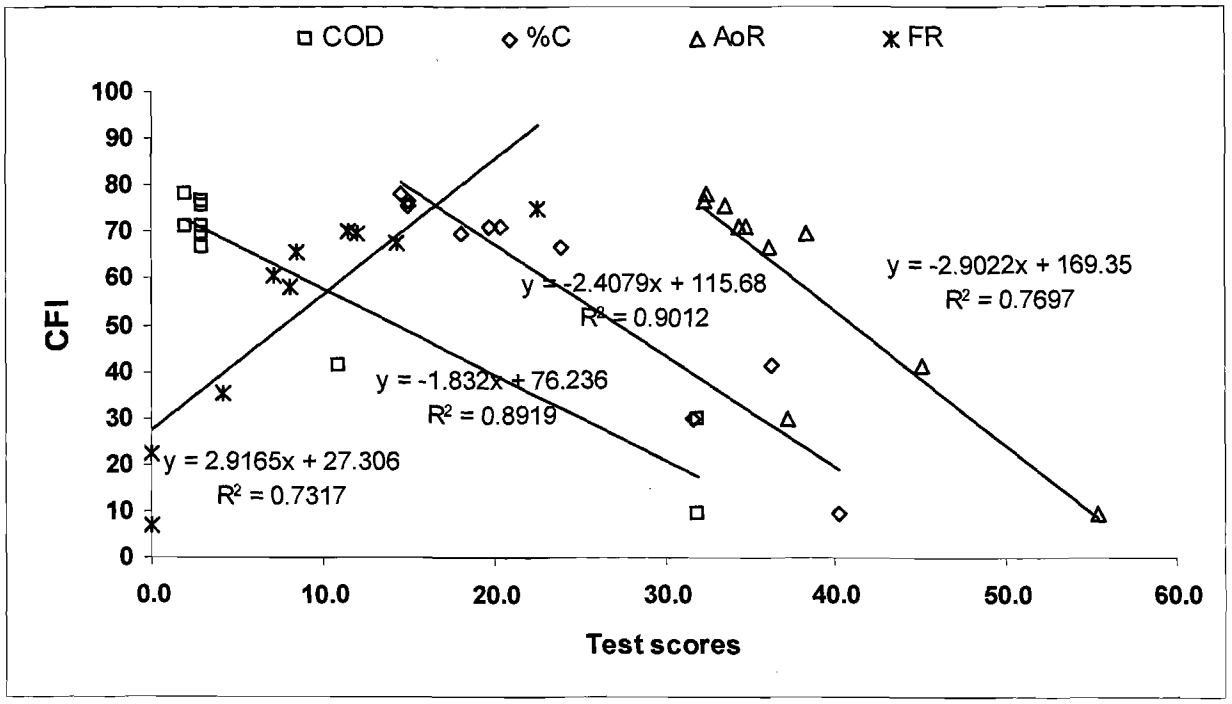


Figure 4.3: Correlation between various test scores and CFI.

Comparison of the relationship between the scores obtained for the different tests showed the best correlation between %C and AoR (r^2 = 0.776), little between %C and COD (r^2 = 0.661) and no correlation between COD and AoR (r^2 = 0.000).

4.4 Changing the contribution of the individual test weights

The effect of a variation in the weight percentage of the various tests on the CFI is presented in table 4.5 (no glidant) and figure 4.6 (glidant added).

Table 4.5: Comparison of the rankings of the different weighted CFI in the absence of a glidant.

cod-%c-aor	50-40-10	50-30-20	50-20-30	50-10-40	40-50-10	40-40-20	40-30-30	40-20-40	40-10-50	30-50-20	30-40-30	30-30-40	30-20-50	20-50-30	20/40/40	20-30-50	10-50-40	10-40-50	33/33/33
Avicel® PH200	78.6	78.0	77.5	76.9	75.0	74.5	73.9	73.4	72.8	70.9	70.3	69.8	69.3	66.8	66.2	65.7	62.7	62.1	71.4
Cellactose® 80	85.0	83.5	82.1	80.7	82.8	81.4	80.0	78.5	77.1	79.3	77.9	76.4	75.0	75.7	74.3	72.9	72.2	70.8	78.1
Chitosan	46.8	48.0	49.1	50.2	42.0	43.2	44.3	45.4	46.6	38.4	39.5	40.6	41.8	34.7	35.8	37.0	31.0	32.2	41.5
Emcocel® 50M	21.4	23.1	24.8	26.5	24.1	25.8	27.6	29.3	31.0	28.6	30.3	32.0	33.7	33.0	34.7	36.4	37.4	39.2	29.9
Emcompress®	78.6	76.7	74.9	73.0	75.9	74.1	72.2	70.3	68.4	71.4	69.5	67.6	65.7	66.8	64.9	63.0	62.2	60.3	69.7
FlowLac® 100	83.1	81.7	80.4	79.0	81.2	79.8	78.5	77.1	75.7	77.9	76.6	75.2	73.8	74.7	73.3	71.9	71.4	70.0	76.8
Lactose monohydrate	8.9	8.7	8.5	8.3	9.5	9.3	9.1	8.9	8.8	9.9	9.7	9.5	9.4	10.3	10.1	10.0	10.7	10.6	9.5
Ludipress®	77.8	77.2	76.6	76.0	74.7	74.1	73.5	72.9	72.3	71.0	70.4	69.8	69.2	67.3	66.7	66.1	63.6	63.0	71.2
Prosolv SMCC® HD90	82.8	81.2	79.5	77.9	80.9	79.3	77.7	76.0	74.4	77.4	75.8	74.1	72.5	73.9	72.2	70.6	70.3	68.7	75.8
Starlac®	73.4	73.3	73.3	73.3	69.1	69.2	69.2	69.2	69.3	65.0	65.1	65.1	65.1	60.9	61.0	61.0	56.8	56.9	66.5
Max	85.0	83.5	82.1	80.7	82.8	81.4	80.0	78.5	77.1	79.3	77.9	76.4	75.0	75.7	74.3	72.9	72.2	70.8	78.1
Min	8.9	8.7	8.5	8.3	9.5	9.3	9.1	8.9	8.8	9.9	9.7	9.5	9.4	10.3	10.1	10.0	10.7	10.6	9.5
Diff	76.1	74.8	73.6	72.3	73.4	72.1	70.9	69.6	68.3	69.4	68.1	66.9	65.6	65.4	64.2	62.9	61.5	60.2	68.6

Table 4.6: Comparison of the rankings of the different weighted CFI in the presence of a glidant (0.25% Aerosil® 200).

coo-%c-aor	50-40-10	50-30-20	50-20-30	50-10-40	40-50-10	40-40-20	40-30-30	40-20-40	40-10-50	30-50-20	30-30-40	30-40-30	30-20-50	20-50-30	20/40/40	20-30-50	10-50-40	10-40-50	33/33/33
Avicel® PH200	82.6	81.1	79.7	78.2	80.1	78.6	77.1	75.6	74.1	76.0	73.0	74.5	71.6	71.9	70.5	69.0	67.9	66.4	74.9
Cellactose® 80	90.2	88.2	86.2	84.2	88.9	86.9	84.9	82.9	80.9	85.6	81.6	83.6	79.6	82.4	80.4	78.4	79.1	77.1	83.4
Chitosan	59.4	60.6	61.8	63.0	52.3	53.5	54.7	55.9	57.1	46.3	48.7	47.5	49.9	40.4	41.6	42.8	34.5	35.7	50.3
Emcocel® 50M	38.0	39.3	40.6	42.0	39.2	40.6	41.9	43.2	44.6	41.8	44.5	43.2	45.9	44.4	45.8	47.1	47.0	48.4	43.2
Emcompress®	82.3	80.2	78.0	75.9	80.4	78.3	76.1	74.0	71.9	76.4	72.1	74.2	70.0	72.4	70.2	68.1	68.3	66.2	74.2
FlowLac® 100	90.3	88.2	86.1	84.0	89.0	86.9	84.8	82.7	80.6	85.7	81.5	83.6	79.4	82.4	80.3	78.2	79.1	77.0	83.3
Lactose monohydrate	18.3	25.2	32.1	39.1	16.9	23.9	30.8	37.7	44.6	22.5	36.3	29.4	43.3	28.1	35.0	41.9	33.6	40.5	32.2
Ludipress®	86.5	84.0	81.6	79.1	84.8	82.4	80.0	77.5	75.1	80.8	75.9	78.4	73.5	76.7	74.3	71.9	72.7	70.2	78.1
Prosolv SMCC® HD90	82.1	80.6	79.2	77.8	79.4	78.0	76.5	75.1	73.7	75.3	72.4	73.8	71.0	71.1	69.7	68.3	67.0	65.6	74.3
Starlac®	83.6	81.5	79.3	77.1	81.4	79.2	77.1	74.9	72.7	77.0	72.7	74.8	70.5	72.6	70.4	68.3	68.2	66.0	74.8
Max	90.3	88.2	86.2	84.2	89.0	86.9	84.9	82.9	80.9	85.7	81.6	83.6	79.6	82.4	80.4	78.4	79.1	77.1	83.4
Min	18.3	25.2	32.1	39.1	16.9	23.9	30.8	37.7	44.6	22.5	36.3	29.4	43.3	28.1	35.0	41.9	33.6	35.7	32.2
Diff	72.0	62.9	54.0	45.1	72.1	63.1	54.1	45.2	36.3	63.2	45.3	54.2	36.4	54.3	45.4	36.5	45.5	41.5	51.2

The results revealed that an increase in the contribution of COD to 50% expanded the range of the CFI (i.e. increased the difference between minimum and maximum scores to more than 70 units / percentage). As the weight of COD was decreased to 10%, the CFI steadily decreased to around 60 units when COD = 10% (see figure 4.4).

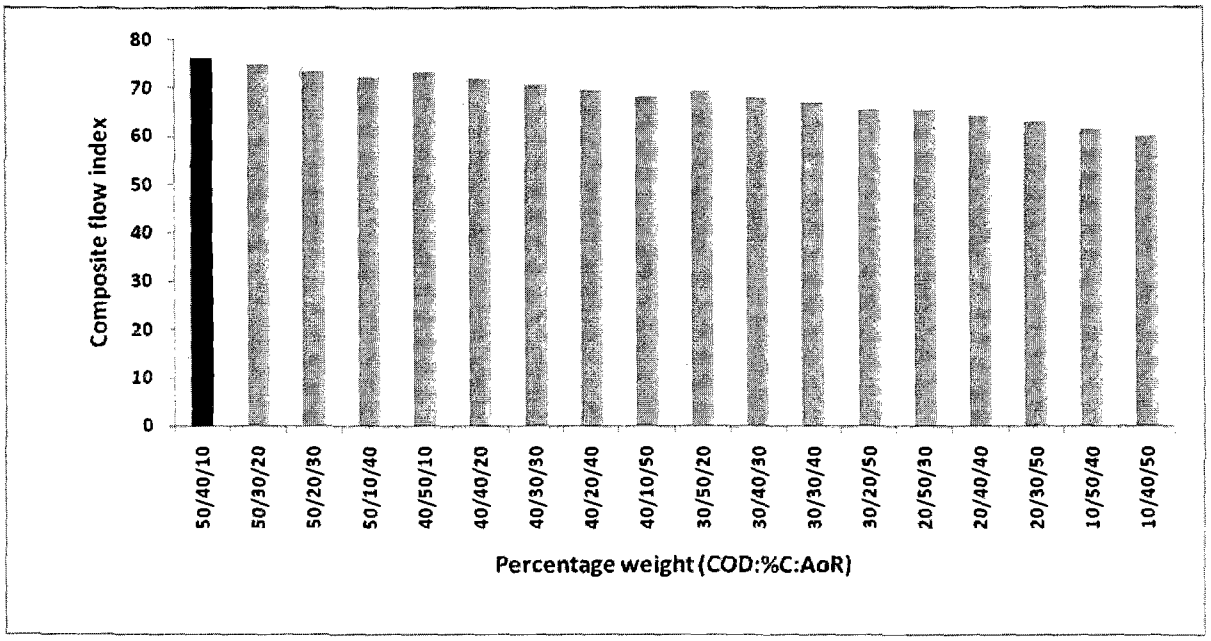


Figure 4.4: Effect of changing the weighted percentage of COD on the CFI.

An interesting trend was observed when the weighted percentage of the %C was decreased from 50% to 10% (see figure 4.5). Whilst the weight of %C was kept constant at a given percentage, the CFI decreased as the weight of the COD decreased from 40 to 10% and the weight of AoR increased from 10 to 40%. This tendency was repeated at each level of %C (i.e. 40%.30%, etc.). These results confirmed the positive contribution of the COD to the CFI and the detrimental influence of an increase in the weight of the AoR.

At a constant weighted percentage of AoR, CFI decreased as %C increased and COD decreased (figure 4.6). As the percentage contribution of AoR was increased (from 10 to 50%), the CFI steadily declined, which corresponded with a decrease in the contribution of %C and an increase in the percentage contribution of the COD.

The results of varying the relative weight of each flow test on the CFI clearly indicated that an increase in the contribution of COD and %C, and a decrease in the weight of AoR, increased the CFI and expanded the range of the index, thus increasing the differences between the various fillers.

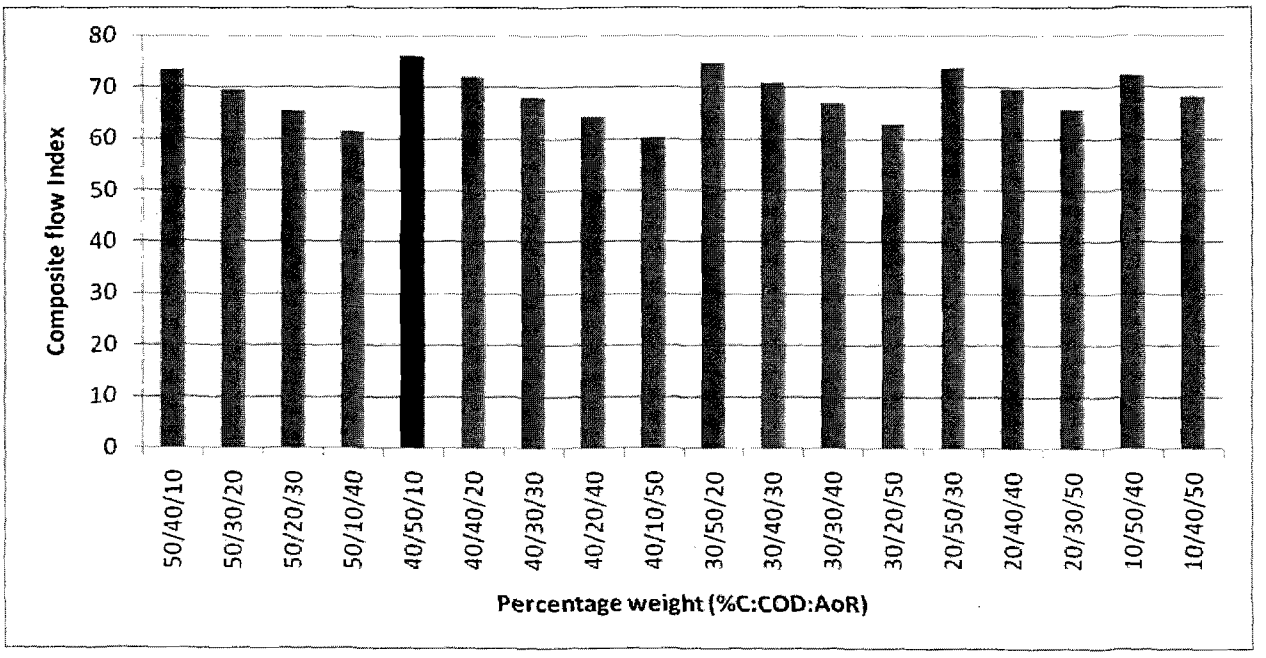


Figure 4.5: Effect of changing the weighted percentage of %C on the CFI.

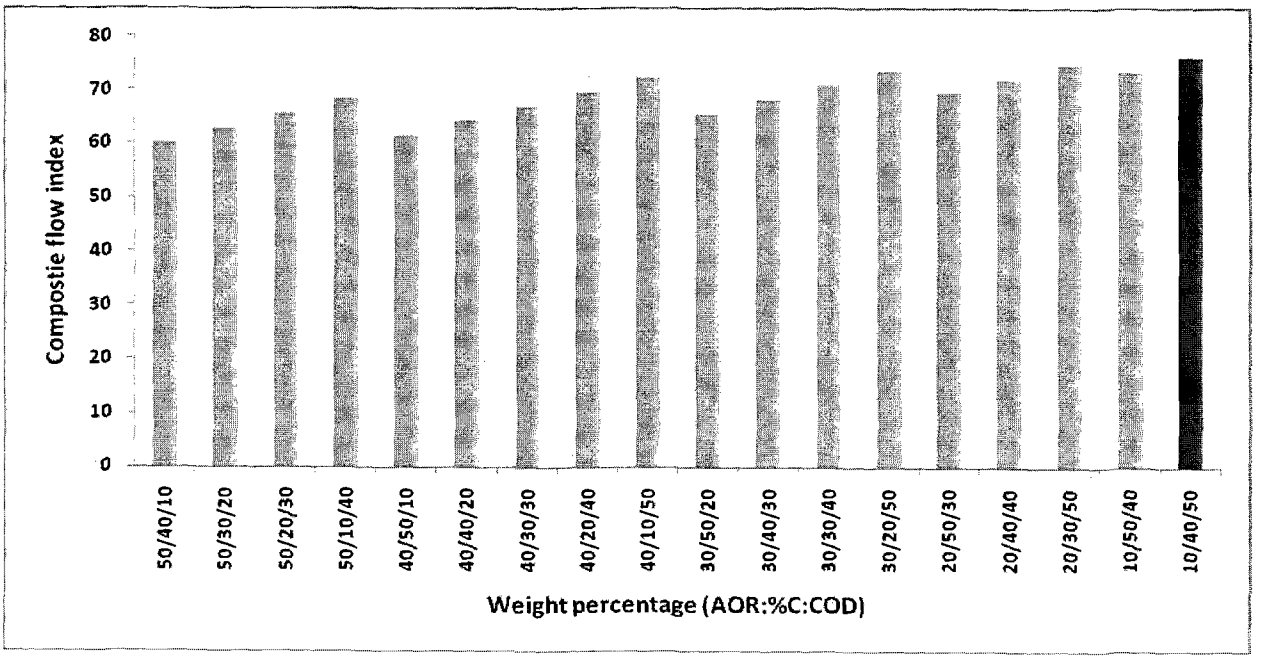


Figure 4.6: Effect of changing the weighted percentage of AoR on the CFI.

The maximum CFI range was obtained at a ratio of 50:40:10 (COD:%C:AoR), indicated by the dark bar in figures 4.4 to 4.6, with the largest difference between the minimum and maximum value (76.1 units). At this ratio, 7 of the 10 fillers achieved their highest CFI (see dark grey coloured blocks in table 4.5). The only fillers that were not at their maximum at this ratio were the ones exhibiting the poorest flow (chitosan, Emcocel® 50M and lactose monohydrate). Chitosan obtained its highest CFI at a combination of 50:10:40 (COD:%C:AoR), Emcocel® 50M at 10:40:50 and lactose monohydrate at 10:50:40. The

main contributing factor to their significantly lower CFI's was their relative poor COD, with chitosan (COD = 11 mm), and Emcocel® 50M and lactose monohydrate (32 mm each), compared to 2-3 mm for the other fillers. The poor performance of the latter two fillers at this "optimum" combination (50:40:10) can be attributed to the fact that their poorest test scores was obtained in the COD test, and since the weight of this test was the highest in the optimum combination (50%), it negatively affected their transformed tests scores, which resulted in the low CFI obtained for these fillers (21.4 and 8.9 respectively).

In general, the same trends were observed when a glidant was added to the fillers with the 50:40:10 (COD:%C:AoR) combination once again, resulting in the highest CFI for the same 7 of the 10 fillers, whilst chitosan, Emcocel® 50M and lactose monohydrate, once again, performing the worst at this combination.

Considering the rank order of the fillers established in section 3.5, determined from their performance in each of the 4 individual flow tests (see table 3.12), it was decided to determine which ratio for the contribution of each test to the CFI would best fit that rank order. Computations and evaluation of various test ratios indicated that a ratio of 16:39:41:4 (COD:%C:AoR:FR) provided a near perfect fit. Comparison of this ratio with the "optimum" ratio of 50:40:10 indicated that simply averaging the test scores of a filler did not compare well with obtaining the optimum CFI for the filler.

4.5 *Classification scale for fillers according to their CFI*

Using the classification system of Taylor *et al.* (2000:6) as presented in table 4.1 the fillers could be separated as indicated in the following table (according to the CFI's of the fillers as obtained with the optimum ratio for each flow test).

Table 4.7: *Classification of fillers based on their respective CFI's computated from the 50:40:10 ratio (COD:%C:AoR) according to the scale used by Taylor & co-workers (2000:6).*

Flow description	CFI range	No glidant present	Glidant added
Good	>70	Avicel® PH200; Cellactose® 80; Emcompress®; FlowLac® 100; Ludipress®; Prosolv SMCC ® HD90; Starlac®	
Average	60 - 70		
Poor	<60	Chitosan; Emcocell® 50M; lactose monohydrate	

The main concern (and shortcoming) of this flow scale is that it grouped fillers together with obvious differences in their flow behaviour, and secondly it does not have any room for indicating an improvement in flow upon the addition of a glidant; i.e. fillers exhibiting good flow without a filler cannot move to a higher (better) group if flow is improved in the presence of the glidant.

Adopting the classification used by the USP (2007:644) for percentage compressibility and angle of repose and assigning appropriate ranges of CFI for each flow description, provided a much better discriminative scale of flow as shown in table 4.8. The value of this scale is clearly demonstrated by the separation into different flow categories of Cellactose® 80; FlowLac® 100 and Prosolv SMCC® HD90 which exhibited superior flow compared to Avicel® PH200; Emcompress®, Ludipress® and Starlac®. Furthermore, it separated poor flowing materials, as was the case with chitosan, which presented better flow (passable) than Emcocel® 50M (poor), with the latter being superior to lactose monohydrate (very, very poor). The scale also allowed for recognition in the improvement of flow, for example the improvement observed for chitosan upon the addition of a glidant resulted in an upward movement of the material from the class of passable flow to the class indicating fair flow. The same trend was observed for the class of fillers initially (no glidant) grouped in the class exhibiting good flow, which was elevated to the status of excellent flow after addition of the glidant.

Table 4.8: *Classification of fillers based on their respective CFI's computated from the 50:40:10 ratio (COD:%C:AoR) according to the USP flow description scale (2007:644).*

Flow description	CFI range	No glidant present	Glidant added
Excellent	>80	Cellactose® 80; FlowLac®; Prosolv SMCC® HD90	Avicel® PH200; Cellactose® 80; Emcompress®; FlowLac®; Ludipress®; Prosolv SMCC® HD90; Starlac®
Good	>65 - 80	Avicel® PH200; Emcompress®; Ludipress®; Starlac®	
Fair (aid not required)	>50 – 65		Chitosan
Passable (may hang up)	>35 – 50	Chitosan	Emcocel® 50M
Poor (must agitate, vibrate)	>20 – 35	Emcocel® 50M	
Very poor	>10 – 20		Lactose monohydrate
Very, very poor (highly cohesive with little , if any, natural flowability)	≤10	Lactose monohydrate	

4.6 CONCLUSION

The advantage of the use of a composite flow index (CFI) to describe flow of powders and to differentiate between the flow properties of powders with noticeable differences in flowability was confirmed. The CFI provided a significant better parameter than any single flow test to reflect, compare and categorise pharmaceutical powders based on their flow characteristics. Since the CFI combined the results from various flow tests, it automatically integrated the various components (properties) of each individual test and provided a "true" reflection of powder flow.

Somewhat unexpectedly, the inclusion of the flow rate of the fillers in the computation of the CFI did not positively contribute to the index. No explanation for this could be offered at this time and it may need further investigation to clarify. Omission of one of the other tests from the CFI resulted in a decline of the index for all fillers and condensed the CFI range (i.e. minimise the difference between maximum and minimum CFI-values) with a decrease in the ability to discriminate / distinguish between the flowability of fillers with obvious different flow

characteristics. Results confirmed that the rank order of the relative importance of each test to the index was as follows: COD > %C > AoR.

Changing the relative contribution of the three flow tests (COD, %C and AoR) in computing the CFI seemed to be advantageous (compared to an equal weighted percentage of 33.3% for each) in terms of an increase in the range of the CFI (better spreading of the values of different powders which allowed for better discrimination between powders). An increase in the weighted percentage of both the COD and %C tests scores for individual powders increased their CFI, with a change in the contribution of the COD being more pronounced than %C or AoR. An increase in the contribution of the AoR negatively affected the CFI (lower index values) for each of the fillers, confirming that this test does not reflect powder flow truly and accurately.

An "optimum" ratio between the contribution of the three tests to the CFI was established at a ratio of 50%:40%:10% (COD:%C:AoR), which resulted in the highest values for the individual powders that exhibited good flow properties, whilst it suppressed the CFI 's of the powders with poor flowability. This confirmed the relevance of this ratio to group powders according to their true flowability and to accurately distinguish between powders with different flow characteristics.

The flow scale used by the USP (2007:644) for the flow description and classification of powders according to results obtained from the tests for %C and AoR, and adapted for this study to reflect CFI-values provided a more accurate scale for powder classification based on the flowability.

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MEGGLE, See MEGGLE EXCIPIENTS & TECHNOLOGY

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. Starlac®. (Certificate of analysis. Copy in possession of author.)

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ANNEXURE A

Characterzation of Avicel® PH200, Emcocel® 50M, Prosolv SMCC® HD90, Cellactose® 80, FlowLac® 100, Lactose monohydrate, Ludipress®, Starlac®, Chitosan, Emcompress® and Aerosil® 200.

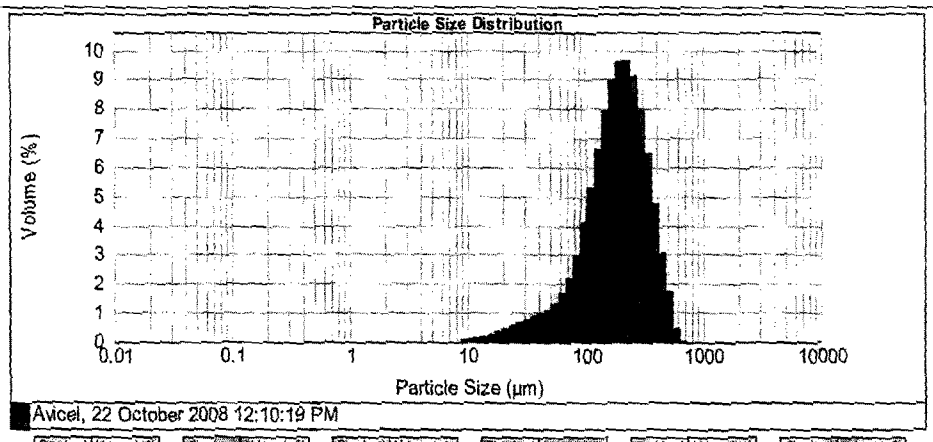
Table A.1.1.1: *Particle size analysis of Avicel® PH200. Sample 1.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Avicel	**SOP Name:** Eben (grondstowwe)	**Measured:** 22 October 2008 12:10:19 PM	
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 22 October 2008 12:10:20 PM	
Sample bulk lot ref: Sample 1	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 16.43 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.614 %	**Result Emulation:** Off
Concentration: 0.3208 %Vol	**Span :** 1.534	**Uniformity:** 0.469	**Result units:** Volume
Specific Surface Area: 0.047 m^2/g	**Surface Weighted Mean D[3,2]:** 127.535 um	**Vol. Weighted Mean D[4,3]:** 205.897 um	

d(0.1): 72.488 um **d(0.5):** 189.178 um **d(0.9):** 362.714 um



Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %
0.010	0.00	0.109	0.00	1.096	0.00	11.482	0.11	120.226	6.61	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.17	138.038	7.91	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.24	158.489	8.96	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.33	181.970	9.59	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.44	208.930	9.85	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.55	239.883	9.98	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.67	275.423	7.96	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.77	316.228	6.42	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.86	363.078	4.73	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.96	416.869	3.05	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	1.09	478.630	1.70	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.31	549.541	0.46	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.66	630.957	0.03	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.21	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.01	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	4.04	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.07	104.713	5.28	1096.479	0.00		
0.105	0.00	1.096	0.00	11.482	0.08	120.226	6.61	1258.925	0.00		

Operator notes:

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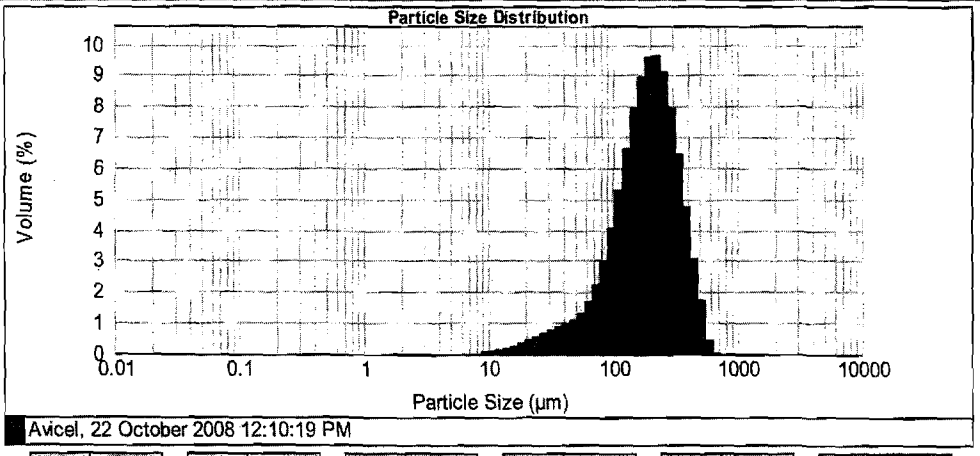
Table A.1.1.2.: *Particle size analysis of Avicel® PH200. Sample 2.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Avicel	**SOP Name:** Eben (grondstowwe)	**Measured:** 22 October 2008 12:10:19 PM	
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 22 October 2008 12:10:20 PM	
Sample bulk lot ref: Sample 1	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 16.43 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.614 %	**Result Emulation:** Off
Concentration: 0.3208 %Vol	**Span :** 1.534	**Uniformity:** 0.469	**Result units:** Volume
Specific Surface Area: 0.047 m^2/g	**Surface Weighted Mean D[3,2]:** 127.535 um	**Vol. Weighted Mean D[4,3]:** 265.897 um	

d(0.1): 72.488 um **d(0.5):** 189.178 um **d(0.9):** 362.714 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.11	120.226	6.61	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.17	138.038	7.91	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.24	158.489	8.96	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.33	181.970	9.59	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.44	208.930	9.65	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.55	239.883	9.08	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.67	275.423	7.96	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.77	316.228	6.42	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.86	363.078	4.73	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.96	416.869	3.05	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	1.09	478.630	1.70	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.31	549.541	0.46	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.66	630.957	0.03	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.21	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.01	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	4.04	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.07	104.713	5.28	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.08	120.226		1258.925	0.00		

Operator notes:

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Malvern, UK
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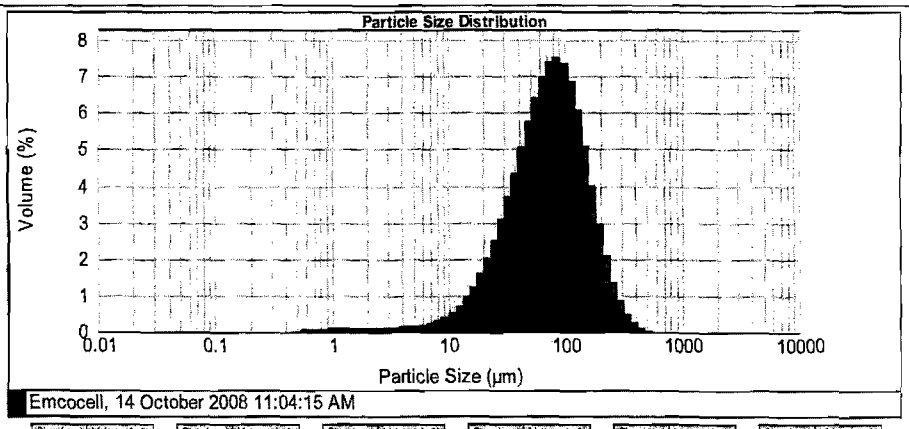
Table A.1.2.1.: *Particle size analysis of Emcocell® 50M. Sample 1.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Emcocell	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 11:04:15 AM	
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 11:04:16 AM	
Sample bulk lot ref: Sample 1	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 16.03 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.638 %	**Result Emulation:** Off
Concentration: 0.0779 %Vol	**Span :** 2.024	**Uniformity:** 0.641	**Result units:** Volume
Specific Surface Area: 0.174 m²/g	**Surface Weighted Mean D[3,2]:** 34.392 um	**Vol. Weighted Mean D[4,3]:** 87.370 um	

d(0.1): 23.346 um **d(0.5):** 72.462 um **d(0.9):** 169.989 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.09	11.482	0.68	120.226	6.06	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.09	13.183	0.92	138.038	5.06	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.09	15.136	1.22	158.489	4.01	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.09	17.378	1.59	181.970	2.98	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.09	19.953	2.03	208.930	2.09	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.10	22.909	2.53	239.883	1.37	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.10	26.303	3.09	275.423	0.84	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.10	30.200	3.70	316.228	0.48	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.11	34.674	4.35	363.078	0.26	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.11	39.811	5.04	416.869	0.11	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.13	45.709	5.75	478.630	0.03	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.14	52.481	6.42	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.04	5.754	0.16	60.256	7.00	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.07	6.607	0.19	69.183	7.39	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.07	7.586	0.23	79.433	7.54	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.08	8.710	0.29	91.201	7.36	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.08	10.000	0.38	104.713	7.06	1096.478	0.00		
0.105	0.00	1.096	0.09	11.482	0.51	120.226	6.66	1258.925	0.00		

Operator notes:

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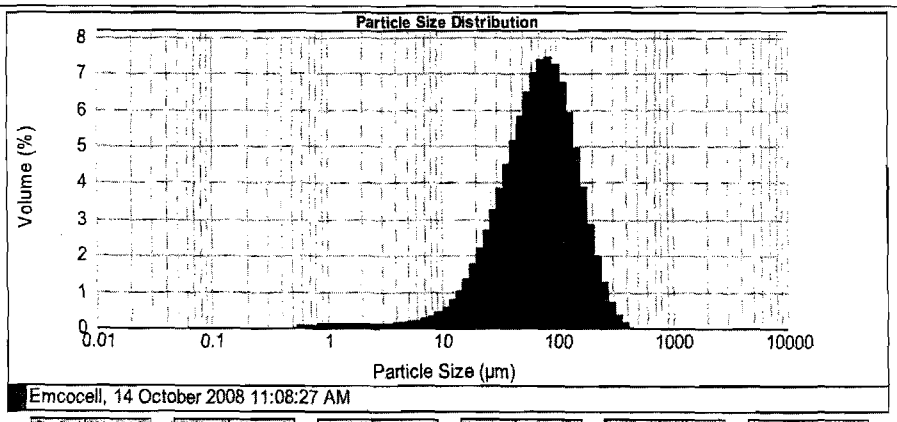
Table A.1.2.2.: *Particle size analysis of Emcocell® 50M. Sample 2.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Emcocell	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 11:08:27 AM	
Sample Source & type: *Eben*	**Measured by:** *Jan Steenekamp*	**Analysed:** 14 October 2008 11:08:28 AM	
Sample bulk lot ref: Sample 2	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 17.34 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.347 %	**Result Emulation:** Off
Concentration: 0.0813 %Vol	**Span :** 2.026	**Uniformity:** 0.638	**Result units:** Volume
Specific Surface Area: 0.182 m^2/g	**Surface Weighted Mean D[3,2]:** 32.997 *um*	**Vol. Weighted Mean D[4,3]:** 84.177 *um*	

d(0.1): 22.248 um **d(0.5):** 70.277 um **d(0.9):** 164.609 um



Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %
0.010	0.00	0.105	0.00	1.096	0.09	11.482	0.75	120.226	5.93	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.10	13.183	1.01	138.038	4.94	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.10	15.136	1.33	158.489	3.88	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.10	17.378	1.73	181.970	2.86	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.10	19.953	2.18	208.930	1.97	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.11	22.909	2.69	239.883	1.24	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.11	26.303	3.25	275.423	0.70	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.11	30.200	3.85	316.228	0.35	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.12	34.674	4.49	363.079	0.13	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.13	39.811	5.15	416.869	0.03	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.15	45.709	5.82	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.17	52.481	6.45	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.05	5.754	0.20	60.256	6.98	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.07	6.607	0.25	69.183	7.34	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.08	7.586	0.32	79.433	7.45	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.08	8.710	0.42	91.201	7.25	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.09	10.000	0.56	104.713	6.73	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925	0.00		

Operator notes:

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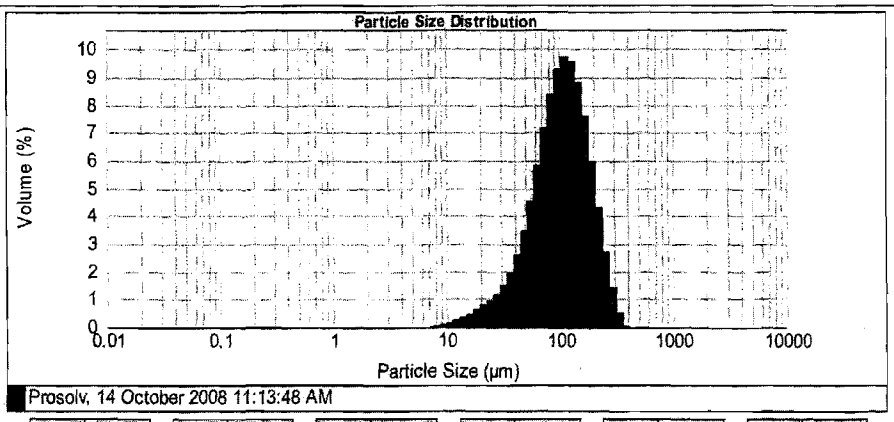
Table A.1.3.1.: *Particle size analysis of Prosolv SMCC®HD90. Sample 1.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Prosolv	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 11:13:48 AM	
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 11:13:49 AM	
Sample bulk lot ref: Sample 1	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 13.20 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.389 %	**Result Emulation:** Off
Concentration: 0.1557 %Vol	**Span :** 1.507	**Uniformity:** 0.463	**Result units:** Volume
Specific Surface Area: 0.0761 m²/g	**Surface Weighted Mean D[3,2]:** 78.827 um	**Vol. Weighted Mean D[4,3]:** 116.095 um	

d(0.1): 44.021 um **d(0.5):** 105.585 um **d(0.9):** 203.106 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.24	120.226	6.58	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.35	138.038	8.62	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.47	158.489	7.56	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.61	181.970	5.98	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.78	208.930	4.29	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.94	239.883	2.70	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	1.16	275.423	1.42	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	1.48	316.228	0.46	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	1.93	363.078	0.03	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	2.57	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	3.44	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	4.54	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	5.82	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	7.15	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.01	79.433	8.38	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.05	91.201	9.30	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.18	104.713	9.73	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482		120.226		1258.925	0.00		

Operator notes:

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14 Oct 2008 12:11:36 PM

Table A.1.3.2.: *Particle size analysis of Prosolv SMCC® HD90. Sample 2.*

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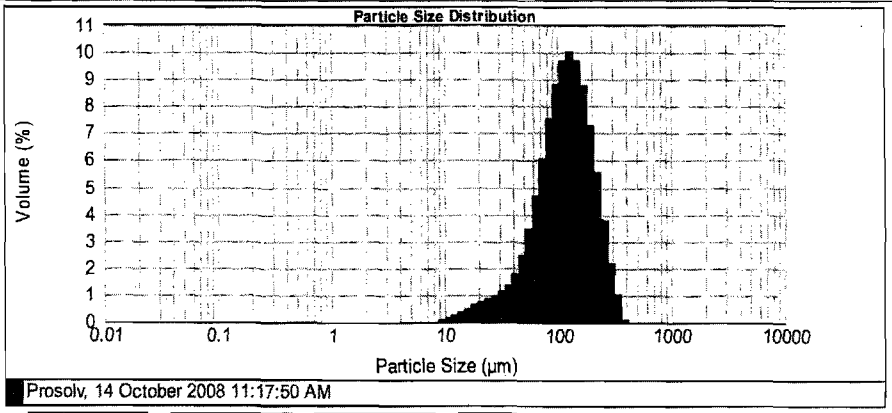
Result Analysis Report

Sample Name: Prosolv	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 11:17:50 AM
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 11:17:51 AM
Sample bulk lot ref: Sample 2	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 13.47 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.634 %	**Result Emulation:** Off

Concentration: 0.1740 %Vol	***Span :*** 1.467	***Uniformity:*** 0.452	**Result units:** Volume
Specific Surface Area: 0.0697 m²/g	**Surface Weighted Mean D[3,2]:** 86.067 um	**Vol. Weighted Mean D[4,3]:** 128.143 um	

d(0.1): 49.282 um **d(0.5):** 117.764 um **d(0.9):** 222.022 um



Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.24	120.226	10.05	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.36	138.038	9.72	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.49	158.489	8.77	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.61	181.970	7.30	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.73	208.930	5.57	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.84	239.883	3.79	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.95	275.423	2.21	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	1.11	316.228	1.02	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	1.37	363.078	0.08	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.80	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	2.48	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	3.43	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	4.67	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	6.08	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	7.54	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	8.82	954.993	0.00	10000.000	
0.091	0.00	0.955	0.00	10.000	0.09	104.713	9.72	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.15	120.226		1258.925	0.00		

Operator notes:

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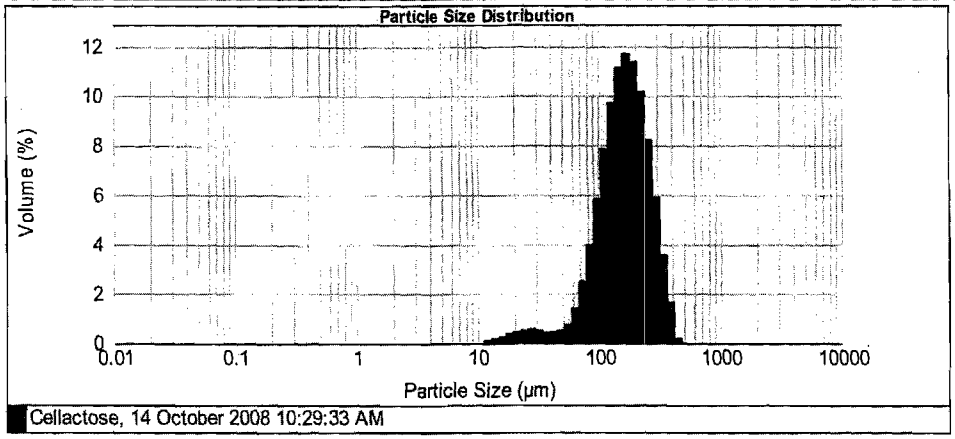
Table A.1.4.1.: *Particle size analysis of Cellactose® 80. Sample 1.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Cellactose	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 10:29:33 AM	
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 10:29:34 AM	
Sample bulk lot ref: Sample 1	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 13.74 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.942 %	**Result Emulation:** Off
Concentration: 0.2625 %Vol	**Span :** 1.216	**Uniformity:** 0.378	**Result units:** Volume
Specific Surface Area: 0.0475 m^2/g	**Surface Weighted Mean D[3,2]:** 126.317 um	**Vol. Weighted Mean D[4,3]:** 173.990 um	

d(0.1): 83.523 um **d(0.5):** 163.881 um **d(0.9):** 282.818 um



Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.07	120.226	9.70	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.14	138.038	11.11	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.24	158.489	11.72	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.34	181.970	11.40	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.44	208.930	10.17	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.51	239.883	8.21	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.53	275.423	5.90	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.51	316.226	3.57	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.45	363.078	1.67	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.41	416.869	0.18	4365.159	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.48	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.77	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.40	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.46	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.96	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	5.81	954.993	0.00	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	7.84	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925			

Operator notes:

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Record Number: 13
14 Oct 2008 12:05:10 PM

Table A.1.4.2.: *Particle size analysis of Cellactose® 80. Sample 2.*

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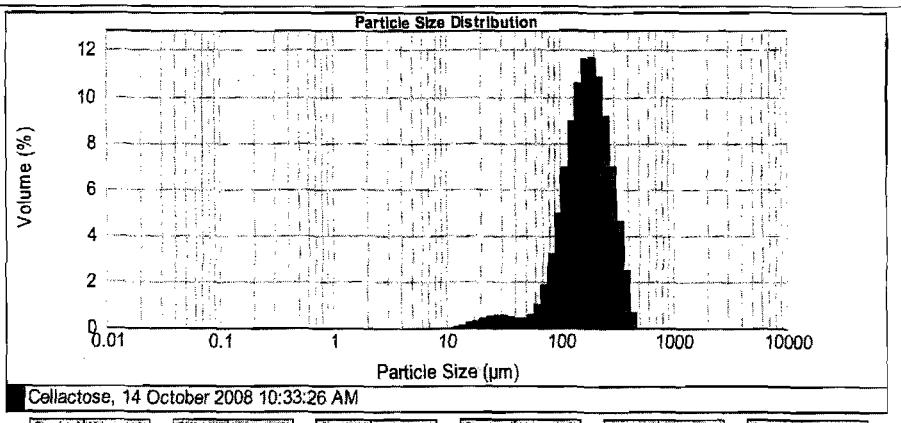
Result Analysis Report

Sample Name: Cellactose	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 10:33:26 AM
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 10:33:27 AM
Sample bulk lot ref: Sample 2	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 16.06 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.913 %	**Result Emulation:** Off

Concentration: 0.3290 %Vol	**Span :** 1.215	**Uniformity:** 0.382	**Result units:** Volume
Specific Surface Area: 0.0449 m²/g	**Surface Weighted Mean D[3,2]:** 133.577 um	**Vol. Weighted Mean D[4,3]:** 185.182 um	

d(0.1): 88.926 um **d(0.5):** 174.515 um **d(0.9):** 300.931 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.135	0.00	1.096	0.00	11.482	0.06	120.226	6.90	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.11	138.038	10.56	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.20	158.489	11.59	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.31	181.970	11.70	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.41	208.930	10.85	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.50	239.883	9.16	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.55	275.423	6.95	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.55	316.228	4.59	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.50	363.078	2.48	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.43	416.869	0.71	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.43	478.630	0.01	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.42	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.58	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	1.02	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	1.86	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	3.17	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	4.89	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	6.90	1258.925	0.00		

Operator notes:

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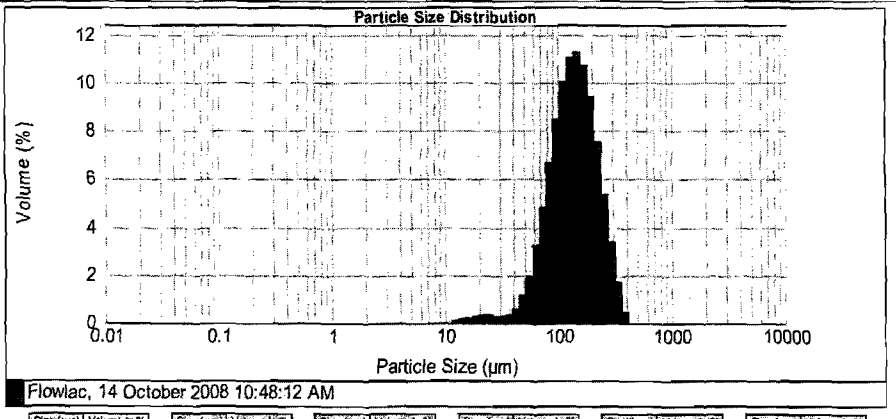
Table A.1.5.1.: *Particle size analysis of FlowLac® 100. Sample 1.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Flowlac	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 10:48:12 AM	
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 10:48:13 AM	
Sample bulk lot ref: Sample 1	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 14.24 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.614 %	**Result Emulation:** Off
Concentration: 0.2428 %Vol	**Span :** 1.263	**Uniformity:** 0.393	**Result units:** Volume
Specific Surface Area: 0.0533 m²/g	**Surface Weighted Mean D[3,2]:** 112.493 um	**Vol. Weighted Mean D[4,3]:** 148.828 um	

d(0.1): 70.920 um **d(0.5):** 137.704 um **d(0.9):** 244.788 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.08	120.226	11.02	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.15	138.038	11.28	1445.440	0.00
0.013	0.00	0.139	0.00	1.445	0.00	15.136	0.22	158.489	10.71	1659.587	0.00
0.015	0.00	0.159	0.00	1.660	0.00	17.378	0.28	181.970	9.37	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.31	208.930	7.52	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.31	239.883	5.40	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.29	275.423	3.38	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.29	316.228	1.70	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.37	363.078	0.44	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.61	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	1.13	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.98	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	3.23	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	4.82	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	6.64	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	8.45	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	10.01	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.00	120.226		1258.925	0.00		

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14 Oct 2008 12:07:27 PM

Table A.1.5.2.: *Particle size analysis of FlowLac® 100. Sample 2.*

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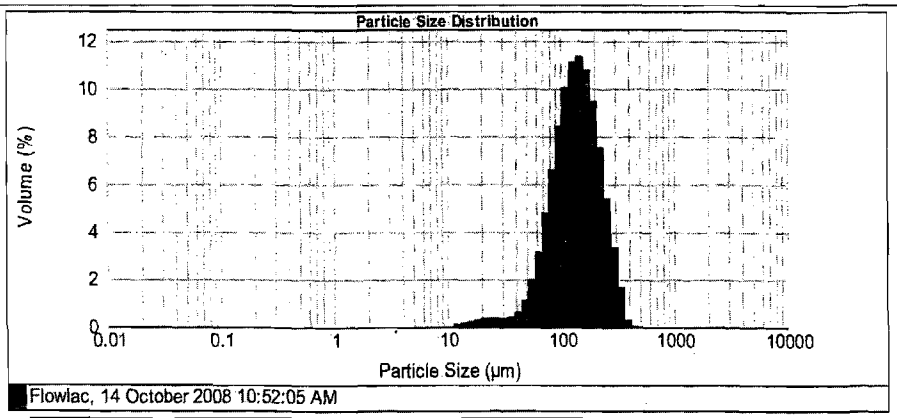
Result Analysis Report

Sample Name: Flowlac	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 10:52:05 AM
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 10:52:06 AM
Sample bulk lot ref: Sample 2	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 14.01 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.596 %	**Result Emulation:** Off

Concentration: 0.2383 %Vol	**Span :** 1.250	**Uniformity:** 0.389	**Result units:** Volume
Specific Surface Area: 0.0534 m^2/g	**Surface Weighted Mean D[3,2]:** 112.355 um	**Vol. Weighted Mean D[4,3]:** 148.377 um	

d(0.1): 71.000 um **d(0.5):** 137.771 um **d(0.9):** 243.274 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.07	120.226	11.09	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.14	138.038	11.38	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.22	158.489	10.82	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.28	181.970	9.45	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.32	208.930	7.55	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.32	239.883	5.39	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.33	275.423	3.32	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.32	316.228	1.67	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.31	363.078	0.25	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.39	416.869	0.01	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.62	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.11	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.255	1.84	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	3.18	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	4.76	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	6.60	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	8.44	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	10.04	1258.925	0.00		

Operator notes:

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File name: 14 Oct 2008.mea
Record Number: 23
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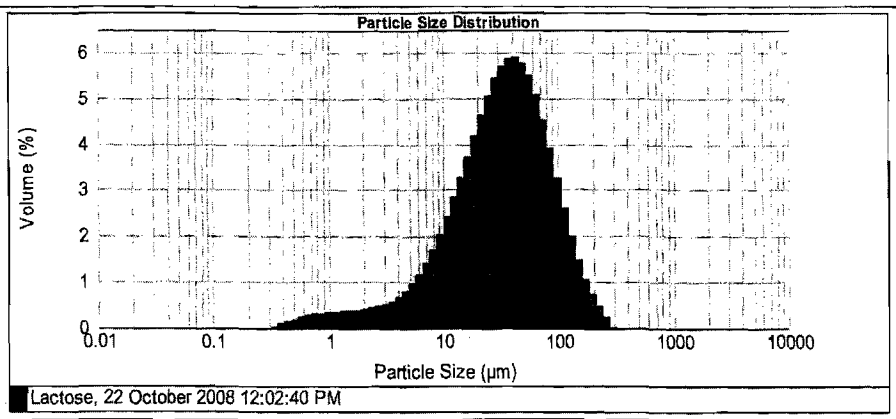
Table A.1.6.1.: *Particle size analysis of Lactose monohydrate. Sample 1.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Lactose	**SOP Name:** Eben (grondstowwe)	**Measured:** 22 October 2008 12:02:40 PM	
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 22 October 2008 12:02:41 PM	
Sample bulk lot ref: Sample 1	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 17.39 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 1.092 %	**Result** Off
Concentration: 0.0262 %Vol	**Span :** 2.735	**Uniformity:** 0.861	**Result units:** Volume
Specific Surface Area: 0.528 m²/g	**Surface Weighted Mean D[3,2]:** 11.365 um	**Vol. Weighted Mean D[4,3]:** 45.067 um	

d(0.1): 7.070 um **d(0.5):** 33.307 um **d(0.9):** 98.163 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.098	0.35	11.482	2.83	120.226	2.00	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.36	13.183	3.27	138.038	1.47	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.37	15.136	3.72	158.489	1.05	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.39	17.378	4.18	181.970	0.72	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.41	19.953	4.63	208.930	0.47	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.43	22.909	5.05	239.883	0.26	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.47	26.303	5.42	275.423	0.01	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.52	30.200	5.70	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.01	3.311	0.58	34.674	5.87	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.10	3.802	0.67	39.811	5.89	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.15	4.365	0.79	45.709	5.77	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.19	5.012	0.95	52.481	5.49	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.23	5.754	1.16	60.256	5.06	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.27	6.607	1.40	69.183	4.53	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.30	7.586	1.70	79.433	3.90	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.32	8.710	2.04	91.201	3.25	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.33	10.000	2.42	104.713	2.59	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925	0.00		

Operator notes:

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File name: 22 Oct 2008.mea
Record Number: 1
22 Oct 2008 01:00:21 PM

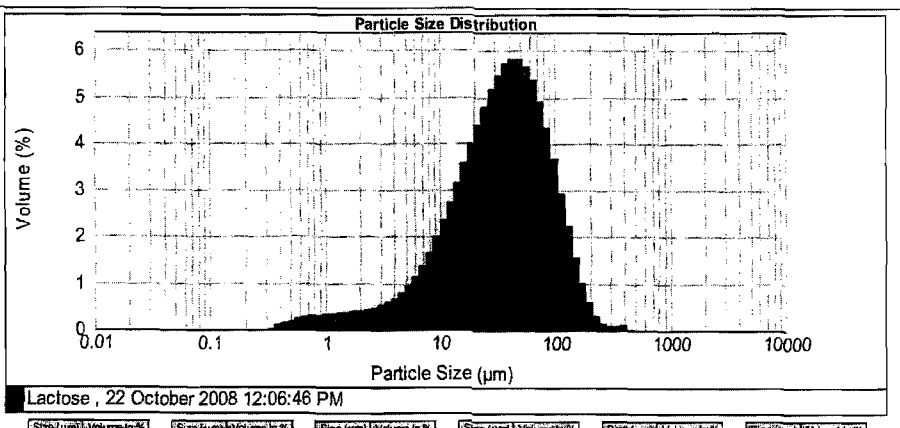
Table A.1.6.2.: *Particle size analysis of Lactose monohydrate. Sample 2.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Lactose	**SOP Name:** Eben (grondstowwe)	**Measured:** 22 October 2008 12:06:46 PM	
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 22 October 2008 12:06:47 PM	
Sample bulk lot ref: Sample 2	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 20.92 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.726 %	**Result Emulation:** Off
Concentration: 0.0328 %Vol	***Span :*** 2.685	***Uniformity:*** 0.856	***Result units:*** Volume
Specific Surface Area: 0.518 m²/g	**Surface Weighted Mean D[3,2]:** 11.577 um	**Vol. Weighted Mean D[4,3]:** 46.767 um	

d(0.1): 7.167 um **d(0.5):** 34.851 um **d(0.9):** 100.747 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.34	11.482	2.73	120.226	2.21	1259.925	0.00
0.011	0.00	0.120	0.00	1.259	0.36	13.183	3.14	138.038	1.55	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.37	15.136	3.56	158.489	1.01	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.39	17.378	3.98	181.970	0.59	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.41	19.953	4.39	208.930	0.31	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.44	22.909	4.79	239.883	0.15	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.47	26.303	5.15	275.423	0.09	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.52	30.200	5.46	316.228	0.09	3311.311	0.00
0.030	0.00	0.316	0.01	3.311	0.58	34.674	5.69	363.078	0.10	3801.894	0.00
0.035	0.00	0.363	0.10	3.802	0.66	39.811	5.81	416.869	0.03	4365.158	0.00
0.040	0.00	0.417	0.14	4.365	0.78	45.709	5.80	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.19	5.012	0.93	52.481	5.65	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.23	5.754	1.13	60.256	5.35	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.26	6.607	1.37	69.183	4.90	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.29	7.586	1.66	79.433	4.32	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.31	8.710	1.98	91.201	3.65	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.33	10.000	2.35	104.713	2.92	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925	0.00		

Operator notes:

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Serial Number : MAL1007548

File name: 22 Oct 2008.mea
Record Number: 3
22 Oct 2008 01:00:28 PM

Table A.1.7.1.: *Particle size analysis of Ludipress®. Sample 1.*

MASTERSIZER 2000

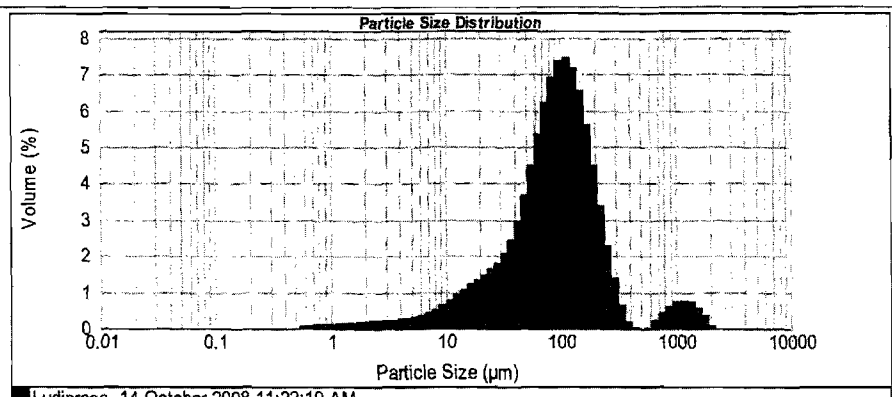
Result Analysis Report

Sample Name: Ludipress	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 11:22:19 AM
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 11:22:20 AM
Sample bulk lot ref: Sample 1	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 16.66 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.217 %	**Result Emulation:** Off

Concentration: 0.0716 %Vol	**Span :** 2.244	***Uniformity:*** 1.08	**Result units:** Volume
Specific Surface Area: 0.195 m^2/g	**Surface Weighted Mean D[3,2]:** 30.811 *um*	**Vol. Weighted Mean D[4,3]:** 148.574 *um*	

d(0.1): 19.704 um **d(0.5):** 92.742 um **d(0.9):** 227.827 um



Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %
0.010	0.00	0.105	0.00	1.096	0.12	11.482	0.91	120.226	7.17	1258.925	0.70
0.011	0.00	0.120	0.00	1.259	0.14	13.183	1.06	138.038	6.53	1445.440	0.58
0.013	0.00	0.138	0.00	1.445	0.16	15.136	1.20	158.489	5.61	1659.587	0.33
0.015	0.00	0.158	0.00	1.660	0.17	17.378	1.34	181.970	4.50	1905.461	0.08
0.017	0.00	0.182	0.00	1.905	0.19	19.953	1.47	208.930	3.38	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.21	22.909	1.61	239.883	2.27	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.22	26.303	1.79	275.423	1.35	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.23	30.200	2.06	316.228	0.65	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.25	34.674	2.44	363.078	0.18	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.28	39.811	2.97	416.869	0.01	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.28	45.709	3.67	478.630	0.00	5011.872	0.00
0.048	0.00	0.479	0.00	5.012	0.31	52.481	4.48	549.541	0.03	5754.399	0.00
0.052	0.00	0.550	0.05	5.754	0.36	60.256	5.37	630.957	0.21	6606.934	0.00
0.060	0.00	0.631	0.07	6.607	0.42	69.183	6.22	724.436	0.42	7585.776	0.00
0.069	0.00	0.724	0.08	7.586	0.51	79.433	6.92	831.764	0.60	8709.636	0.00
0.079	0.00	0.832	0.09	8.710	0.63	91.201	7.36	954.993	0.72	10000.000	0.00
0.091	0.00	0.955	0.11	10.000	0.76	104.713	7.48	1096.478	0.75		
0.105	0.00	1.096	0.12	11.482		120.226		1258.925			

Operator notes:

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File name: 14 Oct 2008.mea
Record Number: 37
14 Oct 2008 12:11:46 PM

Table A.1.7.2.: *Particle size analysis of Ludipress®. Sample 2.*

MASTERSIZER 2000

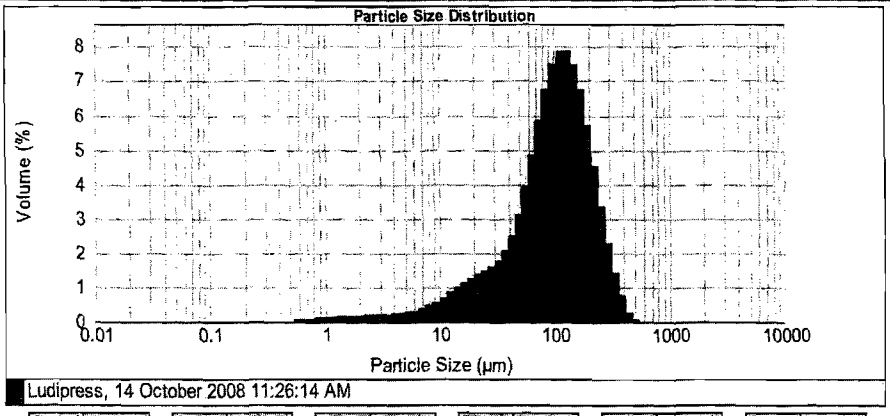
Result Analysis Report

Sample Name: Ludipress	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 11:26:14 AM
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 11:26:15 AM
Sample bulk lot ref: Sample 2	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 17.26 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.510 %	**Result Emulation:** Off

Concentration: 0.0801 %Vol	**Span :** 2.006	**Uniformity:** 0.611	**Result units:** Volume
Specific Surface Area: 0.181 m²/g	**Surface Weighted Mean D[3,2]:** 33.152 um	**Vol. Weighted Mean D[4,3]:** 115.946 um	

d(0.1): 21.846 um **d(0.5):** 101.626 um **d(0.9):** 225.670 um



Ludipress, 14 October 2008 11:26:14 AM

Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.12	11.482	0.83	120.226	7.88	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.13	13.183	0.98	138.038	7.48	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.14	15.136	1.12	158.489	7.08	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.16	17.378	1.24	181.970	6.74	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.17	19.953	1.35	208.930	6.70	2187.762	0.00
0.020	0.00	0.209	0.00	2.189	0.18	22.909	1.45	239.883	4.54	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.19	26.303	1.57	275.423	3.38	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.20	30.200	1.75	316.228	2.29	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.21	34.674	2.04	363.078	1.40	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.22	39.811	2.49	416.869	0.77	4365.158	0.00
0.040	0.00	0.417	0.00	4.366	0.24	45.709	3.11	478.630	0.26	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.26	52.481	3.91	549.541	0.06	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.30	60.256	4.84	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.05	6.607	0.36	69.183	5.82	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.07	7.586	0.44	79.433	6.74	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.08	8.710	0.55	91.201	7.45	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.09	10.000	0.68	104.713	7.86	1096.478	0.00		
0.105	0.00	1.096	0.10	11.482		120.226		1258.925	0.00		

Operator notes:

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Serial Number : MAL1007548

File name: 14 Oct 2008.mea
Record Number: 39
14 Oct 2008 12:11:50 PM

Table A.1.8.1.: *Particle size analysis of Starlac®. Sample 1.*

MASTERSIZER 2000

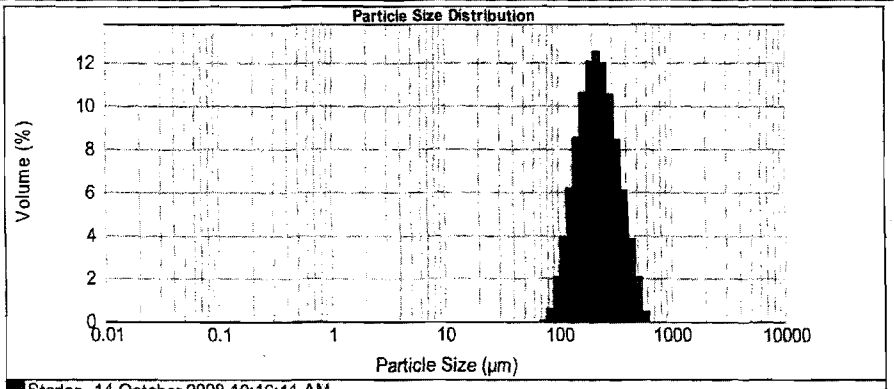
Result Analysis Report

Sample Name: Starlac	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 10:16:11 AM
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 10:16:12 AM
Sample bulk lot ref: Sample 1	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 13.88 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 1.423 %	**Result Emulation:** Off

Concentration: 0.4365 %Vol	**Span :** 1.123	**Uniformity:** 0.344	**Result units:** Volume
Specific Surface Area: 0.0292 m²/g	**Surface Weighted Mean D[3,2]:** 205.832 um	**Vol. Weighted Mean D[4,3]:** 241.892 um	

d(0.1): 130.754 um **d(0.5):** 223.214 um **d(0.9):** 381.414 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.452	0.00	120.226	6.16	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.163	0.00	138.038	8.56	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	10.64	1659.587	0.00
0.015	0.00	0.159	0.00	1.660	0.00	17.378	0.00	181.970	12.08	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	12.56	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	12.01	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	10.55	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	8.44	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	6.12	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	3.84	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	2.07	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.42	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.59	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	2.03	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	3.87	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	5.16	1258.925	0.00		

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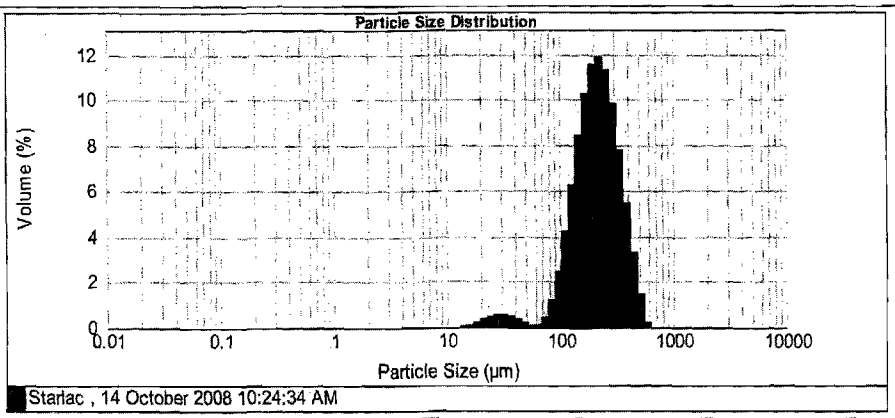
Table A.1.8.2.: *Particle size analysis of Starlac®. Sample 2.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Starlac	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 10:24:34 AM	
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 10:24:35 AM	
Sample bulk lot ref: Sample 2	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 12.64 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.931 %	**Result Emulation:** Off
Concentration: 0.3099 %Vol	**Span :** 1.194	**Uniformity:** 0.377	**Result units:** Volume
Specific Surface Area: 0.0369 m²/g	**Surface Weighted Mean D[3,2]:** 162.647 um	**Vol. Weighted Mean D[4,3]:** 226.703 um	

d(0.1): 113.369 um **d(0.5):** 212.388 um **d(0.9):** 366.954 um



Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	6.28	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	8.43	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.06	158.489	10.28	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.13	181.970	11.55	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.24	208.930	11.92	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.35	239.883	11.93	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.47	275.423	9.87	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.57	316.228	7.79	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.51	363.078	5.49	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.38	416.869	3.28	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.20	478.630	1.50	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.08	549.541	0.23	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.11	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.45	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	1.22	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	2.48	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	4.23	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.00	120.226		1258.925	0.00		

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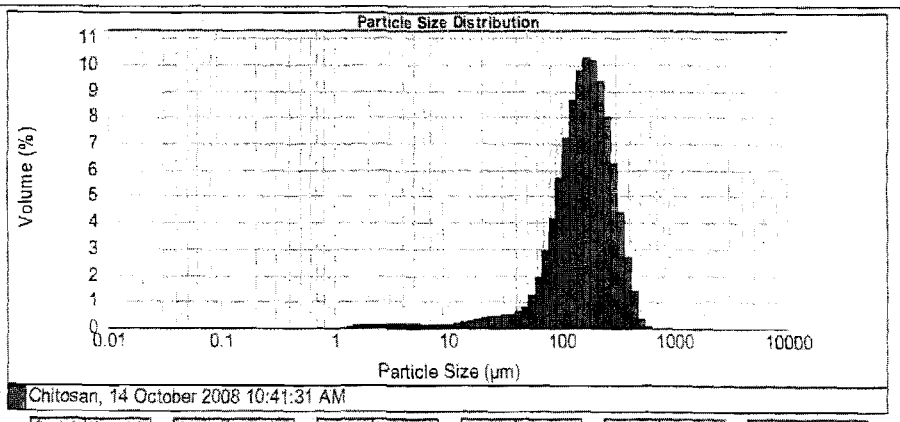
Table A.1.9.1.: *Particle size analysis of Chitosan. Sample 1.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Chitosan	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 10:41:31 AM	
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 10:41:32 AM	
Sample bulk lot ref: Sample 2	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 15.73 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.329	**Weighted Residual:** 0.439 %	**Result Emulation:** Off
Concentration: 0.1901 %Vol	**Span :** 1.420	**Uniformity:** 0.441	**Result units:** Volume
Specific Surface Area: 0.0726 m^2/g	**Surface Weighted Mean D[3,2]:** 82.372 um	**Vol. Weighted Mean D[4,3]:** 178.132 um	

d(0.1): 72.894 um **d(0.5):** 164.370 um **d(0.9):** 306.245 um



Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %
0.010	0.00	0.105	0.00	1.066	0.06	11.482	0.13	120.226	8.50	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.01	13.183	0.18	138.038	9.72	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.24	158.489	10.27	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.31	181.970	10.15	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.07	19.953	0.37	208.930	9.36	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.09	22.909	0.42	239.883	7.99	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.10	26.303	0.44	275.423	6.22	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.11	30.200	0.46	316.228	4.37	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.12	34.674	0.48	363.078	2.87	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.13	39.811	0.49	416.869	1.96	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.13	45.709	0.57	478.630	1.36	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.13	52.481	0.79	549.541	0.90	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.12	60.256	1.21	630.957	0.62	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.11	69.183	1.89	724.436	0.40	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.10	79.433	2.86	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.09	91.201	4.17	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.09	104.713	5.85	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.10	120.226	7.72	1258.925	0.00		

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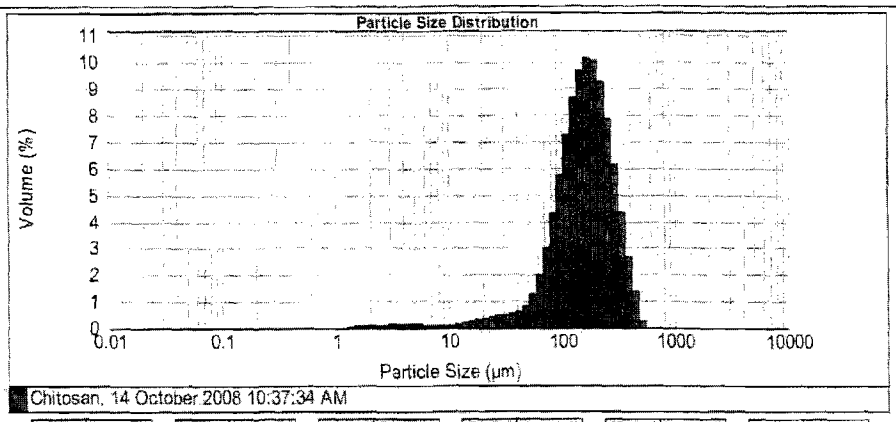
Table A.1.9.2.: *Particle size analysis of Chitosan. Sample 2.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Chitosan	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 10:37:34 AM	
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 10:37:35 AM	
Sample bulk lot ref: Sample 1	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 17.02 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.408 %	**Result Emulation:** Off
Concentration: 0.2042 %Vol	**Span :** 1.434	**Uniformity:** 0.445	**Result units:** Volume
Specific Surface Area: 0.0739 m^2/g	**Surface Weighted Mean D[3,2]:** 81.232 um	**Vol. Weighted Mean D[4,3]:** 176.650 um	

d(0.1): 71.494 um **d(0.5):** 163.065 um **d(0.9):** 305.370 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.099	0.00	11.482	0.14	120.226	8.63	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.01	13.163	0.19	138.038	9.66	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.06	15.136	0.25	158.489	10.18	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.07	17.378	0.31	181.970	10.03	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.09	19.953	0.36	208.930	9.24	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.10	22.909	0.42	239.883	7.56	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.11	26.303	0.45	275.423	6.15	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.12	30.200	0.47	316.228	4.34	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.13	34.674	0.51	363.078	2.66	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.13	39.811	0.61	416.869	1.39	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.13	45.709	0.84	478.630	0.22	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.13	52.481	1.27	549.541	0.00	5754.399	0.00
0.053	0.00	0.550	0.00	5.754	0.12	60.256	1.98	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.11	69.183	2.97	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.10	79.433	4.28	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.09	91.201	5.73	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.09	104.713	7.26	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.11	120.226	7.26	1258.925	0.00		

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Table A.1.10.1.: *Particle size analysis of Emcompress®. Sample 1.*

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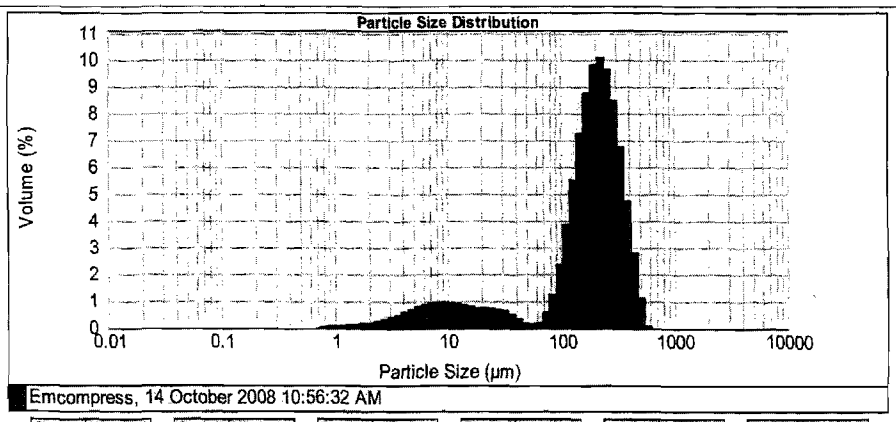
Result Analysis Report

Sample Name: Emcompress	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 10:56:32 AM
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 10:56:33 AM
Sample bulk lot ref: Sample 1	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 13.68 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 1.128 %	**Result Emulation:** Off

Concentration: 0.0623 %Vol	**Span :** 1.776	**Uniformity:** 0.493	**Result units:** Volume
Specific Surface Area: 0.182 m²/g	**Surface Weighted Mean D[3,2]:** 33.046 um	**Vol. Weighted Mean D[4,3]:** 195.209 um	

d(0.1): 12.864 um **d(0.5):** 191.566 um **d(0.9):** 353.083 um



Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %
0.010	0.00	0.105	0.00	1.096	0.10	11.482	0.90	120.226	5.54	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.12	13.183	0.85	138.038	7.28	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.15	15.136	0.81	158.489	8.77	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.18	17.378	0.77	181.970	9.79	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.22	19.953	0.75	208.930	10.11	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.27	22.909	0.73	239.883	9.65	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.33	26.303	0.69	275.423	8.47	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.41	30.200	0.62	316.228	6.74	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.50	34.674	0.50	363.078	4.75	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.60	39.811	0.36	416.869	2.82	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.70	45.709	0.20	478.630	1.11	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.79	52.481	0.12	549.541	0.11	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.88	60.256	0.21	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.94	69.183	0.55	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.04	7.586	0.97	79.433	1.28	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.08	8.710	0.97	91.201	2.38	954.993	0.00	10000.000	
0.091	0.00	0.955	0.09	10.000	0.95	104.713	3.85	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925			

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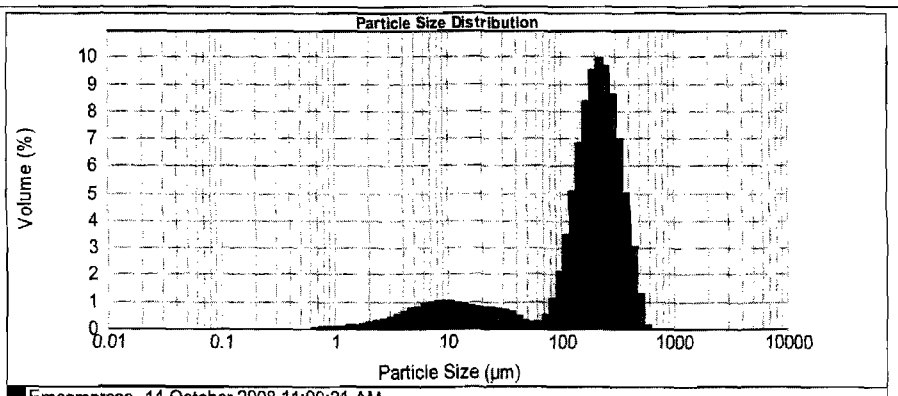
Table A.1.10.2.: *Particle size analysis of Emcompress®. Sample 2.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Emcompress	**SOP Name:** Eben (grondstowwe)	**Measured:** 14 October 2008 11:00:21 AM	
Sample Source & type: Eben	**Measured by:** Jan Steenekamp	**Analysed:** 14 October 2008 11:00:22 AM	
Sample bulk lot ref: Sample 2	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 14.53 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 1.049 %	**Result Emulation:** Off
Concentration: 0.0616 %Vol	**Span :** 1.790	**Uniformity:** 0.506	**Result units:** Volume
Specific Surface Area: 0.194 m²/g	**Surface Weighted Mean D[3,2]:** 30.883 um	**Vol. Weighted Mean D[4,3]:** 196.562 um	

d(0.1): 11.946 um **d(0.5):** 193.997 um **d(0.9):** 359.132 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.099	0.11	11.482	0.85	120.226	5.10	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.13	13.183	0.90	138.038	6.81	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.16	15.136	0.85	158.489	8.35	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.19	17.378	0.82	181.970	9.49	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.23	19.953	0.80	208.930	9.98	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.28	22.909	0.76	239.883	9.68	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.35	26.303	0.76	275.423	8.65	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.43	30.200	0.70	316.228	7.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.52	34.674	0.61	363.078	5.04	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.62	39.811	0.47	416.869	3.05	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.72	45.709	0.32	478.630	1.28	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.82	52.481	0.22	549.541	0.15	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.91	60.256	0.26	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.04	6.607	0.97	69.183	0.53	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.07	7.586	1.01	79.433	1.14	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.08	8.710	1.01	91.201	2.12	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.09	10.000	0.99	104.713	3.48	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925	0.00		

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ANNEXURE B

Critical orifice diameter results of Avicel® PH200, Emcocel® 50M, Prosolv SMCC® HD90, Cellactose® 80, FlowLac® 100, Lactose monohydrate, Ludipress®, Starlac®, Chitosan and Emcompress®.

Table B.1: *Results of the critical orifice diameter of the various powders without a glidant.*

Material	Avicel® PH200 (mm)	Emcocel® 50M (mm)	Prosolv SMCC® HD90 (mm)	Cellactose® 80 (mm)	FlowLac® 100 (mm)	Lactose monohydrate (mm)	Ludipress® (mm)	Starlac® (mm)	Chitosan (mm)	Emcompress® (mm)
Sample 1	2	32	2	2	3	32	3	3	24	3
Sample 2	2	32	2	2	3	32	3	3	24	3
Sample 3	2	32	2	2	3	32	3	3	24	3
Average	2	32	2	2	3	32	3	3	24	3
Standard deviation	0	0	0	0	0	0	0	0	0	0
% Relative standard deviation	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

Table B.2: *Results of the critical orifice diameter of the various powders with a glidant.*

Material	Avicel® PH200 (mm)	Emcocel® 50M (mm)	Prosolv SMCC® HD90 (mm)	Cellactose® 80 (mm)	FlowLac® 100 (mm)	Lactose monohydrate (mm)	Ludipress® (mm)	Starlac® (mm)	Chitosan (mm)	Emcompress® (mm)
Sample 1	2	24	3	1.5	1.5	28	2	2	3	3
Sample 2	2	24	3	1.5	1.5	28	2	2	3	3
Sample 3	2	24	3	1.5	1.5	28	2	2	3	3
Average	2	24	3	1.5	1.5	28	2	2	3	3
Standard deviation	0	0	0	0	0	0	0	0	0	0
% Relative standard deviation	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

ANNEXURE C

Percentage compressibility results of Avicel® PH200, Emcocel® 50M, Prosolv SMCC® HD90, Cellactose® 80, FlowLac® 100, Lactose monohydrate, Ludipress®, Starlac®, Chitosan and Emcompress®.

Table C.1.1: *Percentage compressibility determination of Avicel® PH200 without a glidant.*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped Density (g/ml)	Percentage compressibility
Sample 1	37.77	100.00	0.38	100.00	79.00	0.48	21.00
Sample 2	37.99	100.00	0.38	100.00	80.00	0.47	20.00
Sample 3	37.99	100.00	0.38	100.00	80.00	0.47	20.00
Sample 4	38.02	100.00	0.38	100.00	79.00	0.48	21.00
Sample 5	38.31	100.00	0.38	100.00	80.00	0.48	20.00
Sample 6	37.61	100.00	0.38	100.00	79.00	0.48	21.00
Average	37.95	100.00	0.38	100.00	79.50	0.48	20.50
Standard deviation	0.24	0.00	0.00	0.00	0.55	0.00	0.55
% Relative standard deviation	0.63%	0.00%	0.63%	0.00%	0.69%	0.53%	2.67%

Table C.1.2: *Percentage compressibility determination of Emcocel® 50M without a glidant.*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped Density (g/ml)	Percentage compressibility
Sample 1	30.82	100.00	0.31	100.00	68.00	0.45	32.00
Sample 2	30.96	100.00	0.31	100.00	68.00	0.46	32.00
Sample 3	31.14	100.00	0.31	100.00	68.00	0.46	32.00
Sample 4	30.52	100.00	0.31	100.00	67.00	0.46	33.00
Sample 5	30.92	100.00	0.31	100.00	69.00	0.45	31.00
Sample 6	31.41	100.00	0.31	100.00	70.00	0.45	30.00
Average	30.96	100.00	0.31	100.00	68.33	0.45	31.67
Standard deviation	0.30	0.00	0.00	0.00	1.03	0.00	1.03
% Relative standard deviation	0.97%	0.00%	0.97%	0.00%	1.51%	0.87%	3.26%

Table C.1.3: *Percentage compressibility determination of Prosolv SMCC® HD90 without a glidant.*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	50.41	100.00	0.50	100.00	85.00	0.59	15.00
Sample 2	50.18	100.00	0.50	100.00	84.00	0.60	16.00
Sample 3	50.93	100.00	0.51	100.00	85.00	0.60	15.00
Sample 4	51.07	100.00	0.51	100.00	85.00	0.60	15.00
Sample 5	50.78	100.00	0.51	100.00	85.00	0.60	15.00
Sample 6	50.71	100.00	0.51	100	86.00	0.59	14.00
Average	50.68	100.00	0.51	100.00	85.00	0.60	15.00
Standard deviation	0.33	0.00	0.00	0.00	0.63	0.00	0.63
% Relative standard deviation	0.65%	0.00%	0.65%	0.00%	0.74%	0.69%	4.22%

Table C.1.4: *Percentage compressibility determination of Cellactose® 80 without a glidant.*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	57.69	100.00	0.58	100.00	85.00	0.68	15.00
Sample 2	58.03	100.00	0.58	100.00	86.00	0.67	14.00
Sample 3	57.67	100.00	0.58	100.00	85.00	0.68	15.00
Sample 4	57.88	100.00	0.58	100.00	85.00	0.68	15.00
Sample 5	58.27	100.00	0.58	100.00	85.00	0.69	15.00
Sample 6	58.27	100.00	0.58	100.00	86.00	0.68	14.00
Average	57.97	100.00	0.58	100.00	85.33	0.68	14.67
Standard deviation	0.27	0.00	0.00	0.00	0.52	0.00	0.52
% Relative standard deviation	0.46%	0.00%	0.46%	0.00%	0.61%	0.54%	3.52%

Table C.1.5: *Percentage compressibility determination of FlowLac® 100 without a glidant.*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	63.92	100.00	0.64	100.00	85.00	0.75	15.00
Sample 2	63.71	100.00	0.64	100.00	85.00	0.75	15.00
Sample 3	63.54	100.00	0.64	100.00	85.00	0.75	15.00
Sample 4	63.89	100.00	0.64	100.00	85.00	0.75	15.00
Sample 5	64.38	100.00	0.64	100.00	85.00	0.76	15.00
Sample 6	64.38	100.00	0.64	100.00	85.00	0.76	15.00
Average	63.97	100.00	0.64	100.00	85.00	0.75	15.00
Standard deviation	0.35	0.00	0.00	0.00	0.00	0.00	0.00
% Relative standard deviation	0.54%	0.00%	0.54%	0.00%	0.00%	0.54%	0.00%

Table C.1.6: *Percentage compressibility determination of Lactose monohydrate without a glidant.*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	50.77	100.00	0.51	100.00	60.00	0.85	40.00
Sample 2	49.52	100.00	0.50	100.00	59.00	0.84	41.00
Sample 3	51.16	100.00	0.51	100.00	60.00	0.85	40.00
Sample 4	50.42	100.00	0.50	100.00	60.00	0.84	40.00
Sample 5	50.19	100.00	0.50	100.00	60.00	0.84	40.00
Sample 6	50.28	100.00	0.50	100	60.00	0.84	40.00
Average	50.39	100.00	0.50	100.00	59.83	0.84	40.17
Standard deviation	0.56	0.00	0.01	0.00	0.41	0.01	0.41
% Relative standard deviation	1.10%	0.00%	1.10%	0.00%	0.68%	0.73%	1.02%

Table C.1.7: *Percentage compressibility determination of Ludipress® without a glidant.*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	53.32	100.00	0.53	100.00	80.00	0.67	20.00
Sample 2	53.47	100.00	0.53	100.00	80.00	0.67	20.00
Sample 3	53.86	100.00	0.54	100.00	80.00	0.67	20.00
Sample 4	53.91	100.00	0.54	100.00	80.00	0.67	20.00
Sample 5	53.97	100.00	0.54	100.00	80.00	0.67	20.00
Sample 6	54.64	100.00	0.55	100	81.00	0.67	19.00
Average	53.86	100.00	0.54	100.00	80.17	0.67	19.83
Standard deviation	0.46	0.00	0.00	0.00	0.41	0.00	0.41
% Relative standard deviation	0.86%	0.00%	0.86%	0.00%	0.51%	0.52%	2.06%

Table C.1.8: *Percentage compressibility determination of Starlac® without a glidant.*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	40.03	100.00	0.40	100.00	76.00	0.53	24.00
Sample 2	40.58	100.00	0.41	100.00	77.00	0.53	23.00
Sample 3	40.23	100.00	0.40	100.00	75.00	0.54	25.00
Sample 4	40.56	100.00	0.41	100.00	76.00	0.53	24.00
Sample 5	40.92	100.00	0.41	100.00	75.00	0.55	25.00
Sample 6	40.92	100.00	0.41	100.00	77.00	0.53	23.00
Average	40.54	100.00	0.41	100.00	76.00	0.53	24.00
Standard deviation	0.36	0.00	0.00	0.00	0.89	0.01	0.89
% Relative standard deviation	0.89%	0.00%	0.89%	0.00%	1.18%	1.32%	3.73%

Table C.1.9: *Percentage compressibility determination of Chitosan without a glidant.*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	31.90	100.00	0.32	100.00	64.00	0.50	36.00
Sample 2	31.79	100.00	0.32	100.00	63.00	0.50	37.00
Sample 3	31.61	100.00	0.32	100.00	63.00	0.50	37.00
Sample 4	31.56	100.00	0.32	100.00	63.00	0.50	37.00
Sample 5	31.62	100.00	0.32	100.00	64.00	0.49	36.00
Sample 6	32.21	100.00	0.32	100	65.00	0.50	35.00
Average	31.78	100.00	0.32	100.00	63.67	0.50	36.33
Standard deviation	0.25	0.00	0.00	0.00	0.82	0.00	0.82
% Relative standard deviation	0.77%	0.00%	0.77%	0.00%	1.28%	0.80%	2.25%

Table C.1.10: *Percentage compressibility determination of Emcompress® without a glidant.*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	90.19	100.00	0.90	100.00	82.00	1.10	18.00
Sample 2	90.09	100.00	0.90	100.00	82.00	1.10	18.00
Sample 3	90.34	100.00	0.90	100.00	81.00	1.12	19.00
Sample 4	89.77	100.00	0.90	100.00	81.00	1.11	19.00
Sample 5	89.45	100.00	0.89	100.00	82.00	1.09	18.00
Sample 6	91.92	100.00	0.92	100	83.00	1.11	17.00
Average	90.29	100.00	0.90	100.00	81.83	1.10	18.17
Standard deviation	0.86	0.00	0.01	0.00	0.75	0.01	0.75
% Relative standard deviation	0.95%	0.00%	0.95%	0.00%	0.92%	0.78%	4.14%

Table C.2.1: *Percentage compressibility determination of Avicel® PH200 with a glidant (0.25% Aerosil®).*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped Density (g/ml)	Percentage compressibility
Sample 1	41.81	100.00	0.42	100.00	82.00	0.51	18.00
Sample 2	41.54	100.00	0.42	100.00	83.00	0.50	17.00
Sample 3	40.43	100.00	0.40	100.00	82.00	0.49	18.00
Sample 4	41.11	100.00	0.41	100.00	84.00	0.49	16.00
Sample 5	41.76	100.00	0.42	100.00	85.00	0.49	15.00
Sample 6	41.89	100.00	0.42	100	85.00	0.49	15.00
Average	41.42	100.00	0.41	100.00	83.50	0.50	16.50
Standard deviation	0.56	0.00	0.01	0.00	1.38	0.01	1.38
% Relative standard deviation	1.36%	0.00%	1.36%	0.00%	1.65%	1.55%	8.35%

Table C.2.2: *Percentage compressibility determination of Emcocel® 50M with a glidant (0.25% Aerosil®).*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped Density (g/ml)	Percentage compressibility
Sample 1	34.44	100.00	0.34	100.00	72.00	0.48	28.00
Sample 2	33.60	100.00	0.34	100.00	72.00	0.47	28.00
Sample 3	34.33	100.00	0.34	100.00	72.00	0.48	28.00
Sample 4	34.91	100.00	0.35	100.00	73.00	0.48	27.00
Sample 5	34.07	100.00	0.34	100.00	71.00	0.48	29.00
Sample 6	34.86	100.00	0.35	100.00	73.00	0.48	27.00
Average	34.37	100.00	0.34	100.00	72.17	0.48	27.83
Standard deviation	0.49	0.00	0.00	0.00	0.75	0.00	0.75
% Relative standard deviation	1.44%	0.00%	1.44%	0.00%	1.04%	1.01%	2.70%

Table C.2.3: *Percentage compressibility determination of Prosolv SMCC® HD90 with a glidant (0.25% Aerosil®).*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	52.16	100.00	0.52	100.00	83.00	0.63	17.00
Sample 2	52.21	100.00	0.52	100.00	83.00	0.63	17.00
Sample 3	52.07	100.00	0.52	100.00	83.00	0.63	17.00
Sample 4	52.60	100.00	0.53	100.00	83.00	0.63	17.00
Sample 5	52.20	100.00	0.52	100.00	83.00	0.63	17.00
Sample 6	52.37	100.00	0.52	100	83.00	0.63	17.00
Average	52.27	100.00	0.52	100.00	83.00	0.63	17.00
Standard deviation	0.19	0.00	0.00	0.00	0.00	0.00	0.00
% Relative standard deviation	0.36%	0.00%	0.36%	0.00%	0.00%	0.36%	0.00%

Table C.2.4: *Percentage compressibility determination of Cellactose® 80 with a glidant (0.25% Aerosil®).*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	60.18	100.00	0.60	100.00	89.00	0.68	11.00
Sample 2	62.42	100.00	0.62	100.00	89.00	0.70	11.00
Sample 3	60.49	100.00	0.60	100.00	88.00	0.69	12.00
Sample 4	62.03	100.00	0.62	100.00	90.00	0.69	10.00
Sample 5	61.37	100.00	0.61	100.00	90.00	0.68	10.00
Sample 6	61.37	100.00	0.61	100.00	90.00	0.68	10.00
Average	61.31	100.00	0.61	100.00	89.33	0.69	10.67
Standard deviation	0.86	0.00	0.01	0.00	0.82	0.01	0.82
% Relative standard deviation	1.40%	0.00%	1.40%	0.00%	0.91%	1.27%	7.65%

Table C.2.5: *Percentage compressibility determination of FlowLac® 100 with a glidant (0.25% Aerosil®).*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	65.28	100.00	0.65	100.00	89.00	0.73	11.00
Sample 2	65.45	100.00	0.65	100.00	90.00	0.73	10.00
Sample 3	66.12	100.00	0.66	100.00	90.00	0.73	10.00
Sample 4	65.97	100.00	0.66	100.00	89.00	0.74	11.00
Sample 5	65.81	100.00	0.66	100.00	90.00	0.73	10.00
Sample 6	65.81	100.00	0.66	100.00	89.00	0.74	11.00
Average	65.74	100.00	0.66	100.00	89.50	0.73	10.50
Standard deviation	0.32	0.00	0.00	0.00	0.55	0.01	0.55
% Relative standard deviation	0.48%	0.00%	0.48%	0.00%	0.61%	0.71%	5.22%

Table C.2.6: *Percentage compressibility determination of Lactose monohydrate with a glidant (0.25% Aerosil®).*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	54.15	100.00	0.54	100.00	57.00	0.95	43.00
Sample 2	53.90	100.00	0.54	100.00	57.00	0.95	43.00
Sample 3	53.15	100.00	0.53	100.00	56.00	0.95	44.00
Sample 4	54.76	100.00	0.55	100.00	57.00	0.96	43.00
Sample 5	54.56	100.00	0.55	100.00	57.00	0.96	43.00
Sample 6	55.38	100.00	0.55	100	57.00	0.97	43.00
Average	54.32	100.00	0.54	100.00	56.83	0.96	43.17
Standard deviation	0.77	0.00	0.01	0.00	0.41	0.01	0.41
% Relative standard deviation	1.41%	0.00%	1.41%	0.00%	0.72%	1.00%	0.95%

Table C.2.7: *Percentage compressibility determination of Ludipress® with a glidant (0.25% Aerosil®).*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	58.87	100.00	0.59	100.00	87.00	0.68	13.00
Sample 2	59.74	100.00	0.60	100.00	87.00	0.69	13.00
Sample 3	59.29	100.00	0.59	100.00	87.00	0.68	13.00
Sample 4	58.31	100.00	0.58	100.00	87.00	0.67	13.00
Sample 5	59.70	100.00	0.60	100.00	88.00	0.68	12.00
Sample 6	60.13	100.00	0.60	100	88.00	0.68	12.00
Average	59.34	100.00	0.59	100.00	87.33	0.68	12.67
Standard deviation	0.66	0.00	0.01	0.00	0.52	0.01	0.52
% Relative standard deviation	1.12%	0.00%	1.12%	0.00%	0.59%	0.85%	4.08%

Table C.2.8: *Percentage compressibility determination of Starlac® with a glidant (0.25% Aerosil®).*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	44.48	100.00	0.44	100.00	84.00	0.53	16.00
Sample 2	44.65	100.00	0.45	100.00	84.00	0.53	16.00
Sample 3	45.20	100.00	0.45	100.00	85.00	0.53	15.00
Sample 4	45.27	100.00	0.45	100.00	85.00	0.53	15.00
Sample 5	44.63	100.00	0.45	100.00	85.00	0.53	15.00
Sample 6	44.63	100.00	0.45	100.00	86.00	0.52	14.00
Average	44.81	100.00	0.45	100.00	84.83	0.53	15.17
Standard deviation	0.34	0.00	0.00	0.00	0.75	0.01	0.75
% Relative standard deviation	0.75%	0.00%	0.75%	0.00%	0.89%	1.00%	4.96%

Table C.2.9: *Percentage compressibility determination of Chitosan with a glidant (0.25% Aerosil®).*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	30.91	100.00	0.31	100.00	63.00	0.49	37.00
Sample 2	31.11	100.00	0.31	100.00	64.00	0.49	36.00
Sample 3	30.82	100.00	0.31	100.00	64.00	0.48	36.00
Sample 4	30.89	100.00	0.31	100.00	64.00	0.48	36.00
Sample 5	31.42	100.00	0.31	100.00	65.00	0.48	35.00
Sample 6	31.24	100.00	0.31	100	64.00	0.49	36.00
Average	31.07	100.00	0.31	100.00	64.00	0.49	36.00
Standard deviation	0.23	0.00	0.00	0.00	0.63	0.00	0.63
% Relative standard deviation	0.75%	0.00%	0.75%	0.00%	0.99%	0.72%	1.76%

Table C.2.10: *Percentage compressibility determination of Emcompress® with a glidant (0.25% Aerosil®).*

Material	Mass (g)	Volume (ml)	Bulk Density (g/ml)	Bulk volume (ml)	Tapped volume (ml)	Tapped density (g/ml)	Percentage compressibility
Sample 1	93.54	100.00	0.94	100.00	85.00	1.10	15.00
Sample 2	94.28	100.00	0.94	100.00	85.00	1.11	15.00
Sample 3	92.92	100.00	0.93	100.00	85.00	1.09	15.00
Sample 4	93.46	100.00	0.93	100.00	85.00	1.10	15.00
Sample 5	93.81	100.00	0.94	100.00	84.00	1.12	16.00
Sample 6	93.41	100.00	0.93	100	85.00	1.10	15.00
Average	93.57	100.00	0.94	100.00	84.83	1.10	15.17
Standard deviation	0.45	0.00	0.00	0.00	0.41	0.01	0.41
% Relative standard deviation	0.48%	0.00%	0.48%	0.00%	0.48%	0.77%	2.69%

ANNEXURE D

Angle of repose results of Avicel® PH200, Emcocel® 50M, Prosolv SMCC® HD90, Cellactose® 80, FlowLac® 100, Lactose monohydrate, Ludipress®, Starlac®, Chitosan and Emcompress®.

Table D.1.1: *Angle of repose determination of Avicel® PH200 without a glidant.*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	27.00	39.00	34.70
Sample 2	31.00	46.00	33.98
Sample 3	29.00	40.00	35.94
Average	29.00	41.67	34.87
Standard Deviation	2.00	3.79	0.99
% Relative standard deviation	6.90%	9.09%	2.85%

Table D.1.2: *Angle of repose determination of Emcocel® 50M without a glidant.*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	19.00	30.00	32.35
Sample 2	10.00	13.00	37.57
Sample 3	18.00	20.00	41.99
Average	15.67	21.00	37.30
Standard Deviation	4.93	8.54	4.83
% Relative standard deviation	31.49%	40.69%	12.94%

Table D.1.3: *Angle of repose determination of Prosolv SMCC® HD90 without a glidant.*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	21.00	31.00	34.11
Sample 2	20.00	32.00	32.01
Sample 3	25.00	36.00	34.78
Average	22.00	33.00	33.63
Standard Deviation	2.65	2.65	1.45
% Relative standard deviation	12.03%	8.02%	4.30%

Table D.1.4: *Angle of repose determination of Cellactose® 80 without a glidant.*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	27.00	42.00	32.74
Sample 2	30.00	49.00	31.48
Sample 3	23.00	35.00	33.31
Average	26.67	42.00	32.51
Standard Deviation	3.51	7.00	0.94
% Relative standard deviation	13.17%	16.67%	2.89%

Table D.1.5: *Angle of repose determination of FlowLac® 100 without a glidant.*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	22.00	39.00	29.43
Sample 2	31.00	43.00	35.79
Sample 3	25.00	40.00	32.01
Average	26.00	40.67	32.41
Standard Deviation	4.58	2.08	3.20
% Relative standard deviation	17.63%	5.12%	9.87%

Table D.1.6: *Angle of repose determination of Lactose monohydrate without a glidant.*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	23.00	11.00	64.44
Sample 2	30.00	24.00	51.34
Sample 3	29.00	24.00	50.39
Average	27.33	19.67	55.39
Standard Deviation	3.79	7.51	7.85
% Relative standard deviation	13.85%	38.16%	14.18%

Table D.1.7: *Angle of repose determination of Ludipress® without a glidant.*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	22.00	35.00	32.15
Sample 2	22.00	30.00	36.25
Sample 3	37.00	53.00	34.92
Average	27.00	39.33	34.44
Standard Deviation	8.66	12.10	2.09
% Relative standard deviation	32.08%	30.75%	6.07%

Table D.1.8: *Angle of repose determination of Starlac® without a glidant.*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	22.00	32.00	34.51
Sample 2	35.00	44.00	38.50
Sample 3	30.00	42.00	35.54
Average	29.00	39.33	36.18
Standard Deviation	6.56	6.43	2.07
% Relative standard deviation	22.61%	16.35%	5.73%

Table D.1.9: *Angle of repose determination of Chitosan without a glidant.*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	27.00	26.00	46.08
Sample 2	34.00	32.00	46.74
Sample 3	23.00	25.00	42.61
Average	28.00	27.67	45.14
Standard Deviation	5.57	3.79	2.21
% Relative standard deviation	19.88%	13.68%	4.91%

Table D.1.10: *Angle of repose determination of Emcompress® without a glidant.*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	42.00	56.00	36.87
Sample 2	38.00	46.00	39.56
Sample 3	31.00	39.00	38.48
Average	37.00	47.00	38.30
Standard Deviation	5.57	8.54	1.35
% Relative standard deviation	15.05%	18.18%	3.53%

Table D.2.1: *Angle of repose determination of Avicel® PH200 with a glidant (0.25% Aerosil®200).*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	27.00	39.00	34.70
Sample 2	31.00	46.00	33.98
Sample 3	29.00	40.00	35.94
Average	29.00	41.67	34.87
Standard Deviation	2.00	3.79	0.99
% Relative standard deviation	6.90%	9.09%	2.85%

Table D.2.2: *Angle of repose determination of Emcocel® 50M with a glidant (0.25% Aerosil®200).*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	39.00	56.00	34.85
Sample 2	29.00	43.00	34.00
Sample 3	28.00	40.00	34.99
Average	32.00	46.33	34.64
Standard Deviation	6.08	8.50	1.78
% Relative standard deviation	19.01%	18.36%	1.56%

Table D.2.3: *Angle of repose determination of Prosolv SMCC® HD90 with a glidant (0.25% Aerosil®200).*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	21.00	30.00	34.99
Sample 2	31.00	45.00	34.56
Sample 3	33.00	47.00	35.07
Average	28.33	40.67	34.88
Standard Deviation	6.43	9.29	0.27
% Relative standard deviation	22.69%	22.85%	0.79%

Table D.2.4: *Angle of repose determination of Cellactose® 80 with a glidant (0.25% Aerosil®200).*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	29.00	48.00	31.14
Sample 2	32.00	56.00	29.74
Sample 3	32.00	55.00	30.19
Average	31.00	53.00	30.36
Standard Deviation	1.73	4.36	0.71
% Relative standard deviation	5.59%	8.22%	2.34%

Table D.2.5: *Angle of repose determination of FlowLac® 100 with a glidant (0.25% Aerosil®200).*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	32.00	55.00	30.19
Sample 2	27.00	45.00	30.96
Sample 3	25.00	42.00	30.76
Average	28.00	47.33	30.64
Standard Deviation	3.61	6.81	0.40
% Relative standard deviation	12.88%	14.38%	1.31%

Table D.2.6: *Angle of repose determination of Lactose monohydrate with a glidant (0.25% Aerosil®200).*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	21.00	36.00	30.26
Sample 2	18.00	43.00	22.71
Sample 3	27.00	52.00	27.44
Average	22.00	43.67	26.80
Standard Deviation	4.58	8.02	3.81
% Relative standard deviation	20.83%	18.37%	14.22%

Table D.2.7: *Angle of repose determination of Ludipress® with a glidant (0.25% Aerosil®200).*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	15.00	21.00	35.54
Sample 2	28.00	45.00	31.89
Sample 3	28.00	38.00	36.38
Average	23.67	34.67	34.60
Standard Deviation	7.51	12.34	2.39
% Relative standard deviation	31.71%	35.60%	6.90%

Table D.2.8: *Angle of repose determination of Starlac® with a glidant (0.25% Aerosil®200).*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	36.00	49.00	36.30
Sample 2	33.00	45.00	36.25
Sample 3	34.00	47.00	35.88
Average	34.33	47.00	36.15
Standard Deviation	1.53	2.00	0.23
% Relative standard deviation	4.45%	4.26%	0.64%

Table D.2.9: *Angle of repose determination of Chitosan with a glidant (0.25% Aerosil®200).*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	38.00	38.00	45.00
Sample 2	52.00	55.00	43.39
Sample 3	34.00	34.00	45.00
Average	41.33	42.33	44.46
Standard Deviation	9.45	11.15	0.93
% Relative standard deviation	22.87%	26.34%	2.09%

Table D.2.10: *Angle of repose determination of Emcompress® with a glidant (0.25% Aerosil®200).*

	Height (mm)	Radius (mm)	Angle (degrees)
Sample 1	33.00	45.00	36.25
Sample 2	39.00	55.00	35.34
Sample 3	27.00	37.00	36.12
Average	33.00	45.67	35.90
Standard Deviation	6.00	9.02	0.49
% Relative standard deviation	18.18%	19.75%	1.37%

ANNEXURE E

Flow rate results of Avicel® PH200, Emcocel® 50M, Prosolv SMCC® HD90, Cellactose® 80, FlowLac® 100, Lactose monohydrate, Ludipress®, Starlac®, Chitosan and Emcompress®.

Table E.1.1: *Flowrate determination of Avicel® PH200 without a glidant.*

	Sample1	Sample 2	Sample 3
Mass (g)	37.92	37.96	37.6
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	6.042	6.718	4.445
	21.166	19.568	19.131
	35.752	33.345	33.106
	37.609	37.841	37.448
	37.92	-	-
Time (sec)	6	5	5
Flowrate ($g.sec^{-3}$)	6.32	7.592	7.52
Average flowrate ($g.sec^{-3}$)	7.14		
Standard Deviation	0.71		
%Relative standard deviation	10.00%		

Table E.1.2: *Flowrate determination of Emcocel® 50M without a glidant.*

	Sample1	Sample 2	Sample 3
Mass (g)	30.82	31.66	30.66
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
Time (sec)	0	0	0
Flowrate ($g.sec^{-3}$)	0.000	0.000	0.000
Average flowrate ($g.sec^{-3}$)	0.00		
Standard Deviation	0.00		
%Relative standard deviation	0.00%		

Table E.1.3: *Flowrate determination of Prosolv SMCC® HD90 without a glidant.*

	Sample1	Sample 2	Sample 3
Mass (g)	50.89	49.97	50.22
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	0.906	0.210	1.484
	13.347	12.760	13.358
	33.913	30.697	29.377
	51.249	49.641	49.395
	50.554	-	49.968
	-	-	49.969
Time (sec)	6	5	7
Flowrate ($g.sec^{-3}$)	8.48	9.99	7.17
Average flowrate ($g.sec^{-3}$)	8.55		
Standard Deviation	1.41		
%Relative standard deviation	16.50%		

Table E.1.4: *Flowrate determination of Cellactose® 80 without a glidant.*

	Sample1	Sample 2	Sample 3
Mass (g)	57.96	57.35	56.91
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	0.037	0.036	0.517
	23.267	25.020	25.056
	49.214	47.103	47.726
	57.644	57.082	56.597
Time (sec)	5	5	5
Flowrate ($g.sec^{-3}$)	11.592	11.470	11.382
Average flowrate ($g.sec^{-3}$)	11.48		
Standard Deviation	0.11		
%Relative standard deviation	0.92%		

Table E.1.5: *Flowrate determination of FlowLac® 100 without a glidant.*

	Sample1	Sample 2	Sample 3
Mass (g)	63.89	63.8	63.35
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	0.300	0.001	0.030
	19.257	23.165	17.797
	49.869	50.528	44.952
	63.564	63.546	63.072
	-	-	63.073
Time (sec)	5	5	6
Flowrate ($g.sec^{-3}$)	12.778	12.760	10.558
Average flowrate ($g.sec^{-3}$)	12.03		
Standard Deviation	1.28		
%Relative standard deviation	10.61%		

Table E.1.6: *Flowrate determination of Lactose monohydrate without a glidant.*

	Sample1	Sample 2	Sample 3
Mass (g)	52.92	53.22	52.64
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
Time (sec)	0	0	0
Flowrate ($g.sec^{-3}$)	0.000	0.000	0.000
Average flowrate ($g.sec^{-3}$)	0.000		
Standard Deviation	0.000		
%Relative standard deviation	0.00%		

Table E.1.7: *Flowrate determination of Ludipress® without a glidant.*

	Sample1	Sample 2	Sample 3
Mass (g)	57.78	57.55	56.7
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	11.649	2.261	4.852
	38.568	31.482	34.786
	57.763	57.176	56.350
Time (sec)	4	4	4
Flowrate ($g.sec^{-3}$)	14.445	14.388	14.175
Average flowrate ($g.sec^{-3}$)	14.34		
Standard Deviation	0.14		
%Relative standard deviation	0.99%		

Table E.1.8: *Flowrate determination of Starlac® without a glidant.*

	Sample1	Sample 2	Sample 3
Mass (g)	40.98	40.42	40.65
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	0.368	0.953	1.883
	14.022	13.794	14.101
	27.046	26.977	28.308
	40.709	40.159	40.371
Time (sec)	5	5	5
Flowrate ($g.sec^{-3}$)	8.196	8.084	8.130
Average flowrate ($g.sec^{-3}$)	8.14		
Standard Deviation	0.06		
%Relative standard deviation	0.69%		

Table E.1.9: *Flowrate determination of Chitosan without a glidant.*

	Sample1	Sample 2	Sample 3
Mass (g)	32.09	32.25	32.61
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	0.512	0.113	0.112
	7.124	11.576	7.502
	19.723	20.380	22.392
	31.123	32.029	32.234
	31.802	32.029	32.235
	31.802	32.029	32.236
	31.803	32.030	-
Time (sec)	8	8	7
Flowrate ($g.sec^{-3}$)	4.011	4.031	4.659
Average flowrate ($g.sec^{-3}$)	4.23		
Standard Deviation	0.37		
%Relative standard deviation	8.69%		

Table E.1.10: *Flowrate determination of Emcompress® without a glidant.*

	Sample1	Sample 2	Sample 3
Mass (g)	89.45	91.16	90.38
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	12.942	12.803	23.804
	53.27	52.958	60.504
	89.23	90.268	90.124
Time (sec)	4	4	4
Flowrate ($g.sec^{-3}$)	22.363	22.790	22.595
Average flowrate ($g.sec^{-3}$)	22.58		
Standard Deviation	0.21		
%Relative standard deviation	0.95%		

Table E.2.1: *Flowrate determination of Avicel® PH200 with a glidant (0.25% Aerosil® 200).*

	Sample1	Sample 2	Sample 3
Mass (g)	41.47	42.13	41.06
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	4.395	1.183	4.465
	20.724	19.46	22.847
	38.295	36.382	40.886
	41.265	41.954	41.023
Time (sec)	5	5	5
Flowrate ($g.sec^{-3}$)	8.294	8.426	8.212
Average flowrate ($g.sec^{-3}$)	8.31		
Standard Deviation	0.11		
%Relative standard deviation	1.30%		

Table E.2.2: *Flowrate determination of Emcocel® 50M with a glidant (0.25% Aerosil® 200).*

	Sample1	Sample 2	Sample 3
Mass (g)	36.22	35.68	36.55
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
Time (sec)	0	0	0
Flowrate ($g.sec^{-3}$)	0.000	0.000	0.000
Average flowrate ($g.sec^{-3}$)	0.00		
Standard Deviation	0.00		
%Relative standard deviation	0.00%		

Table E.2.3: *Flowrate determination of Prosolv SMCC® HD90 with a glidant (0.25% Aerosil® 200).*

	Sample1	Sample 2	Sample 3
Mass (g)	52.09	52.44	51.97
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	1.241	1.353	0.089
	11.795	12.308	10.081
	25.538	23.817	24.733
	39.702	40.619	42.058
	51.554	51.884	51.490
	51.576	51.943	51.491
Time (sec)	7	7	7
Flowrate ($g.sec^{-3}$)	7.441	7.491	7.424
Average flowrate ($g.sec^{-3}$)	7.45		
Standard Deviation	0.03		
%Relative standard deviation	0.47%		

Table E.2.4: *Flowrate determination of Cellactose® 80 with a glidant (0.25% Aerosil® 200).*

	Sample1	Sample 2	Sample 3
Mass (g)	62.6	62.4	62.22
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	5.646	0.791	8.057
	39.589	36.345	42.651
	62.331	62.075	61.892
	62.211	62.075	-
	-	62.075	-
	-	62.076	-
Time (sec)	5	7	4
Flowrate ($g.sec^{-3}$)	12.520	8.914	15.555
Average flowrate ($g.sec^{-3}$)	12.33		
Standard Deviation	3.32		
%Relative standard deviation	26.96%		

Table E.2.5: *Flowrate determination of FlowLac® 100 with a glidant (0.25% Aerosil® 200).*

	Sample1	Sample 2	Sample 3
Mass (g)	65.69	65.5	65.49
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	8.641	5.114	5.946
	43.413	39.715	40.429
	65.410	65.272	65.239
Time (sec)	4	4	4
Flowrate ($g.sec^{-3}$)	16.423	16.375	16.373
Average flowrate ($g.sec^{-3}$)	16.39		
Standard Deviation	0.03		
%Relative standard deviation	0.17%		

Table E.2.6: *Flowrate determination of Lactose monohydrate with a glidant (0.25% Aerosil® 200).*

	Sample1	Sample 2	Sample 3
Mass (g)	54.15	40.83	39.76
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
	0.000	0.000	0.000
Time (sec)	0	0	0
Flowrate ($g.sec^{-3}$)	0.000	0.000	0.000
Average flowrate ($g.sec^{-3}$)	0.000		
Standard Deviation	0.000		
%Relative standard deviation	0.00%		

Table E.2.7: *Flowrate determination of Ludipress® with a glidant (0.25% Aerosil® 200).*

	Sample1	Sample 2	Sample 3
Mass (g)	59.13	59.72	59.28
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	14.327	17.559	6.432
	43.760	45.068	35.001
	58.704	59.296	58.888
Time (sec)	4	4	4
Flowrate ($g.sec^{-3}$)	14.783	14.930	14.820
Average flowrate ($g.sec^{-3}$)	14.84		
Standard Deviation	0.08		
%Relative standard deviation	0.52%		

Table E.2.8: *Flowrate determination of Starlac® with a glidant (0.25% Aerosil® 200).*

	Sample1	Sample 2	Sample 3
Mass (g)	45.93	44.74	45.63
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	0.821	1.320	1.211
	21.338	20.390	18.123
	41.625	40.481	36.544
	45.488	44.304	45.228
	45.489	44.303	45.229
	-	44.304	45.230
	-	44.305	45.230
	-	-	45.231
Time (sec)	6	8	9
Flowrate ($g.sec^{-3}$)	7.655	5.593	5.070
Average flowrate ($g.sec^{-3}$)	6.11		
Standard Deviation	1.37		
%Relative standard deviation	22.39%		

Table E.2.9: *Flowrate determination of Chitosan with a glidant (0.25% Aerosil® 200).*

	Sample1	Sample 2	Sample 3
Mass (g)	31.86	31.57	31.44
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	3.531	0.370	3.992
	16.817	11.679	17.824
	23.277	21.164	25.549
	31.577	28.966	31.207
	31.577	31.372	-
	31.578	31.373	-
Time (sec)	8	8	5
Flowrate ($g.sec^{-3}$)	4.551	4.510	6.288
Average flowrate ($g.sec^{-3}$)	5.12		
Standard Deviation	1.01		
%Relative standard deviation	19.83%		

Table E.2.10: *Flowrate determination of Emcompress® with a glidant (0.25% Aerosil® 200).*

	Sample1	Sample 2	Sample 3
Mass (g)	93.11	92.53	92.59
Measurement of powder mass at each second (g)	0.000	0.000	0.000
	13.372	25.683	0.025
	60.266	67.893	53.943
	92.753	92.170	92.208
	92.755	-	-
Time (sec)	5	4	4
Flowrate ($g.sec^{-3}$)	18.622	23.133	23.148
Average flowrate ($g.sec^{-3}$)	21.63		
Standard Deviation	2.61		
%Relative standard deviation	12.06%		

ANNEXURE F

Statistical analysis of the results of Avicel® PH200, Emcocel® 50M, Prosolv SMCC® HD90, Cellactose® 80, FlowLac® 100, Lactose monohydrate, Ludipress®, Starlac®, Chitosan and Emcompress®.

Table F.1.1: *P-values of the powders for percentage compressibility without the glidant (Tukey test).*

	Material	{1} 20.500	{2} 14.667	{3} 36.333	{4} 31.667	{5} 18.167	{6} 15.000	{7} 40.167	{8} 19.833	{9} 15.000	{10} 24.000
1	Avicel® PH200		0.000151	0.000151	0.000151	0.000155	0.000151	0.000151	0.767188	0.000151	0.000151
2	Cellatose® 80	0.000151		0.000151	0.000151	0.000151	0.996764	0.000151	0.000151	0.996764	0.000151
3	Chitosan	0.000151	0.000151		0.000151	0.000151	0.000151	0.000151	0.000151	0.000151	0.000151
4	Emcocel® 50M	0.000151	0.000151	0.000151		0.000151	0.000151	0.000151	0.000151	0.000151	0.000151
5	Emcompress®	0.000155	0.000151	0.000151	0.000151		0.000151	0.000151	0.002575	0.000151	0.000151
6	FlowLac® 100	0.000151	0.996764	0.000151	0.000151	0.000151		0.000151	0.000151	1.000000	0.000151
7	Lactose	0.000151	0.000151	0.000151	0.000151	0.000151	0.000151		0.000151	0.000151	0.000151
8	Ludipress®	0.767188	0.000151	0.000151	0.000151	0.002575	0.000151	0.000151		0.000151	0.000151
9	Prosolv SMCC® HD90	0.000151	0.996764	0.000151	0.000151	0.000151	1.000000	0.000151	0.000151		0.000151
10	Starlac®	0.000151	0.000151	0.000151	0.000151	0.000151	0.000151	0.000151	0.000151	0.000151	

Table F.1.2: *P-values of the powders for angle of repose without the glidant (Tukey test).*

	Material	{1} 34.871	{2} 32.508	{3} 45.144	{4} 37.301	{5} 38.303	{6} 32.407	{7} 55.390	{8} 34.442	{9} 33.633	{10} 36.182
1	Avicel® PH200		0.996340	0.034916	0.995512	0.955722	0.995036	0.000191	1.000000	0.999980	0.999967
2	Cellatose® 80	0.996340		0.005663	0.764828	0.549008	1.000000	0.000186	0.999211	0.999991	0.934532
3	Chitosan	0.034916	0.005663		0.189055	0.337033	0.005241	0.035602	0.025251	0.013561	0.090294
4	Emcocel® 50M	0.995512	0.764828	0.189055		0.999997	0.744721	0.000241	0.985996	0.935143	0.999991
5	Emcompress®	0.955722	0.549008	0.337033	0.999997		0.527009	0.000320	0.914344	0.788601	0.998393
6	FlowLac® 100	0.995036	1.000000	0.005241	0.744721	0.527009		0.000186	0.998832	0.999981	0.924107
7	Lactose	0.000191	0.000186	0.035602	0.000241	0.000320	0.000186		0.000189	0.000187	0.000206
8	Ludipress®	1.000000	0.999211	0.025251	0.985996	0.914344	0.998832	0.000189		0.999999	0.999659
9	Prosolv SMCC® HD90	0.999980	0.999991	0.013561	0.935143	0.788601	0.999981	0.000187	0.999999		0.993650
10	Starlac®	0.999967	0.934532	0.090294	0.999991	0.998393	0.924107	0.000206	0.999659	0.993650	

Table F.1.3: *P-values of the powders for flow rate without the glidant (Tukey test).*

	Material	{1} 7.1440	{2} 11.481	{3} 4.2337	{4} 0.0000	{5} 22.583	{6} 12.032	{7} 0.0000	{8} 14.336	{9} 8.5500	{10} 8.1367
1	Avicel® PH200		0.000187	0.001021	0.000179	0.000179	0.000179	0.000179	0.000179	0.274030	0.702610
2	Cellatose® 80	0.000187		0.000179	0.000179	0.000179	0.987007	0.000179	0.001244	0.000950	0.000311
3	Chitosan	0.001021	0.000179		0.000187	0.000179	0.000179	0.000187	0.000179	0.000187	0.000195
4	Emcocel® 50M	0.000179	0.000179	0.000187		0.000179	0.000179	1.000000	0.000179	0.000179	0.000179
5	Emcompress®	0.000179	0.000179	0.000179	0.000179		0.000179	0.000179	0.000179	0.000179	0.000179
6	FlowLac® 100	0.000179	0.987007	0.000179	0.000179	0.000179		0.000179	0.010621	0.000253	0.000195
7	Lactose	0.000179	0.000179	0.000187	1.000000	0.000179	0.000179		0.000179	0.000179	0.000179
8	Ludipress®	0.000179	0.001244	0.000179	0.000179	0.000179	0.010621	0.000179		0.000179	0.000179
9	Prosolv SMCC® HD90	0.274030	0.000950	0.000187	0.000179	0.000179	0.000253	0.000179	0.000179		0.998388
10	Starlac®	0.702610	0.000311	0.000195	0.000179	0.000179	0.000195	0.000179	0.000179	0.998388	

Table F.2.1: *P-values of the powders for percentage compressibility with the glidant (Aerosil®200), (Tukey test).*

	Material	{1} 16.500	{2} 10.667	{3} 36.000	{4} 27.833	{5} 15.167	{6} 10.500	{7} 43.167	{8} 12.667	{9} 17.000	{10} 15.167
1	Avicel® PH200		0.000151	0.000151	0.000151	0.056023	0.000151	0.000151	0.000151	0.964754	0.056023
2	Cellatose® 80	0.000151		0.000151	0.000151	0.000151	0.999994	0.000151	0.000543	0.000151	0.000151
3	Chitosan	0.000151	0.000151		0.000151	0.000151	0.000151	0.000151	0.000151	0.000151	0.000151
4	Emcocel® 50M	0.000151	0.000151	0.000151		0.000151	0.000151	0.000151	0.000151	0.000151	0.000151
5	Emcompress®	0.056023	0.000151	0.000151	0.000151		0.000151	0.000151	0.000155	0.001700	1.000000
6	FlowLac® 100	0.000151	0.999994	0.000151	0.000151	0.000151		0.000151	0.000245	0.000151	0.000151
7	Lactose	0.000151	0.000151	0.000151	0.000151	0.000151	0.000151		0.000151	0.000151	0.000151
8	Ludipress®	0.000151	0.000543	0.000151	0.000151	0.000155	0.000245	0.000151		0.000151	0.000155
9	Prosolv SMCC® HD90	0.964754	0.000151	0.000151	0.000151	0.001700	0.000151	0.000151	0.000151		0.001700
10	Starlac®	0.056023	0.000151	0.000151	0.000151	1.000000	0.000151	0.000151	0.000155	0.001700	

Table F.2.2: *P-values of the powders for angle of repose with the glidant (Aerosil®200), (Tukey test).*

	Material	{1} 34.614	{2} 30.358	{3} 44.465	{4} 34.636	{5} 35.904	{6} 30.639	{7} 26.804	{8} 34.604	{9} 34.876	{10} 36.147
1	Avicel® PH200		0.087511	0.000190	1.000000	0.989755	0.131105	0.000403	1.000000	1.000000	0.968506
2	Cellatose® 80	0.087511		0.000179	0.084746	0.011389	1.000000	0.229540	0.088814	0.059003	0.007646
3	Chitosan	0.000190	0.000179		0.000190	0.000240	0.000179	0.000179	0.000190	0.000193	0.000271
4	Emcocel® 50M	1.000000	0.084746	0.000190		0.990884	0.127170	0.000395	1.000000	1.000000	0.971168
5	Emcompress®	0.989755	0.011389	0.000240	0.990884		0.018030	0.000205	0.989198	0.998029	1.000000
6	FlowLac® 100	0.131105	1.000000	0.000179	0.127170	0.018030		0.158853	0.132960	0.090004	0.012130
7	Lactose	0.000403	0.229540	0.000179	0.000395	0.000205	0.158853		0.000407	0.000320	0.000197
8	Ludipress®	1.000000	0.088814	0.000190	1.000000	0.989198	0.132960	0.000407		1.000000	0.967219
9	Prosolv SMCC® HD90	1.000000	0.059003	0.000193	1.000000	0.998029	0.090004	0.000320	1.000000		0.990769
10	Starlac®	0.968506	0.007646	0.000271	0.971168	1.000000	0.012130	0.000197	0.967219	0.990769	

Table F.2.3: *P-values of the powders for flow rate with the glidant (Aerosil®200), (Tukey test).*

	Material	{1} 8.3107	{2} 12.330	{3} 5.1165	{4} 0.0000	{5} 21.634	{6} 16.390	{7} 0.0000	{8} 14.844	{9} 7.4524	{10} 6.1058
1	Avicel® PH200		0.064441	0.232593	0.000201	0.000179	0.000211	0.000201	0.000781	0.998914	0.685153
2	Cellatose® 80	0.064441		0.000339	0.000179	0.000187	0.060110	0.000179	0.525146	0.014180	0.001282
3	Chitosan	0.232593	0.000339		0.009175	0.000179	0.000179	0.009175	0.000186	0.617730	0.996775
4	Emcocel® 50M	0.000201	0.000179	0.009175		0.000179	0.000179	1.000000	0.000179	0.000279	0.001561
5	Emcompress®	0.000179	0.000187	0.000179	0.000179		0.007270	0.000179	0.000544	0.000179	0.000179
6	FlowLac® 100	0.000211	0.060110	0.000179	0.000179	0.007270		0.000179	0.938850	0.000189	0.000179
7	Lactose	0.000201	0.000179	0.009175	1.000000	0.000179	0.000179		0.000179	0.000279	0.001561
8	Ludipress®	0.000781	0.525146	0.000186	0.000179	0.000544	0.938850	0.000179		0.000292	0.000191
9	Prosolv SMCC® HD90	0.998914	0.014180	0.617730	0.000279	0.000179	0.000189	0.000279	0.000292		0.973089
10	Starlac®	0.685153	0.001282	0.996775	0.001561	0.000179	0.000179	0.001561	0.000191	0.973089	

Table F.3.1.1: *P-value of Avicel® PH200 for percentage compressibility (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Avicel T-tests; Grouping: Kondisie (Perc_compress.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	16.50000	20.50000	-6.60578	10	0.000060	-6.60578	6.540541	0.000404	6	6	1.378405	0.547723

Table F.3.1.2: *P-value of Emcocel® 50M for percentage compressibility (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Emcocell T-tests; Grouping: Kondisie (Perc_compress.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	27.83333	31.66667	-7.34708	10	0.000025	-7.34708	9.143184	0.000040	6	6	0.752773	1.032796

Table F.3.1.3: *P-value of Prosolv SMCC® HD90 for percentage compressibility (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Prosolv T-tests; Grouping: Kondisie (Perc_compress.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	17.00000	15.00000	7.745967	10	0.000016	7.745967	5.000000	0.000573	6	6	0.00	0.632456

Table F.3.1.4: *P-value of Cellactose® 80 for percentage compressibility (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Cellatose T-tests; Grouping: Kondisie (Perc_compress.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	10.66667	14.66667	-10.1419	10	0.000001	-10.1419	8.448276	0.000005	6	6	0.816497	0.516398

Table F.3.1.5: *P-value of FlowLac® 100 for percentage compressibility (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Flowlac T-tests; Grouping: Kondisie (Perc_compress.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	10.50000	15.00000	-20.1246	10	0.000000	-20.1246	5.000000	0.000006	6	6	0.547723	0.00

Table F.3.1.6: *P-value of lactose monohydrate for percentage compressibility (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Lactose
T-tests; Grouping: Kondisie (Perc_compress.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	43.16667	40.16667	12.72792	10	0.000000	12.72792	10.00000	0.000000	6	6	0.408248	0.408248

Table F.3.1.7: *P-value of Ludipress®for percentage compressibility (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Ludipress
T-tests; Grouping: Kondisie (Perc_compress.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	12.66667	19.83333	-26.6675	10	0.000000	-26.6675	9.494382	0.000000	6	6	0.516398	0.408248

Table F.3.1.8: *P-value of Starlac®for percentage compressibility (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Starlac
T-tests; Grouping: Kondisie (Perc_compress.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	15.16667	24.00000	-18.5084	10	0.000000	-18.5084	9.716763	0.000000	6	6	0.752773	0.894427

Table F.3.1.9: *P-value of chitosan for percentage compressibility (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Chitosan
T-tests; Grouping: Kondisie (Perc_compress.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev L
Meting	36.00000	36.33333	-0.790569	10	0.447538	-0.790569	9.411765	0.448657	6	6	0.632456	0.8164

Table F.3.1.10: *P-value of chitosan for percentage compressibility (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Emcompress
T-tests; Grouping: Kondisie (Perc_compress.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	15.16667	18.16667	-8.58116	10	0.000006	-8.58116	7.707006	0.000033	6	6	0.408248	0.752773

Table F.3.2.1: *P-value of Avicel® PH200 for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Avicel
T-tests; Grouping: Kondisie (Angle_of_repose.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	34.61431	34.87127	-0.393360	4	0.714119	-0.393360	3.083170	0.719683	3	3	0.539479	0.99454

Table F.3.2.2: *P-value of Emcocel® 50M for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Emcocell
T-tests; Grouping: Kondisie (Angle_of_repose.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	34.63602	37.30108	-0.897569	4	0.420156	-0.897569	2.533603	0.446421	3	3	1.778643	4.825449

Table F.3.2.3: *P-value of Prosolv SMCC® HD90 for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Prosolv
T-tests; Grouping: Kondisie (Angle_of_repose.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	34.87610	33.63256	1.461734	4	0.217623	1.461734	2.143754	0.273342	3	3	0.274622	1.447686

Table F.3.2.4: *P-value of Cellactose® 80 for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Cellatose
T-tests; Grouping: Kondisie (Angle_of_repose.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L	V
Meting	30.35849	32.50757	-3.16140	4	0.034138	-3.16140	3.730234	0.037618	3	3	0.711868	0.937854	

Table F.3.2.5: *P-value of FlowLac® 100 for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Flowlac
T-tests; Grouping: Kondisie (Angle_of_repose.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	30.63937	32.40727	-0.949571	4	0.396101	-0.949571	2.062674	0.439932	3	3	0.400574	3.199744

Table F.3.2.6: *P-value of lactose monohydrate for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Lactose
T-tests; Grouping: Kondisie (Angle_of_repose.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	26.80353	55.38985	-5.67283	4	0.004764	-5.67283	2.892735	0.011967	3	3	3.811050	7.852100

Table F.3.2.7: *P-value of Ludipress®for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Ludipress
T-tests; Grouping: Kondisie (Angle_of_repose.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	34.60427	34.44184	0.088620	4	0.933643	0.088620	3.932061	0.933713	3	3	2.387771	2.092058

Table F.3.2.8: *P-value of Starlac®for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Starlac
T-tests; Grouping: Kondisie (Angle_of_repose.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.D L
Meting	36.14682	36.18228	-0.029452	4	0.977915	-0.029452	2.049515	0.979122	3	3	0.230621	2.072

Table F.3.2.9: *P-value of chitosan for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Chitosan
T-tests; Grouping: Kondisie (Angle_of_repose.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	44.46467	45.14356	-0.489707	4	0.649984	-0.489707	2.680093	0.661586	3	3	0.927226	2.214945

Table F.3.2.10: *P-value of chitosan for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

Vulstof=Emcompress
T-tests; Grouping: Kondisie (Angle_of_repose.sta)
Group 1: A
Group 2: L

Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	35.90443	38.30325	-2.88397	4	0.044834	-2.88397	2.522099	0.077892	3	3	0.493322	1.353587

Table F.3.3.1: *P-value of Avicel® PH200 for flow rate (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Avicel T-tests; Grouping: Kondisie (Flowrate.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	8.310667	7.144000	2.796373	4	0.048992	2.796373	2.091288	0.102430	3	3	0.107969	0.714512

Table F.3.3.2: *P-value of Emcocel® 50M for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Emcocell T-tests; Grouping: Kondisie (Flowrate.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	0.00	0.00		4					3	3	0.00	0.00

Table F.3.3.3: *P-value of Prosolv SMCC® HD90 for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Prosolv T-tests; Grouping: Kondisie (Flowrate.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	7.452381	8.549984	-1.34684	4	0.249280	-1.34684	2.002445	0.310215	3	3	0.034886	1.411098

Table F.3.3.4: *P-value of Cellactose® 80 for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Cellatose T-tests; Grouping: Kondisie (Flowrate.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	12.32976	11.48133	0.441813	4	0.681459	0.441813	2.004025	0.701728	3	3	3.324442	0.105458

Table F.3.3.5: *P-value of FlowLac® 100 for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Flowlac T-tests; Grouping: Kondisie (Flowrate.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	16.39000	12.03211	5.912315	4	0.004098	5.912315	2.001949	0.027374	3	3	0.028174	1.276361

Table F.3.3.6: *P-value of lactose monohydrate for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Lactose T-tests; Grouping: Kondisie (Flowrate.sta) Group 1: A Group 2: L										
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	0.00	0.00		4					3	3	0.00	0.00

Table F.3.3.7: *P-value of Ludipress®for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Ludipress T-tests; Grouping: Kondisie (Flowrate.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	14.84417	14.33583	5.449470	4	0.005508	5.449470	3.071742	0.011410	3	3	0.076662	0.142222

Table F.3.3.8: *P-value of Starlac®for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Starlac T-tests; Grouping: Kondisie (Flowrate.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	6.105833	8.136667	-2.57132	4	0.061892	-2.57132	2.006786	0.123367	3	3	1.366817	0.05629

Table F.3.3.9: *P-value of chitosan for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Chitosan T-tests; Grouping: Kondisie (Flowrate.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	5.116476	4.233690	1.416453	4	0.229591	1.416453	2.517342	0.267753	3	3	1.014781	0.368094

Table F.3.3.10: *P-value of chitosan for angle of repose (T-test, Group: 1: A – With 0.25% Aerosil®200, Group 2: L – Pharmaceutical powder only).*

	Vulstof=Emcompress T-tests; Grouping: Kondisie (Flowrate.sta) Group 1: A Group 2: L											
Variable	Mean A	Mean L	t-value	df	p	t separ. var.est.	df	p 2-sided	Valid N A	Valid N L	Std.Dev. A	Std.Dev. L
Meting	21.63400	22.58250	-0.627702	4	0.564252	-0.627702	2.026927	0.593567	3	3	2.608479	0.2140

ANNEXURE G

Certificates and specifications of Cellactose® 80, FlowLac® 100 and Starlac®

Table G.1: *Specifications of Cellactose® 80*

Specification

MEGGLE

Doc.-No. S-3720-E | Revision 8 | Page 1/5

PRODUCT

CELLACTOSE 80

Definition
Cellactose 80 is a spraydried mixture of 75 parts lactose monohydrate (Ph.Eur.) and 25 parts cellulose powder (Ph.Eur.).

Characters
A white or almost white and odourless powder, partly soluble in water.

Identification		
A. Cellactose 80	IR-absorption (Ph.Eur.2.2.24) Cellactose 80-monograph	conforms
B. Lactose	Thin layer chromatography (Ph.Eur. 2.2.27) Cellactose 80-monograph	conforms
C. Cellulose powdered	1.method 1 Cellactose 80-monograph	conforms
	2.method 2 Cellactose 80-monograph	conforms
Tests		
pH	Ph.Eur. 2.2.3 Cellactose 80-monograph	4.0 - 7.0
Loss on drying	Ph.Eur. 2.2.32 Cellactose 80-monograph	NMT 3.5 %

Date of issue: 04.08.2006

	Check			Approval
Date of issue	03.08.2006	04.08.2006	04.08.2006	04.08.2006
Electronic Signature	Egmont Pfeifer, Sales Excip.-Tech.	Anett Schober, Regulatory Affairs	Eugen Schwarz, R&D	Gabriele Mueller, QA/QM
Date of issue	03.08.2006	03.08.2006	03.08.2006	
Electronic Signature	Albert Speckmaier, Production	Klothilde Wimmer, QC	Markus Zimmer, QC	

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Specification

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Water	Ph.Eur. 2.5.12 Cellactose 80-monograph	4.0 - 7.0 %
Sulphated ash	Ph.Eur. 2.4.14 Cellactose 80-monograph	NMT 0.2 %
Heavy metals	Ph.Eur. 2.4.8 method C Cellactose 80-monograph	NMT 5 ppm
Microbial contamination		
Total viable aerobic count	Ph.Eur. 2.6.12	NMT 10^2 / g
Moulds	Ph.Eur. 2.6.12	NMT 10 / g
Yeasts	Ph.Eur. 2.6.12	NMT 10 / g
Escherichia coli	Ph.Eur. 2.6.13	absent / 10 g
Salmonella species	Ph.Eur. 2.6.13	absent / 10 g
Assay		
Lactose as lactose monohydrate calculated on the dried basis	Cellactose 80-monograph	73.0-77.0 %
Cellulose powdered calculated on the dried basis	Cellactose 80-monograph	23.0 - 27.0 %
Particle size distribution	Ph.Eur. 2.9.12 Cellactose 80-monograph	
< 32 µm		NMT 20 %
<160 µm		35 - 65 %
<250 µm		NLT 80 %

Storage (Ph.Eur.):
At room temperature, in well closed containers, under dry and odour free conditions.

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Specification

MEGGLE

Monograph to Spez.No. 3720 Page 3-5

Definition
Cellactose 80 is a spraydried mixture of 75 parts lactose monohydrate (Ph.Eur.) and 25 parts cellulose powder (Ph.Eur.).

Characters
A white and odourless powder, partly soluble in water.

Identification

A. Cellactose 80
The identification is carried out by Infrared Absorption (Ph.Eur. 2.2.24). The spectrum of a sample exhibits maxima at the same wavelengths and with the same relative intensities as a 3+1 mixture of lactose monohydrate (Ph.Eur.) and cellulose powder (Ph.Eur.). Sample preparation is performed by preparation of KBr pellets or direct placing of the sample onto an attenuated reflectance crystal. Spectra are recorded between 2.5 and 15 µm (4000-670 cm^{-1}).

B. Lactose
Test solution: add 40 mg sample to a mixture of 24 ml water and 36 ml methanol R and stir on a magnetic stirrer for approx. 10 min. Centrifuge the resulting suspension at 3000 rpm. Decant the supernatant and filter through a white ribbon ("Weißband"-) filter. Use this filtrate for the identification of lactose. Dry the residue from centrifugation for 2 hours at 100-105°C in the drying oven and use this residue for the identification of cellulose powder.

Reference solution (a): Dissolve 10 mg of lactose CRS in a mixture of 2 volumes of water and 3 volumes of methanol R and dilute to 20 ml with the same mixture of solvents.

Reference solution (b): Dissolve 10 mg each of dextrose (glucose) CRS, lactose CRS, laevulose (fructose) CRS and sucrose CRS in a mixture of 2 volumes of water and 3 volumes of methanol R and dilute to 20 ml with the same mixture of solvents.

Apply separately to the plate 2 µl of each solution and thoroughly dry the starting points. Develop over a path of 15 cm using a mixture of 10 volumes of water, 15 volumes of methanol R, 25 volumes of anhydrous acetic acid R and 50 volumes of ethylene chloride R. Dry the plate in a current of warm air. Repeat the development immediately, after renewing the mobile phase. Dry the plate in a current of warm air and spray evenly with a

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solution of 0.5 g of thymol R in a mixture of 5 ml of sulphuric acid R and 95 ml of alcohol R. Heat at 130°C for 10 min. The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows four clearly separated spots.

C. Cellulose powder

Method 1:
The identification of cellulose powder is carried out according to identification test A (Ph.Eur.). Place the dried residue obtained from B on a watch glass and disperse in 2 ml of zinc chloride solution containing iodine.
Result: the substance takes on a violett-blue colour.

Method 2:
Mix 120 g with 750 ml water on a magnetic stirrer. Filter the dispersion through a white ribbon (Weißband-) filter and wash with 500 ml water. Complete the filter residue with water to 300 g. Mix the dispersion in a blender at 18 000 rpm for 5 minutes. Transfer 100 ml of the dispersion to a 100 ml graduated cylinder and allow to stand for 1 hour: the powdered Cellulose settles in the cylinder and a supernatant liquid appears above the layer of the cellulose.

Tests

pH (Ph.Eur. 2.2.3): Shake 5 g with 40 ml of carbon dioxide-free water R for 20 min and centrifuge. The pH of the supernatant liquid is 4.0 to 7.0.

Loss on drying (Ph.Eur. 2.2.32): not more than 3.5 percent of its weight. Dry 1.0-2.0 g at 80°C for 2 hours.

Water (Ph.Eur. 2.5.12): 4.0 to 7.0 percent.
Grind Cellactose 80 to a fine powder using a mortar. Add 40 ml formamid/methanol 1:2 (V/V) into a titration flask. Afterwards add approximately 150 mg Cellactose 80 accurately weighed and titrate with an appropiate titrans (e.g.Hydranal-Composite 5).

Sulphated ash (Ph.Eur. 2.4.14): not more than 0.2 percent, determined on 1.0 g.

Heavy metals (Ph.Eur.2.4.8 according method C): not more than 5 ppm, determined on 2 g.

Specification

Microbial contamination
Total viable aerobic count does not exceed 10^2 per g, moulds do not exceed 10 per g and yeasts do not exceed 10 per g, determined by plate count (Ph.Eur. 2.6.12).

Cellactose 80 complies with the tests for Escherichia coli and Salmonella spp. (absent/10 g) (Ph.Eur. 2.6.13).

Assay

Lactose 73.0 to 77.0 percent as lactose monohydrate, calculated on the dried basis.

Grind Cellactose 80 to a fine powder in a mortar. Afterwards add approximately 260 mg Cellactose 80 accurately weighed into a 250 ml iodine flask and suspend in 90 ml water. Then add 0.560 g dried anhydrous sodium carbonate and stirr until the sodium carbonate dissolves. Add 30 ml iodine solution (0.05 mol/l) with a volumetric pipette. Keep the iodine flask in the dark for 40 minutes at room temperature. Afterwards add 10 ml hydrochloric acid (5 mol/l) and titrate with sodium thiosulfate 0.1 mol/l until the solution turns yellow. As the next step add 2.0 ml 1% starch solution and titrate until the blue colour dissapears. Additionally carry out a blank titration.
1 ml 0.1 M sodiumthiosulphate solution is equivalent to 18.02 mg lactose monohydrate.

Cellulose powder 23.0 to 27.0 percent calculated on the dried basis.

Add 1 to 2 g of the sample accurately weighed to 100 ml of hot dest.water (70-80°C). Stirr the mixture for 15 minutes on a magnetic stirrer. Suck off the suspension in a G4-type glass filter crucible (pore size 10-16 µm) which is dried to constant weight and thorough ly tared. Dry the glass filter crucible with the residue at 102±2°C to constant weight and determine the weight of the residue after cooling in a desiccator. Calculate the content of cellulose powder on the dried basis.

Particle size distribution (Ph.Eur. 2.9.12): The classification is carried out using an air jet sieve equipped with constant and controlable suction head of 1500-2500 Pascal. Weigh a sample of approx. 10.0 g accurately, weighed add 0.1 g Al_2O_3 and sieve for 2 minutes.

Storage (Ph.Eur.):
At room temperature, in well closed containers, under dry and odour free conditions.

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Table G.2: *Certificate of analysis of FlowLac® 100*

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P O Box 40441, Moreleta Park, 0044
Tel : +27 12 997 6582

Molkerei MEGGLE Wasserburg GmbH & Co. KG

MEGGLE

Delivery-No.: 701171
Man.Date: YEAR 2006 WEEK 44
Exp.Date: YEAR 2008 WEEK 18

CERTIFICATE OF ANALYSIS (Spec. 3030/02)

Product: **FLOWLAC 100**

DEFINITION

FlowLac 100 is the brandname for a spraydried lactose.
FlowLac 100 conforms with the monograph "lactose monohydrate" in the european pharmacopoeia (Ph.Eur.). This monograph is harmonized between Ph.Eur., USP/NF und JP.

CHARACTERS

FlowLac 100 is a direct compressible lactose.
FlowLac 100 is a white or almost white, odourless, free flying powder. It is freely but slowly soluble in water, practically insoluble in alcohol.

Date: 15.11.2006
Lot-No.: L0644 A 4950

	Method / Specification	Unit	Result
IDENTIFICATION			
Identification	Ph.Eur./A IR Spectrum /conforms Ph.Eur./D Water /conforms		conforms
TEST			
Appearance of solution	Ph.Eur./Solution is clear, not more coloured than reference solution BY 7		conforms
Acidity or alkalinity	Ph.Eur. /NMT 0,4 0,1 n NaOH	ml	0,20
Spec. optical rotation	Ph.Eur. /+54,4 - +55,9		55,2
Absorbance 400 nm	Ph.Eur. /NMT 0,04		0,00
Absorbance 210-220 nm	Ph.Eur. /NMT 0,25		0,04
Absorbance 270-300 nm	Ph.Eur. /max. 0,07		0,02

Molkerei MEGGLE Wasserburg GmbH & Co. KG, Megglestr. 6-12, D-83512 Wasserburg, Tel. +49(0)8071/73-0, Fax +49(0)8071/73-444
info@meggle.de, www.meggle-group.com - Geschäftsführung MEGGLE Wasserburg Verwaltungs GmbH vertreten durch: drs. Sil H. van der Ploeg MBA
HRA 7828 Amtsgericht Traunstein USt-IdNr.: DE813697582, Steuernr. 158/169/01000

This is a copy of the certified Certificate of Analysis on the Letterhead of the approved merchant:

9 Hoyt Crescent, Moreleta Park, 0044
P O Box 40441, Moreleta Park, 0044
Tel : +27 12 997 6582
Fax: +27 12 997 6580

Molkerei MEGGLE Wasserburg GmbH & Co. KG

MEGGLE

Delivery-No.: 701171
Man.Date: YEAR 2006 WEEK 44
Exp.Date: YEAR 2008 WEEK 18

Date: 15.11.2006 T40P

Lot-No.: L0644 A 4950

	Method / Specification	Unit	Result
Heavy metals	Ph.Eur. /NMT 5	ppm	conforms
Water	Ph.Eur. /4,5-5,5	%	5,06
Loss on drying	USP/NF /NMT 1,0	%	0,5
Sulphated ash	Ph.Eur. /NMT 0,1	%	0,10
Particle size distribution	< 32 µm NMT 10	%	conforms
Air jet sieve	<100 µm 20-45	%	conforms
	<200 µm NLT 80	%	conforms

MICROBIAL CONTAMINATION

Total viable aerobic count	Ph.Eur. /NMT 10^2	/g	0
Moulds	Ph.Eur. /NMT 10	/g	conforms
Yeasts	Ph.Eur. /NMT 10	/g	conforms
Escherichia coli	Ph.Eur. /negative	/10g	conforms
Salmonella spp.	Ph.Eur. /negative	/10g	conforms

STORAGE

At room temperature, in tight containers, under dry and odourfree conditions.

This certificate of analysis is computer generated, thus no signature required.

Quality Control
Dr. G. Müller

The above data does not release purchaser from performing an incoming control. A legally binding assurance for the suitability of the product for a defined application purpose cannot be derived from the above.

2

Molkerei MEGGLE Wasserburg GmbH & Co. KG, Megglestr. 6 - 12, D-83512 Wasserburg, Tel. +49(0)8071/73-0, Fax +49(0)8071/73-444
info@meggle.de, www.meggle-group.com · Geschäftsführung MEGGLE Wasserburg Verwaltungs GmbH vertreten durch: dis. Sil H. van der Ploeg MBA
HRA 7828 Amtsgericht Traunstein · USt-IdNr.: DE813497582, Steuernr. 156/159/41000

This is a copy of the certified Certificate of Analysis on the Letterhead of the approved merchant:

Table G.3: *Certificate of analysis of Starlac®*

9 Hoyt Crescent, Moreleta Park, 0044
P O Box 40441, Moreleta Park, 0044
Tel : +27 12 997 6582
Fax: +27 12 997 6580

Molkerei MEGGLE Wasserburg GmbH & Co. KG

MEGGLE

CERTIFICATE OF ANALYSIS (Spec.3730 (E))

Delivery No.: 610741
Man.Date: YEAR 2005 WEEK 25
Exp.Date: YEAR 2005 WEEK 28

STARLAC®
Lot-No.: L 0629 A 4942

DEFINITION:

CHARACTER:

IDENTIFICATION:

	Method	Specification	Result
A. Starlac		conforms	conforms
B. Maize starch		conforms	conforms
		max. 0.2%	0.1%

TESTS:

Maize starch		12.0-18.0 %	14.6 %
Loss on drying		max. 5.0 %	4.6 %

This is a copy of the certified Certificate of Analysis on the Letterhead of the approved merchant:
Amchem Pty Ltd

9 Hoyt Crescent, Moreleta Park, 0044
P O Box 40441, Moreleta Park, 0044
Tel : +27 12 997 6582
Fax: +27 12 997 6580

Molkerei MEGGLE Wasserburg GmbH & Co. KG

MEGGLE

Delivery-No: 510741
Man.Date: YEAR 2008 WEEK 26
Exp.Date: YEAR 2009 WEEK 25

CERTIFICATE OF ANALYSIS (Spec.3733-07)

Product: STARLAC®
Item-No: L 0629 A 4942

	Method	Specification	Result
Sulphated ash	Ph.Eur.2.4.14	NMT 0.25 %	0.06 %
Heavy metals	Ph.Eur.2.4.8	<5 ppm	conforms
Particle size distribution			
32 µm		NMT 15 %	conforms
[illegible]		[illegible]	conforms
2 µm		NLT 85 %	conforms

MICROBIAL CONTAMINATION:

Total viable aerobic count	Ph.Eur.2.6.12	NMT [illegible]	[illegible]
Moulds and Yeasts	[illegible]	NMT [illegible]	conforms
Escherichia coli	Ph.Eur.2.6.13	negative/10 g	conforms
Salmonella spp	Ph.Eur.2.6.13	negative/10 g	conforms

Storage:
[illegible] temperature [illegible] sealed containers, under dry and odour free conditions.

This certificate is computer generated, therefore no signature required.

Quality Control
Dr. [illegible]

[illegible]

[illegible]

This is a copy of the certified Certificate of Analysis on the Letterhead of the approved merchant:
Amchem Pty Ltd