CHARACTERIZATION OF THE FLOW AND COMPRESSION PROPERTIES OF CHITOSAN

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"WE SET OUR EYES NOT ON WHAT WE SEE BUT ON WHAT WE CANNOT SEE...WHAT WE CANNOT SEE WILL LAST FOREVER" 2 COR. 4:18

Lord Jesus, thank you for giving me the knowledge and opportunity to complete my study. Without You I would not have been able to do this.

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ABSTRACT

The most useful dosage form taken from a patient's point of view is tablets because of its simplicity and portability (Takeuchi *et al.*, 2004:132). Manufacturing of tablets can be done by wet granulation or direct compression of powders. For direct compression it is important that the powder has good particle flowability and compactability. Various methods to investigate these properties of the powder have been developed, which provide comparative indices to assist in the process and formulation design (Li *et al.*, 2004:77).

Chitin is the second most abundant naturally occurring biopolymer after cellulose (Asada *et al.*, 2004:169). Chitosan is produced by the partial alkaline *N*-deacetylation of chitin (Berger *et al.*, 2004:36). The structure of chitosan is similar to that of cellulose, an excipient with acceptable compression properties. According to Olsson and Nyström (2001:204) hydrogen bonds are considered to be one of the dominating bonding mechanisms for most pharmaceutical powders. The extent of the effect will depend on the particle shape and surface characteristics (Hiestand, 1997:237-241). Considering the structure of chitosan it predicts the ability to form H-bonds, and produce tablets with acceptable mechanical strength.

The two major problems identified in terms of the use of chitosan as directly compressible filler in tablet formulations is its poor flow and compressibility properties (Aucamp, 2004; Buys, 2006; De Kock, 2005). During the characterization of chitosan raw material the aim was to determine to which extend its physical properties affects the flow of the material and to compare its flow properties to that of other commonly used tablet fillers. Two batches chitosan were compared to each other to determine the effect of morphology on their physical properties. When ranking the composite index of the powders it was clear that in regards to the other materials used, chitosan was ranked the lowest. These results confirmed the poor flow of chitosan. The characterization of the two chitosan batches used in this study revealed significant differences in the morphology of the particles of the different batches. Because of these large inter-batch variations with respect to the physical properties of the different batches even when manufactured by the same company via the same method, these variations also affected the flow characteristics of the two batches.

From the particle characterization in chitosan it could be concluded that the previously observed poor compression characteristics (De Kock, 2005; Aucamp, 2004) could be attributed to the low density and high porosity of the material. Only one of the batches studied could be compressed on a standard eccentric press, which could be attributed to the differences between the physical properties of two batches. Chitosan showed promising

compression characteristics at specific machine settings (limited range of upper punch settings), with good crushing strength and low friability. The drawbacks of the compression properties for chitosan on the standard press was the relative low tablet weights that could be compressed for a specific die size and the narrow range for the upper punch setting to achieve an acceptable mechanical tablet strength and friability.

The results of Buys (2006) showed promising results for chitosan when changing the compression cycle from a single fill to a double die fill for each compression cycle. The advantage of the modified eccentric tablet press in terms of improvement of the compactibility of low density materials was clearly demonstrated by the results from the compression studies of both chitosan batches. With the double fill cycle on the modified press it was possible to fill the die with a sufficient amount of powder to produce acceptable tablets with sufficient crushing strength and low friability. The modified tablet press made it possible to compress the batch (021010) chitosan which couldn't be compressed on the standard tablet press. Batch (030912), which was compressed on the standard as well as the modified press, showed improved results in the crushing strength and friability with increase of the percentage compression setting at a constant upper punch setting. Batch 030912 showed better results than that of batch 021010 and this could be attributed to the physical differences between the two batches.

Key words: Chitosan; Flow; Compressibility; Standard eccentric press; Modified eccentric press; Crushing Strength

OPSOMMING

Vanuit die pasiënt se oogpunt bly tablette een van die gewildste doseervorme vir die behandeling van siektetoestande, veral as gevolg van gemak van gebruik (Takeuchi *et al.*, 2004:132). Die vervaardiging van tablette geskied hoofsaaklik volgens natgranulering of direkte samepersing. In die geval van direkte samepersing is dit noodsaaklik dat poeiers oor goeie vloei- en saampersbaarheideienskappe moet beskik. Verskeie metodes is beskikbaar om dié eienskappe van poeiers te meet en vergelykbare indekse is hieruit ontwikkel om die proses- en formuleringsontwerp te ondersteun (Li *et al.*, 2004:77).

Naas sellulose is kitien die volopste biopolimeer wat in die natuur voorkom (Asada *et al.*, 2004:132). Kitosaan word vervaardig deur gedeeltelike alkaliese *N*-deasetilase van kitien (Berger *et al.*, 2004:36). Die chemiese struktuur van kitosaan toon groot ooreenkomste met die van sellulose 'n verbinding met goeie saampersbaarheideienskappe wat toegeskryf kan word aan die vorming van sterk waterstofbindings tydens samepersing. Volgens Olsson en Nyström (2001:204) is waterstofbindings een van die sterkste "natuurlike" bindingmeganismes vir verskeie farmaseuties poeiers, wat hoofsaaklik beïnvloed word deur die deeltjiegrootte en – oppervlakte van die poeierdeeltjies (Hiestand, 1997:237-241). Op grond van die chemiese struktuur van kitosaan kan daar verwag word dat hierdie verbinding goeie saampersbaarheideienskappe behoort te toon en dus tablette behoort te lewer met voldoende meganiese sterkte.

Die swak vloeibaarheid en saampersbaarheid van kitosaan in direksaampersbare tabletformulerings, soos aangetoon deur Aucamp (2004) en De Kock (2005), is hoofsaaklik toegeskryf aan die lae digtheid en hoë porositeit van die grondstof. Tydens die eerste fase van die studie is die vloeibaarheid en saampersbaarheid van twee kitosaanlotte bepaal en met die van ander vulstowwe, wat algemeen in tabletformulerings gebruik word, vergelyk. Die doel tydens hierdie fase was om vas te stel tot watter mate die fisiese eienskappe van die kitosaanpoeierdeeltjies hul vloeibaarheid en tableteienskappe beïnvloed (m.a.w. hul saampersbaarheid). In vergelyking met verskeie ander algemeen-gebruikte tabletvulstowwe, het beide kitosaanlotte die swakste vloeibaarheideienskappe getoon. Vergelyking van vloeibaarheid van die twee kitosaanlotte het groot verskille aangetoon, wat herlei kon word na verskille tussen die fisiese eienskappe van die poeierdeeltjies van die twee lotte.

Saampersbaarheidstudies op 'n standaard enkeltabletpers het die effek van die verskille in die fisiese eienskappe van die twee kitosaanlotte op tableteienskappe bevestig, en slegs lot 030912 het tablette gelewer met voldoende meganiese sterkte (geskik vir hantering en toetsing). Die vernaamste beperkinge ten opsigte van die tablette was egter die beperkte

massagrense (100 – 200 mg) en bostempelverstelling (wat persdruk bepaal) wat vir 'n bepaalde stempelgrootte (8 mm) beskikbaar was om tablette met aanvaarbare breeksterkte en verbrokkeling te lewer. Hierdie resultate het bevestig dat die saampersbaarheidprobleme van kitosaan herlei kon word na die lae digtheid (en hoë porositeit) van die grondstof, en nie toegeskryf kon word aan die onvermoë van deeltjies om effektiewe bindingkragte te vorm nie.

Uit die resultate van Buys (2006) is afgelei dat, met 'n toename in die volume poeier in die matrys, kitosaan wel goeie saampersbaarheideienskappe kan lewer. 'n Verhoging in die poeier volume is verkry deur 'n modifikasie waartydens die enkel vulsiklus van die standaard enkeltabletpers verander is na 'n dubbel vulsiklus. Gedeeltelike samepersing van die poeier na die eerste vulling is opgevolg met 'n tweede vulling van die matrys waarna samepersing dan weer plaasgevind het. Die samepersingresultate op die gemodifiseerde pers het getoon dat beide kitosaanlotte wel saamgepers kon word; en dat hoër tabletmassas (steeds in 'n 8 mm matrys) met hoër breeksterktes en laer verbrokkeling verkry kon word. Lot 030912 het steeds beter saampersbaarheideienskappe as lot 021010 gelewer met beduidende hoër tabletmassas breeksterktes en laer verbrokkeling. Hierdie verskille is weereens toegeskryf aan die verskille tussen die poeiereienskappe van die twee lotte. Die saampersbaarheidresultate op die gemodifiseerde pers het ook getoon dat kitosaan wel oor goeie saampersbaarheideienskappe beskik, mits die volume poeier in die matrys (en dus die poeierdigtheid) verhoog kon word.

Sleutelwoorde: Kitosaan; Vloeibaarheid; Saampersbaarheid; Standaard tabletpers; Gewysigde tabletpers; Breeksterkte

AIM AND OBJECTIVES OF THE STUDY

AIM

The aim of the study was to investigate the flow and compression properties of chitosan. The study included a comparison of two different batches of chitosan obtained from the same manufacturer in order to determine the effect of inter-batch variation on their physical properties and compression characteristics.

BACKGROUND

Chitosan, a natural occurring and abundant polysaccharide, is widely used in the pharmaceutical and cosmetic industry as an excipient in a wide range of dosage forms and applications, mostly due to its low toxicity, biodegradability and biocompatibility. The properties of chitosan relate to its polyelectrolyte and polymeric carbohydrate character. The presence of a number of amino groups allows chitosan to react chemically with anionic systems (Jones & Mawhinney, 2005). The most significant pharmaceutical importance of chitosan can be ascribed to its muco-adhesive properties and its ability to open the epithelial tight junctions in the gastro-intestinal tract which allows for the oral absorption of large molecule drugs (Kotzé *et al.,* 1997:251-252). Recently, chitosan has gained importance as a disintegration agent due to its strong ability to absorb water. It has been observed that chitosan contained in tablets at levels below 70% acts as a disintegration agent (Kumar, 2000:19). Previous studies (Aucamp, 2004; De Kock, 2005) showed its limited use as a filler in directly compressible tablet formulations, mainly due to its low apparent density, poor flow and compressibility (especially on standard eccentric tablet presses), resulting in tablets with very low mechanical strength. Even granulation or the inclusion of dry binders seemed to fail to induce the required mechanical strength. The chemical structure of chitosan shows a high resemblance with that of cellulose which possesses excellent compression characteristics due to the formation of hydrogen bonds under pressure. Results from the study of Buys (2006) on the use of chitosan in minitablets showed promising compression profiles for the material when the powder volume in the die cavity was increased through a double filling cycle on a modified tablet press. It was therefore postulated that if enough powder could be filled into the die cavity of a tablet press to increase the packing density of the material, then efficient particle bonding during compression should be able to produce tablets of acceptable mechanical strength.

OBJECTIVES

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

- Characterization of the morphology and flow properties of two chitosan batches.
- Compression studies on an eccentric tablet press.
- Compression studies on a modified (double fill) tablet press.

CHAPTER 1

THE FLOW AND COMPRESSION PROPERTIES OF PHARMACEUTICAL POWDERS

1.1 INTRODUCTION

There are various types of oral dosage forms such as tablets, granules and capsules. Tablets are the most useful dosage form for its simplicity and portability to take from the patient's point of view (Takeuchi *et al.*, 2004:132). The majority of prescriptions dispensed by pharmacists are for solid dosage forms such as tablets, capsules or sachets. These are manufactured on an industrial scale involving extremely sophisticated equipment and processes. To ensure efficient manufacture a fundamental understanding of the processes is essential (Podczeck &Wood., 2003:57).

Two essential process parameters tested when a pharmaceutical material is formulated for a tabletting process are particle flowability and compactability. Geometrical, physical, chemical and mechanical particle properties, as well as operational conditions strongly affect these behavioural descriptions. Various measurement methods have been separately developed for each of these properties, which provide comparative indices to assist in process and formulation design (Li *et al.*, 2004:77).

The pharmaceutical industry relies on powder processing since approximately 80% of pharmaceutical products are in solid form, i.e. tablets and capsules (Jivraj *et al.*, 2000:58). Pharmaceuticals have especially demanding quality requirements with regard to uniformity in content, consistent appearance, longevity for storage, transportation and shelf life, demanding an incomparable degree of control and precision in their manufacture (Muzzio *et al.*, 2002:3). An added complexity is that medicinal products are often blended mixtures of many different powders comprising active ingredients and various excipients for improving the dosage delivery and bioavailability. Among the many particle properties, flowability and compactability are two essential characterizations to ensure a successful tabletting process (Guerin *et al.*, 1999:92).

Various excipients are added in tablet formulations acting as binders, lubricants and disintegrants in order to improve the process ability and bioavailability of the tablet product, often through granulation processes. However, direct compaction without granulation, is gaining interest as alternative means of changing particle properties become available.

Direct compression offers a number of advantages; it requires fewer unit operations in production which means less equipment and space, lower labour costs, less processing time, and lower energy consumption (Bolhuis &Chowha, 1996:435). The following flow diagram (figure 1.1) shows the two general methods used by pharmaceutical industries for manufacturing tablets.

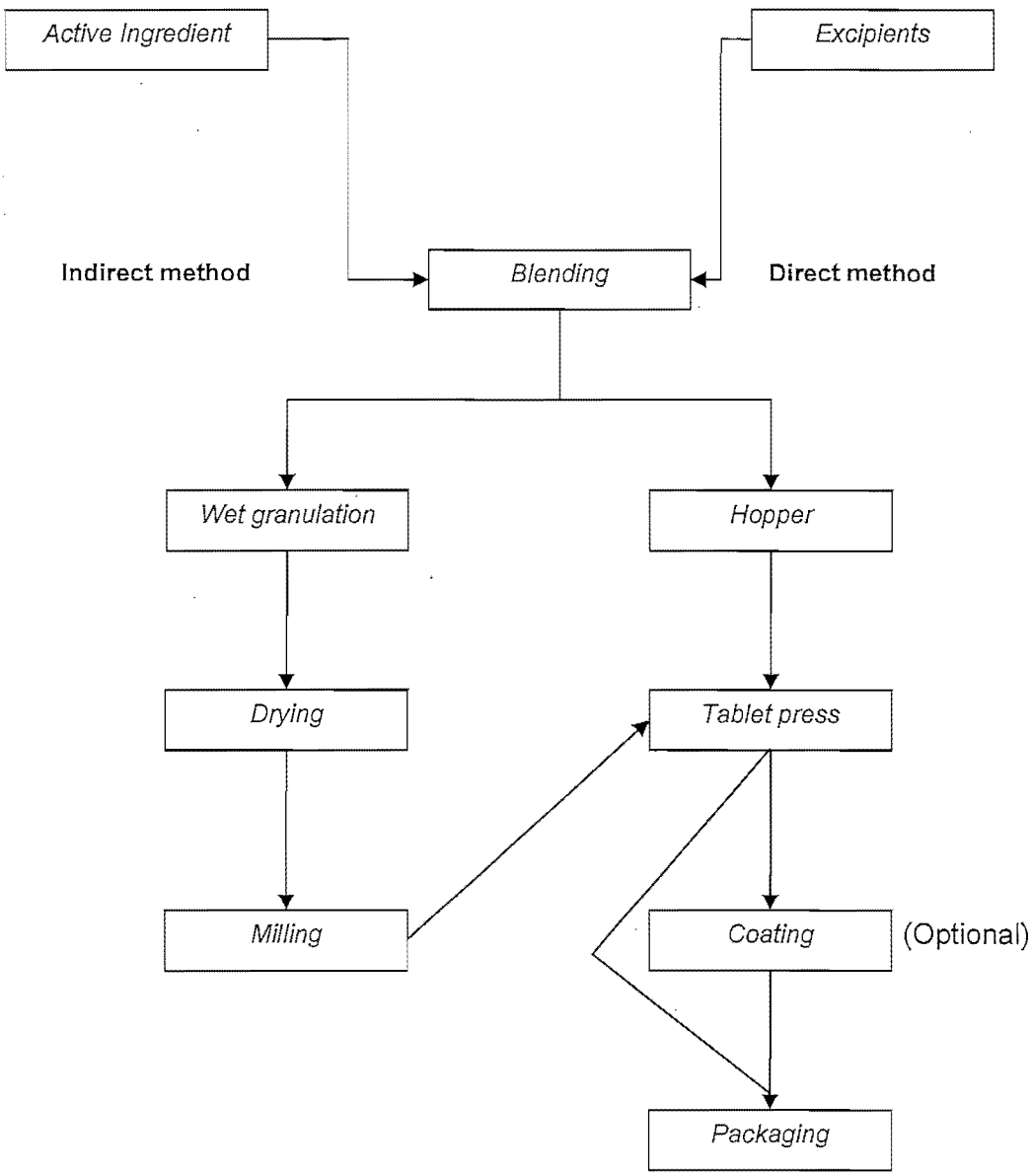

Figure 1.1: *Flow chart of pharmaceutical tablet production (Bodhmage, 2006:1)*

The indirect method shown in figure 1.1 may be considered as a particle size magnification method. Small particles adhere to each other, facilitated by certain mechanisms to form larger and physically stronger granules than the original particles (Aucamp, 2004:8). Agglomeration is the formation of powder particle assemblies. Agglomeration can occur spontaneously, but for purposes of dosage form manufacture it is generally forced either by

dry or by wet granulation (Podczeck & Wood, 2003:57). The formation of wet granules depends on the particle size of the powder, the viscosity of the liquid binder, the contact angle between binder liquid and solid, and the interfacial free energy (Keningley *et al.*, 1997:98). The main objectives of granulation are to improve the flow properties and compression characteristics of the powder mix and to prevent segregation of the constituents. The granulation process improves the flow properties and the compression characteristics of the powder (Aucamp, 2004:8-9).

Powders used in direct compression formulations have to adhere to certain prerequisites. The powder should have good flow properties, ensuring that the powder flows into the die. Furthermore, the powder should have high bulk density to ensure that sufficient powder fill the die, otherwise the resultant tablet will be correspondingly thin. Particle flowability and compactibility are the two critical bulk properties in the tabletting process. The lack of either is detrimental to the production. Particle flowability and compactibility are shown to share fundamental similarities, although the behavioural outcomes may be different depending on the dominating factors in particular circumstances (Li *et al.*, 2004:92).

1.2 POWDER FLOW

Pharmaceutical tablets are produced on a commercial scale by filling the die of the tablet press by volume. The flow properties of the powder mixture are important to ensure uniformity of tablet mass (Lindberg *et al.*, 2004:785). The flowability of the powdered materials used in a tablet formulation is a major consideration in the production of this popular dosage form. Flowability may be defined as the powder's ability to flow evenly, by means of gravity and other forces from the top to the bottom of the hopper and then on to the dosage, compaction, and crushing chambers (Gioia, 1980:1).

Given the importance of powder flow, the pharmaceutical industry still relies surprisingly heavy on flow properties that are poorly understood and applied. Powder flow is complex. Flow behaviour is multidimensional and depends on many powder characteristics. For this reason, no one test could accurately quantify flowability (Prescott & Barnum, 2000:60; Kamath *et al.*, 1993:277). There are many parameters that determine the flowability of powder i.e.: particle size; fines; unit surface; particle shape; tapped density; bulk density; porosity; air permeability through the powder; electrostatic charge; humidity; settling effects; and cohesion forces - all of which can have contrasting and interdependent influence (Gioia, 1980:2). The flow properties of powders depend on the joint effects of an immense number of physical and environmental variables such as packing conditions, particle size distribution, humidity, electrostatics and rate of flow (Freeman, 2000:1).

1.2.1 Methods used to predict powder flow

A powder mixture consists of particles and air. Prescott and Barnum (2000:60-62) suggested that powder flowability is a combined result of the influence of a materials physical properties and the equipment used for handling, storing or processing the material. There are several methods used for measuring flow properties for bulk powders. Each method uses different types of parameters of bulk powder behaviour, and there is no single test that fits all requirements (Lindberg *et al.*, 2004:786).

According to Hancock *et al.* (2004:980) powder characterization is one of the methods used to predict powder flow. The physical powder characterization (mean size and size distribution, particle shape, moisture content and density) influences powder flowability (Velasco *et al.*, 1995:2385). The above physical properties can be characterized using different techniques such as the laser diffraction method, image analysis, pycnometery and halogen moisture analysis to name a few (Bodhmage, 2006:17). According to Lavoie *et al.* (2002:892) the morphology of the powder particles influence the flowability by their packing formation. Carr (1965:163) described two types of flow – free flow and floodable flow. Free-flowing powder will tend to flow steadily and consistently, as individual particles, even through a fine orifice, the individual particles flow stable, uniform and consistent. Floodable flow is an unstable, liquidlike flow that can de discontinuous, gushing, uncontrollable and spattering. The particles of a free flowing powder are usually large (relatively small surface area per unit weight), are more or less spherical in shape, smooth and uniform, and are high in density. The particles of a powder that show floodable flow have a larger available surface area, are spherical in shape and uniform in size, exists as individual particles that can be seen as such under a low-power microscope, are low in density and consist of porous particles. As mentioned above particle size and shape influence the friction and flow properties of powders. The friction properties depend more on the asymmetry or elongation of the particles, while powder flow depends more on the geometric shape. For single bulk powders, the flow factor increases from needle shape, cubic, angular to round particles (Podczeck & Yasmin, 1996:194).

Angle of repose is another popular method to characterize the flowability of powders. There are two main types of angles of repose, i.e. the static and dynamic angles. According to Geldart *et al.* (2006:104-105) there are eight methods of measuring these angles of repose, and each method will give somewhat different values. The particle size, size distribution and particle shape as well as density, porosity and moisture content of the powder influence the angle of repose (Lahdenpää *et al.*, 2001:131). The four most common methods in use for the angle of repose until recently are shown in figure 1.2.

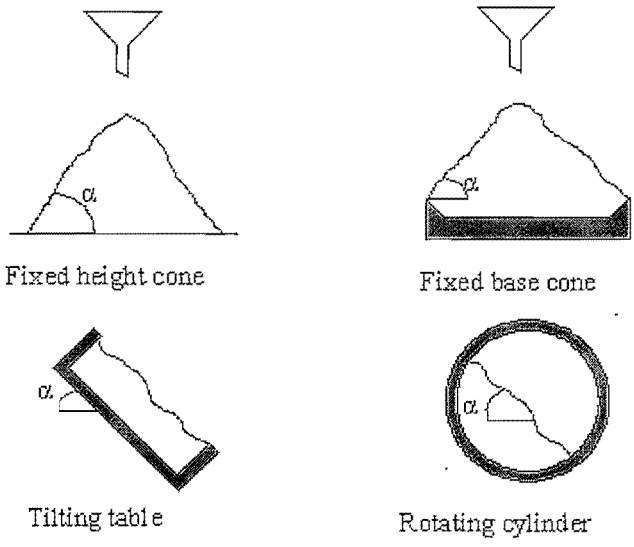

Figure 1.2: *Measurement of static and dynamic angle of repose (Geldart et al., 2006:105).*

In establishing a relation between flowability of powders and some simple physical measures, an angle of repose below 30° indicate good flowability, 30°-45° some cohesiveness, 45°-55° true cohesiveness, and >55° sluggish or very high cohesiveness and very limited flowability (Geldart *et al.*, 2006:104).

Active flow is an important factor in pharmaceutical manufacturing, the most important aspect controlling flow rate is the diameter of the orifice. For free-flowing powders the flow rate for a given orifice increases to a maximum rate as the particle size decreases and then a further reduction of particle size results in a slower flow rate. The flow rate increases as the diameter of the orifice increases. Thus, only bulk powders with the same critical orifice diameter can be compared to each other regarding the flow rate (Danish & Parrott, 1971:549-553). According to Chowhan and Yang (1983:232), the rheological behaviour of cohesive particles is not very well understood. The orifice flow rate decreases as the particle size decreases due to the changing relative magnitude of dispersion forces and gravitational forces per particle as particle size decreases. According to Yamashiro and Yuasa (1983:225), the packing characteristics of powders are fundamental and differ according to the packing method and the action of the external force. A simple test has been developed to evaluate the flowability of a powder by comparing the poured density and tapped density of a powder and the rate at which it packed down. A useful empirical guide is given by Carr's compressibility index (Wells, 2002:133).

1.2.2 The reasons for poor flowability of powder

Powder flows when the forces acting on the powder bed cause the resulting shear force to exceed the shear strength of the bed. Flow properties of powders are influenced by factors

acting on and between the particles in a powder such as air content, state of compaction of the powder, and humidity, as well as particle surface, size, shape, and size distribution (Lindberg *et al.*, 2004:785; Lindberg *et al.*, 2002:16). Particle shape and surface roughness could influence true contact area between solid particles and forces of adhesion. There is a great difference in the packing arrangement of fibrous particles or irregularly shaped particles compared to that of spherical particles. In the former, bridging and mechanical interlocking between individual particles greatly reduce free running characteristics (Tawashi, 1970:48). Fine powders may form a rathole when it flows out of a storage bin or hopper. A rathole is a self-supporting vertical channel extending from the outlet to the top surface of the powder, as seen in figure 1.3 (Bodhmage, 2006:2).

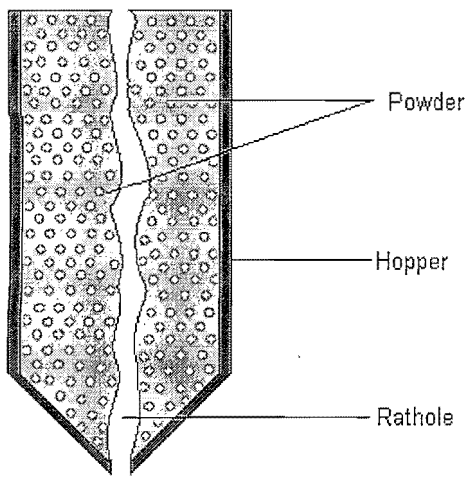

Figure 1.3: *Rathole formation (Bodhmage, 2006:2)*

1.3 COMPRESSION OF POWDERS

Levin (2000:2) defined compression as a reduction in powder volume. According to Sonnergaard (2005:270) compaction properties of pharmaceutical powders are separated in two distinct terms, the compressibility and the compactibility of a powder. Compressibility is the ability of the powder to deform under pressure and the compactibility is the ability of a powder to form coherent compacts or, otherwise stated, the ability of the powder to increase its strength under pressure (Levine, 2000:2; Michrafy *et al.*, 2002:257).

1.3.1 Tablet manufacturing

There are mainly three ways to manufacture tablets i.e. wet granulation, dry granulation and direct compression. Shagraw and Demarest (1993:23) conducted a survey for the

preference for the granulation process. The results were in favour of direct compression, although less than 20 percent of pharmaceutical materials can be compressed directly into tablets.

1.3.1.1 Advantages and disadvantages of direct compression of powders

The primary advantage of direct compression is the reduced production cost (Alderborn, 2002:404; Kawashima *et al.*, 2003: 283). Other advantages include saving space, machinery, personnel and time by fewer processing stages (shorter processing time and lower energy consumption) and the elimination of heat and moisture, therefore, the tablets show an improved chemical and physical stability over the tablets produced by wet granulation. Direct compression is ideal for the manufacture of tablets containing thermolabile and moisture-sensitive drugs. Fewer excipients may be needed in a direct compression formula (Bolhuis & Lerk, 1973:469; Gohel & Jogani, 2005:79; Jivraj *et al.*, 2000:59-61; Khan & Rhodes, 1976:1835).

Although cost effective there are still some disadvantages for this method. There are issues with segregation; however this can be reduced by matching the particle size and density of the active ingredient with the excipients. The active ingredient content is thereby limited to approximately 30%. Direct compression can't compress materials with a low bulk density; tablets produced are too thin or don't compress at all. Another disadvantage is the fact that it isn't suited for poorly flowing excipients. Lastly static charges may develop on the active ingredient or excipients during mixing, which may lead to agglomeration of particles producing poor mixing (Jivraj *et al.*, 2000:59-61; Shangraw & Demarest, 1993:23)

1.3.1.2 Tablet presses

According to Alderborn (2002:399-400) the tablet presses that are used most during production is the single-punch (eccentric press) and the rotary press. In addition, in research and development work hydraulic presses are used as advanced equipment for the evaluation of the tabletting properties of powders.

The single-punch press is the only one that will be discussed here. It possesses one die and one pair of punches (upper and lower punch) as shown in figure 1.4. The powder is held in a hopper which is connected to a hopper shoe located at the die table. The hopper shoe moves over the die table to fill the die with powder by gravity (this movement can either be a rotational or a translational movement). The amount of powder filled into the die is controlled by the position of the lower punch. When the hopper shoe is located beside the die, the upper punch descends and the powder is compressed. The lower punch is stationary during

compression and the pressure is thus applied by the upper punch and controlled by the upper punch displacement. After ejection the tablet is pushed away by the hopper shoe as it moves back to the die for the next filling cycle (Alderborn, 2002:399-400).

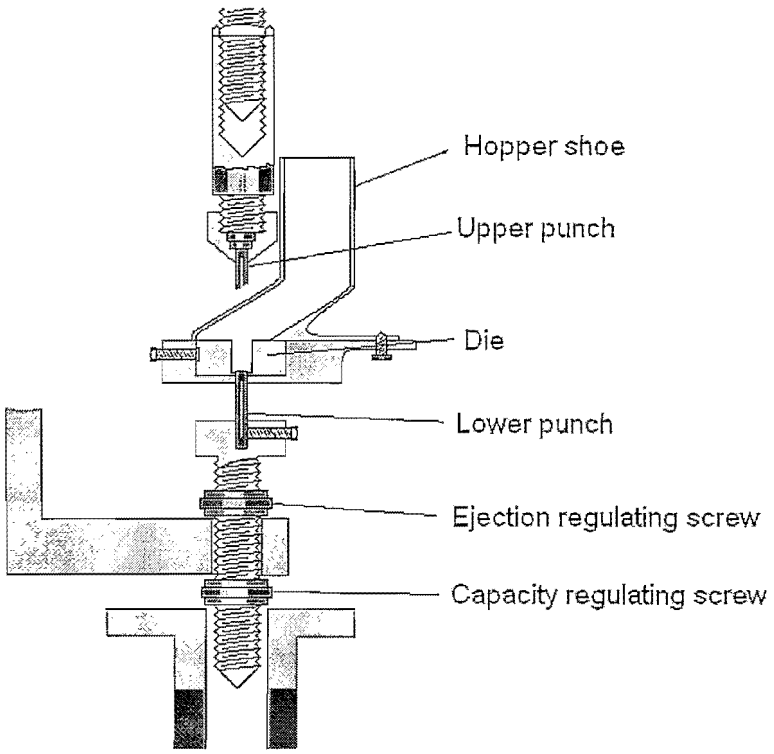

Figure 1.4: *A single-punch tablet press (Alderborn, 2002:400).*

1.3.1.3 The stages in tablet formation

According to Alderborn (2002:399) the process of tabletting can be divided into three stages; die filling, tablet formation and tablet ejection (figure 1.5).

Die filling

The powder fills the die through gravitational flow from the hopper. The volume is determined by the position of the lower punch in the die; the lower the punch is in the die, the heavier the tablet and vice versa (Alderborn, 2002:399).

Tablet formation

The upper punch descends and enters the die and the powder is compressed until a tablet is formed. The lower punch can be stationary or can move upwards in the die. After the maximum applied force is reached, the upper punch leaves the powder and the decompression phase commences (Alderborn, 2002:399).

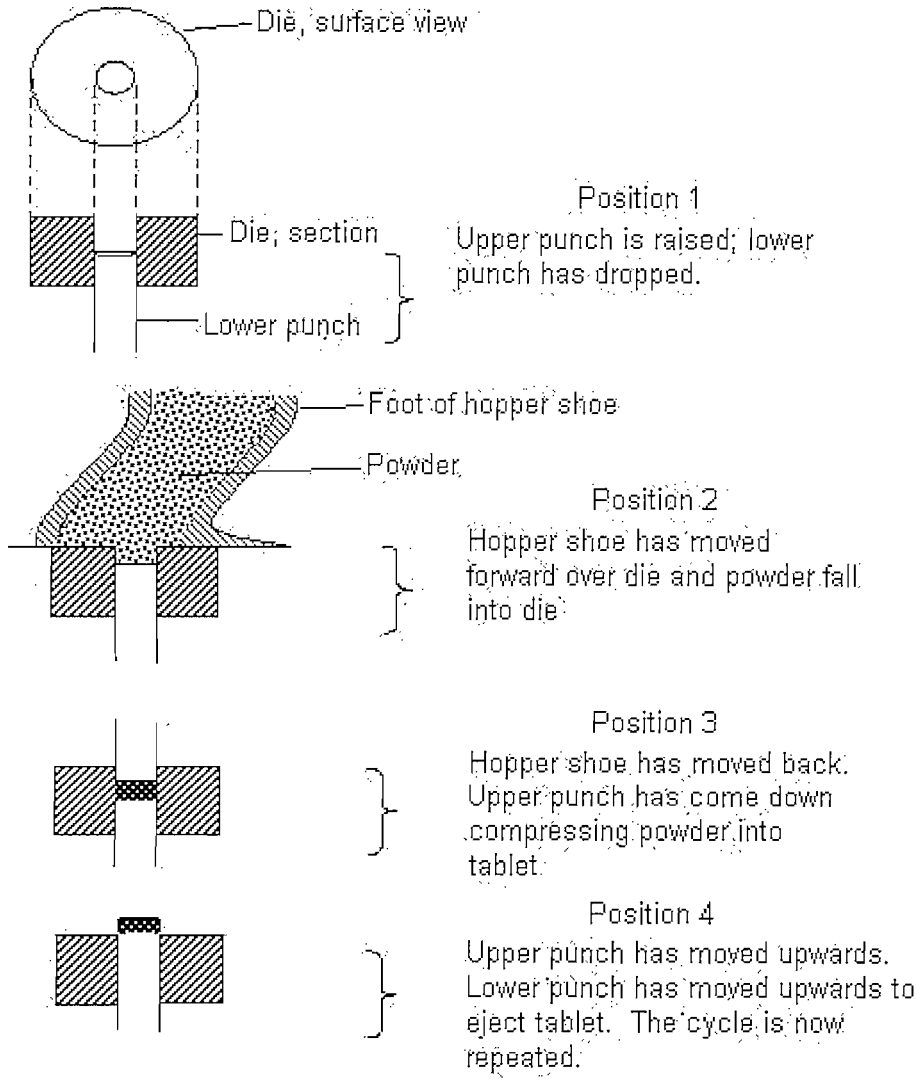

Figure 1.5: The sequence of events involved in the formation of tablets (Alderborn, 2002:399).

Tablet ejection

The lower punch rises until the tip of the punch reaches the level of the top of the die. The tablet is subsequently removed from the die by a pushing device (Alderborn, 2002:399).

1.3.2 Fundamental aspects of the compression of powders

1.3.2.1 Mechanisms of compression of particles

Compression is defined by Levin (2000:2) as a reduction in volume. When looking at powder particles in a die the volume is reduced when a force is applied (Armstrong, 1982:64). A series of events can occur, sequentially or parallel. The particles in the die will undergo

rearrangement to form a less porous structure (voids that exist between the particles is occupied). This will take place at very low forces, the particles sliding past each other. Fragmentation can occur in this stage because of the rough surfaces that move relative to one another and rough points are abraded. As the force increases and the particles can no longer rearrange themselves, the particles can either fragment or deform (or both) -this is called deformation. The deformation characteristics may be elastic, plastic, brittle fracture or a combination of these mechanisms in which one of these mechanisms will dominate depending on the material characteristics, the compaction speed, compaction pressure and/or particle size of the powder. When the elastic limit of the material is exceeded, compaction takes place. Fragmentation is permanent and there is no way in which the fragmented particles will recombine into the original particles when the force is removed. When the force is removed decompression/relaxation takes place. Plastic deformation is also permanent and the particles will remain deformed even after the force has been removed. Plastic deformation will assist bonding because it increases the contact area between particles, and fragmentation produces new surfaces which also favours strong bonding. Elastic deformation is time independent, reversible deformation of a particle, and can create residual stresses within the compact during the decompression/relaxation phase. Because of the reversion of the particle to its original shape, coherence will be lost as the area of interparticulate contact is reduced (figure 1.6) (Armstrong, 1982:64; Celik, 1992:773; Graf *et al.*,1984:280; Jain, 1999:21-22; Jivraj *et al.*, 2000:60).

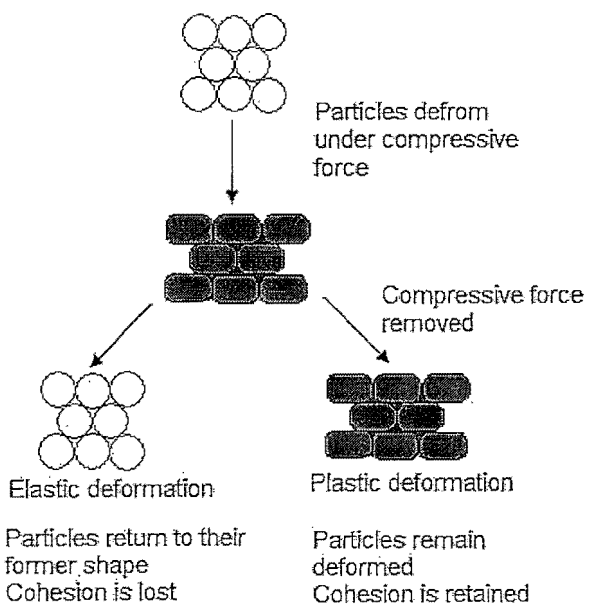

Figure 1.6: *Schematic illustration of particle deformation (elastic and plastic) during compression (Armstrong, 1982:64).*

1.3.2.2 Punch and die-wall forces involved during powder compression

In a single punch tablet press, the force (F_a) of compression is applied by means of the downward movement of the upper punch. The lower punch is static, and will have a force (F_b) transmitted to it through the powder bed. The force from the upper punch also transmits laterally to the die (F_w). Ejection of the tablet involves the application of an ejection force by the lower punch. This force received by the lower punch will always be less than that applied by the upper punch (Alderborn, 2002:429; Armstrong, 1982:65). Figure 1.7 illustrates the punch and die-wall forces involved during powder compression in a cylindrical die. The distribution in pressure will probably be associated with local variations in porosity, pore size and strength within the tablet (Alderborn, 2002:429). When the upper punch force is measured against punch-tip displacement, the resulting curve shows a progressively increasing slope, reaching maximum force as the punch achieves maximum penetration (Jain, 1999:24). The characteristic shape of the force displacement curves, recognizable in terms of its slope and elastic recovery, can be correlated to the ability of material to undergo plastic deformation and form strong compacts. The relation between the forces transmitted to the die wall can be expressed as a "stress ratio", i.e. ratio of radial to axial stress (Carless & Leigh, 1974:289). Bolhuis & Lerk (1973:477-478) found that the ideal ratio of lower to upper punch force and for the ejection force must be high for the upper and lower punch and the ejection force must be low. A high ejection force results in the crushing of the tablets during ejection. They also found that the ejection force showed a corresponding characteristic; a pronounced increase and subsequent slight decrease with increase in applied force.

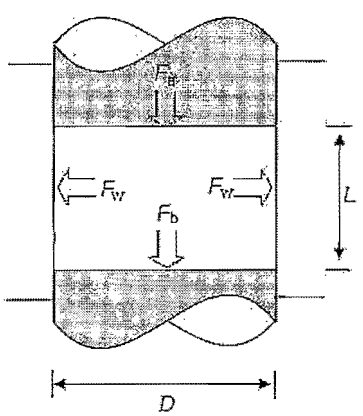

Figure 1.7: *Schematic illustration of punch and die-wall forces involved during powder compression (Alderborn, 2002:429).*

1.3.3 Fundamental aspects of the compaction of powders

1.3.3.1 The bonding process in tablets

The forces believed to hold tablet particles together in a tablet include solid bridges, interfacial forces, adhesive and cohesive forces, attraction forces (coulombic forces between charged species, covalent bonds, hydrogen bonds and Van der Waals forces) and mechanical interlocking of irregular particles (Leuenberger & Rohera, 1986:14; Luangtana-Anan & Fell, 1990:197; Olsson & Nyström, 2001:203).

According to Olsson and Nyström (2001:204) Van der Waals forces, hydrogen bonds, and electrostatic attractions, are considered to be the dominating bonding mechanisms for most pharmaceutical compacts. Solid bridges, the strongest bond type, are described as areas in which particles are partially fused together and can thus be considered as a continuous phase between two particles. Mechanical interlocking is described as the hooking and twisting together of particles in a packed material and may occur in tablets of particles with a fibrous or irregular structure. The extent of the effect will depend on the particle shape and surface characteristics (Hiestand, 1997:237-241; Leuenberger & Rohera, 1986:14; Narayan & Hancock, 2003:24).

According to Adolfsson *et al.* (1997:249-250) knowledge of the chemical structure and volume reduction behaviour of the tested material is necessary. The intraparticulate chemical structure of the powder is of importance for the interparticulate bonding structure. A simple chemical structure facilitates development of solid bridges during compression (it is easier for the particles to orientate in such a way that solid bridges can form). Solid bridges forms easier if the powder undergoes volume reduction by plastic deformation. An increase in compaction pressure also affects the bonding structure within compacts. For powders consisting of irregularly shaped particles a reduction in particle size and an increase in compaction pressure would make it more difficult for the particles to bond by mechanical interlocking.

According to Coffin–Beach and Hollenbeck (1983:324) the energy of formation is a parameter which indicates the development of compact coherence through bond formation. Changes in the internal structure of the tablets (tablet porosity, pore size distribution, and the size and shape of the particles) as well as changes in the bonds between the particles have been reported to affect tablet properties, such as mechanical strength (Olsson & Nyström, 2001:203).

1.3.3.2 The influence of particle shape and size on the compaction of powders

The relevance of particle-size control in pharmaceuticals has been recognized for many years, and is an important parameter in predicting the behaviour of particles and powder (Clark, 1986:45). The compaction process of pharmaceutical powders is concerned with the particle size (fine or ultra fine) and simple geometry (flat, embossed or oval) (Kadiri *et al.*, 2005:176). All this studies were mostly concerned with the influence of particle size on the tabletting characteristics (Khan & Rhodes, 1975:444).

Heckel (1961:1005-1006) found that particle size, particle shape and material had an effect on the relative apparent density (D_o), relative density (D_A) and the density contribution from individual particle movement and rearrangement (D_B). The variation in these densities may be seen to be primarily a function of geometry (Podczeck & Yasmin, 1996:187). The D_o increases as the particle size decreases, while D_B decreases as the particle size decreases. The latter seems to be due to the fact that the increased number of interparticle contacts with decreasing size brings on a more rigid structure. When comparing spherical and non-spherical particles, the D_B for the spherical particles is close to zero and this could be due to the fact that the spherical powders form a dense rigid packing when poured into the die and therefore undergo minimum shifting as the pressure is applied.

Alderborn & Nyström (1982:390) suggested that the direction of the effect of particle size on tablet strength and also the magnitude of the effect varies between substances. When designing a direct compression formulation it is important to be aware of the relationship between particle size and tablet strength. It is preferable that the particles, although varying in size, are as similar as possible with respect to particle shape, crystal form and crystal energy. These parameters may influence the binding properties of a material. The literature also showed that smooth compacts (such as sucrose) were found to be harder, more brittle, and elastic. Rougher compacts were softer, ductile, and less brittle. The surface roughness of compacts was found to be related to their mechanical properties (Narayan & Hancock, 2003:34-35).

Alderborn (2003:371-372) studied the difference in tensile strength between different particle sizes of powders (sodium chloride and sucrose). He found that all the fractions in both powders had an increasing tensile strength as the compaction pressure increased. The smaller fractions however in both materials showed a better tensile strength than that of the larger size particles. Andrès *et al.* (1995:1885) found that although a powder has the same molecular structure there could be a difference in particle size distributions and a difference

in the percentage of fine particles which could influence the flow characteristics as well as the compression of powders.

1.3.3.3 The tensile strength of tablets

A standard procedure for assessing the ability of a powder to be formed into tablets by powder compression is to study the relationship between the tensile strength of a tablet, as calculated from diametral compression, and the compaction pressure (Alderborn, 2003:367). According to Olsson and Nyström (2001:203) tensile strength can be considered to reflect the bond type, where a low value indicates bonding by weak forces and a high value indicates the presence of strong bonds (solid bridges). Olsson & Nyström (2001:205-207) used various powders in their study and found that the tensile strength of the tablets increased with increasing compaction pressure and decreasing particle size for all powders and size fractions. This founding was repeated several times in other studies (Alderborn, 2003:367; Kuentz & Leuenberger, 2000:151; Riippi *et al.*, 1998:339; Sebhatu & Alderborn, 1999:235; Shotton, 1972:256; Sonnergaard, 2005:270). The tensile strength of various tablets can either be correlated with the plastic work or the volume reduction. The volume reduction is associated with the elimination of pores. Reducing the number of pores results in a higher tensile strength of the tablets (Mohammed *et al.*, 2005:3946). The applied pressure reducing the volume is the result of increasing pressure reducing the porosity (particles are deformed plastically and elastically) resulting in an increased area of contact for bonding (Shotton, 1972:257).

The flow and compression properties of a powder are important in the production of a good tablet. Therefore, before manufacturing tablets, it is necessary to investigate the flow and compression properties of the powder that is to be used in the production process. The physical and chemical characteristics of a material play an important role in the compression and flow properties of the material. In this study chitosan raw material was used and will be discussed in the next section.

1.4 CHITOSAN

1.4.1 Introduction to chitosan

A chemist and botanist, Henry Braconnot, discovered chitin in 1881 (Muzzarelli, 2002:1). Chitin, (1-4)-linked 2-acetamido-2-deoxy-β-D-glucan, is the second most abundant naturally occurring biopolymer after cellulose (Asada *et al.*, 2004:169; Brugnerotto *et al.*, 2001:3569; Sankalia *et al.*, 2007:217). Chitin is the principal component of protective cuticles of crustaceans such as crabs, lobsters, prawns, shrimps and cell walls of some fungi such as

aspergillus niger and *mucor rouxii* as well as insects like the true fly and the sulfur butterfly (Berger *et al.*, 2004:36; Ghaffari *et al.*, 2007:3 ; Santos *et al.*, 2002:155; Sinha *et al.*, 2004:4). Chitosan is a copolymer of β-[1-4]-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glycopyranose, it is a cationic natural biopolymer produced by the partial alkaline *N*-deacetylation of chitin (Asada *et al.*, 2004:169; Berger *et al.*, 2004:36; Kumar, 2000:3; Santos *et al.*, 2002:155; Sinha *et al.*, 2004:4). A clear classification with respect to the different degrees of *N*-deacetylation between chitin and chitosan has not been defined, and as such chitosan is not one chemical entity but varies in composition depending on the manufacturer (Kumar, 2000:4-7). The structural details of cellulose, chitin and chitosan are shown in figure 1.8. Cellulose is a homopolymer, while chitin and chitosan are heteropolymers (Kumar, 2000:5).

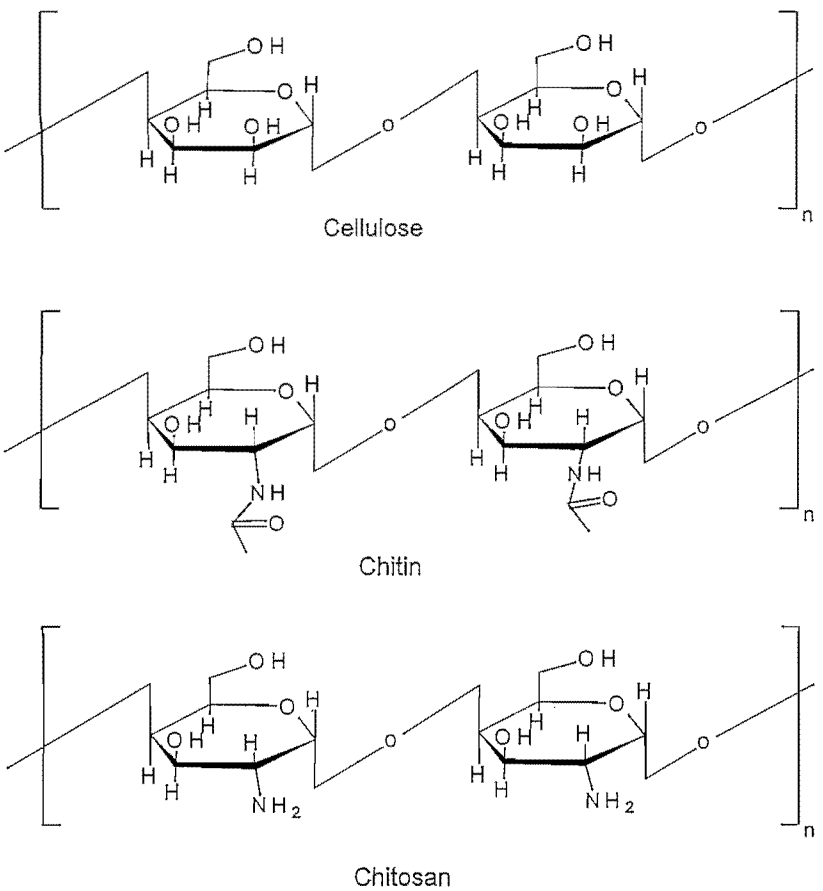

Figure 1.8: *Structures of cellulose, chitin and chitosan*

The production of chitosan-glucan complexes is associated with fermentation processes, similar to those for the production of citric acid from *Aspergillus niger*, *Mucor rouxii,* and *Streptomyces*, which involves alkali treatment yielding chitosan-glucan complexes. The alkali removes the protein and deacetylates chitin simultaneously. Depending on the alkali concentration, some soluble glycans are removed. The processing of crustacean shells

mainly involves the removal of proteins and the dissolution of calcium carbonate which is present in crab shells in high concentrations. The resulting chitin is deacetylated in 40% w/v sodium hydroxide. This treatment produces 70% deacetylated chitosan (figure 1.9) (Kumar, 2000:4).

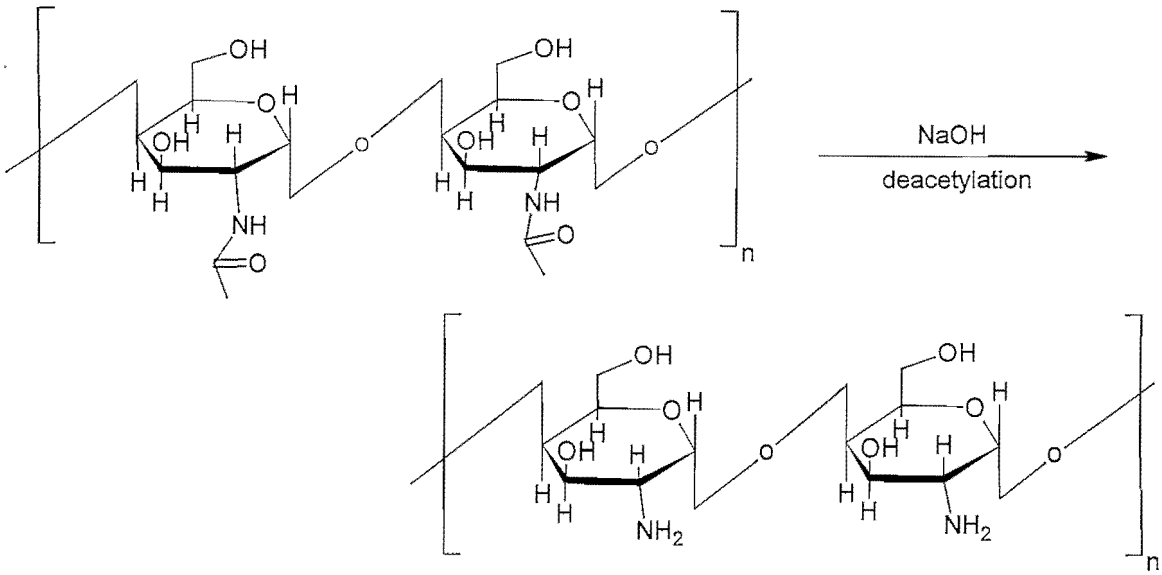

Figure 1.9: *The deacetylation process of chitin.*

1.4.2 The applications of chitosan

The applications of chitosan are numerous. Its important use in photography is due to chitosan's resistance to abrasion, its optical characteristics, and film forming ability. Chitosan has fungicidal and fungistatic properties and is used in cosmetics (creams, lotions and permanent waving lotions). Chitosan also has applications in the food industry and helps for example, the intestinal microflora to utilize whey. Global warming is a huge concern at the moment and therefore, the relevant industries pay attention to the development of technology which does not cause environmental problems. Chitosan is used for metal capture from wastewater and colour removal from textile mill effluents. Another application of chitosan is that it imparts wet strength to paper (Gschaider *et al.*, 2002:347-348; Kotzé *et al.*, 1997a:244; Kumar, 2000:11-15).

The advantages of chitosan include high availability, low cost, high biocompatibility, biodegradability and ease of chemical modification and therefore have many applications in the pharmaceutical industry (Kotzé, 1997b:1197). The applications of chitosan as a component of pharmaceutical formulations for drug delivery have been investigated in several studies (Buys, 2006; Dodane & Vilivalam, 1998; Ghaffari *et al.*, 2007; Kotzé *et al.*, 1997a; Kotzé *et al.*, 1997b; Kumar, 2000; Nunthanid *et al.*, 2004; Sinha *et al.*, 2004). These include controlled drug delivery applications(Cevher *et al.*, 2006; Liu *et al.*, 2007; Rege *et al.*,

1999), use of a component of mucoadhesive dosage forms (Kotzé *et al.*, 2002; Portero *et al.*, 2002), improved peptide delivery that could be of immense application in the future (Hamman & Kotzé *et al.*, 2002; Kim *et al.*, 2003; Krauland *et al.*, 2004; Portero *et al.*, 2002; Senel *et al.*, 2002; Van der Merwe *et al.*, 2004; Verhoef *et al.*, 2002), colonic drug delivery systems (Buys, 2006; Orienti *et al.*, 2002), and use in gene delivery (Murata *et al.*,1997). Other pharmaceutical applications include parenteral, ocular and nasal dug delivery (Dodane & Vilivalam, 1998:249-251; Kumar, 2000:10-14), dentistry (Senel *et al.*, 2000:241-256), dietary supplements (fat trapper) (Muzzarelli, 2000:3-40) and topical delivery systems, e.g. wound dressings (Mi *et al.*, 2002:141-144).

Chitosan has been processed into several pharmaceutical forms e.g. hydrogels (hydrogels are highly swollen, hydrophilic polymer networks that can absorb large amounts of water and drastically increase in volume) that is widely used in controlled-release systems. Another form is tablets; which is usually directly compressed in addition to lactose or potato starch. Chitosan tablets for controlled release (anionic-cationic interpolymer complex) is also manufactured because of the disintegration properties of the powder (chitosan has a strong ability to absorb water). Microcapsules or microspheres of chitosan is another pharmaceutical form. This could either be in the form of crosslinked chitosan microspheres; chitosan/gelatin network polymer microspheres; chitosan microspheres for controlled release or chitosan nanoparticles; or chitosan beads (Kumar, 2000:16-22). Another field that chitosan is used for is biotechnology. According to Kumar (2000:24) chitosan inhibited the growth of *Escherichia coli*, *Fusaium*, *Alternaria* and *Helminthosporium*; the cationic amino groups of chitosan probably bind to anionic groups of these microorganisms. Chitosan sulphates have blood anticoagulant and lipoprotein lipase releasing activities and are also anti-throbogenic and haemostatic. These properties, together with the safe toxicity profile, make chitosan and exciting and promising excipient for the pharmaceutical industry for present and future applications (Kumar, 2000:24).

1.4.3 Pharmaceutical aspect of chitosan

Cellulose like most of the other natural polysaccharides found in nature e.g. dextran, pectin etc. are neutral or acidic in nature, whereas chitosan is an example of a highly basic polysaccharide. The term chitosan describes a series of chitosan polymers with different molecular weight, viscosity and degree of deacetylation (40-98%). Chitosan occurs as an odourless, white or creamy-white powder or flakes. Fiber formation is quite common during precipitation and the chitosan may look cottonlike. It is a linear polyamine with a number of amino groups that are readily available for chemical reaction and salt formation with acids.

Chitosan has a high charge density, adheres to negatively charged surfaces and chelates metal ions (Jones & Mawhinney, 2005; Kumar, 2000: 4; Singla & Chawla, 2001:1048).

Chitosan is an excellent viscosity enhancing agent in an acidic environment due to its linear unbranched structure and its high molecular weight. It acts as a pseudo-plastic material, exhibiting a decrease in viscosity with increasing rates of shear. The viscosity of chitosan solution increases with an increase in chitosan concentration, decreases in temperature and with and increasing degree of deacetylation (Jones & Mawhinney, 2005; Singla & Chawla, 2001:1049).

At a neutral and alkaline pH value, most chitosan molecules will loose their charge and precipitate from solution (insoluble). Chitosan is a weak base and a certain amount of acid is required to transform the glucosamine units into the positively charged, water-soluble form. The solubility of chitosan in inorganic acids (except insoluble in phosphoric and sulfuric acid) is limited when compared with its solubility in common organic acids. Upon dissolution, the amine groups of the polymer become protonated, with a resultant positively charged soluble polysaccharide (RNH_3^+) and chitosan salts (chloride, glutamate, etc.) that are soluble in water. Therefore, the solubility is affected by the degree of deacetylation. The solubility of chitosan is also greatly influenced by the addition of salt to the solution, the higher the ionic strength, the lower the solubility as a result of a salting-out effect, which leads to the precipitation of chitosan in solution (Jones & Mawhinney, 2005; Kotzé *et al.*, 1997b:1197; Singla & Chawla, 2001:1049).

The density of chitosan is between 1.35-1.40 g/cm^3 with a particles size distribution of <30 µm (Jones & Mawhinney, 2005). Chitosan adsorbs moisture form the atmosphere, the amount of which depends upon the initial moisture content, the temperature and the relative humidity of the surrounding air (Gocho *et al.*, 2000:88-90; Jones & Mawhinney, 2005). Chitosan powder is a stable material at room temperature, although it is hygroscopic after drying and should be stored in a tightly closed container in a cool, dry place (Jones & Mawhinney, 2005). In studies done by Arai *et al.* (1968:89-94) they found that the lethal dosage of chitosan is in the same region of sugar and salt. Chitosan has low oral toxicity with an LD_{50} in mouse of 16g/kg; it is generally regarded as a non-toxic and non-irritant material (Jones & Mawhinney, 2005).

According to Davis and Illum (2000:141) various concepts of bioadhesion have been advanced, but most of them rely on the concept of a polymeric material interacting either with the cell surface or with the mucus that lies on top of a cell surface. Interactions involving hydrogen bonding, hydrophobic bonding and electrostatic bonding have been proposed as

potential strategies. Chitosan represents a material where electrostatic interaction between the biopolymer and the charged sialic acid groups of mucin could be of benefit.

1.4.4 Tabletting problems with chitosan

In previous work done by Aucamp (2004), Buys (2006) and De Kock (2005) it could be seen that raw chitosan could not be compressed into tablets on an eccentric tablet press. Aucamp (2004) came to the conclusion that even if combining chitosan with fillers (Avicel PH200 and Prosolv®SMCC™90) the tablet strength was still weak. The combination of chitosan to the filler in the ratio 70:30 gave the best results, her conclusion was that the filler improved the flowability of the powder resulting in better die filling and therefore, increasing the tablet strength. Buys (2006) and De Kock (2005) compressed chitosan into minitablets. De Kock (2005) could not compress raw chitosan powder into tablets with desirable tablet strength, however with the combination of binders and fillers chitosan minitablets could be compressed. Buys (2006) found that chitosan could only be compressed at high compression forces. It was difficult if not impossible to obtain these high compression forces needed to compress the powder when using an eccentric tablet press. The force exerted on the powder was achieved by adjusting the distance between the upper and lower punches. The problem of obtaining these higher compression forces was solved when a sufficient amount of chitosan powder filled the die before compressing the powder. These results concluded that although more chitosan powder could be filled into the die, the tablet weight was still relatively small.

Some questions that remain are:

- How does the difference in the physical properties of different chitosan batches affect their flow and compressibility?
- How do the characteristics of the powders reflect in the physical properties of the tablets?
- What would be the effect when filling the die with a sufficient amount of chitosan powder?
- Would it have an effect on the physical properties of the tablets?

CHAPTER 2

EXPERIMENTAL METHODS, APPARATUS AND MATERIALS

2.1 INTRODUCTION

This chapter discusses the experimental methods and apparatus that were used to conduct this study.

2.2 MATERIALS

The raw materials utilized in this study is presented in Table 2.1

Table 2.1: *Raw materials utilised in the study.*

MATERIALS	LOT NUMBER	MANUFACTURER
Chitosan	021010 & 030912	Warren Chemicals Ltd, Durban, RSA
Emcompress®	8070	penwest, surrey, ENGLAND
Avicel®PH200	M926C	FMC INTERNATIONAL, cork, ireland
Ludipress®	25-0194	BASF, LUDWIGSHAFEN, GERMANY
Tablettose®	I0116	meggle gMBh, wassenberg, germany

2.3 POWDER FLOW

When examining the flow properties of a powder it is useful to be able to quantify the type of behaviour and various methods that have been described, either directly or indirectly (Staniforth, 2002:205). Parameters that were used to determine powder flow was the following: angle of repose, flow rate, Carr's index (also known as percentage compressibility), the critical orifice diameter (COD) and a composite flow index (CI). The following methods were employed to determine these parameters.

2.3.2 Critical orifice diameter

The COD (critical orifice diameter) is defined as the smallest hole through which a powder will flow freely without the application of any external aid. The apparatus developed by Buys & co-workers (2005:40-42) were used to determine the COD of the powders (figure 2.2). The apparatus consists of a set of brass discs between 5 and 10 mm thick which can be stacked on top of each other to form a funnel. Each disc has a different size opening and the orifice of each disc was machined to a set angle. A cylinder could be fitted to the top of the funnel to create a holding chamber for the powder.

The COD of each powder was determined by placing 100 ml of the powder in the holding chamber and then allowing the powder to pass through the hole at the bottom of the funnel. The diameter at the bottom of the funnel was varied (by removing or adding a brass disc) until the smallest diameter was found through which each powder could flow freely. The experiment was done in triplicate.

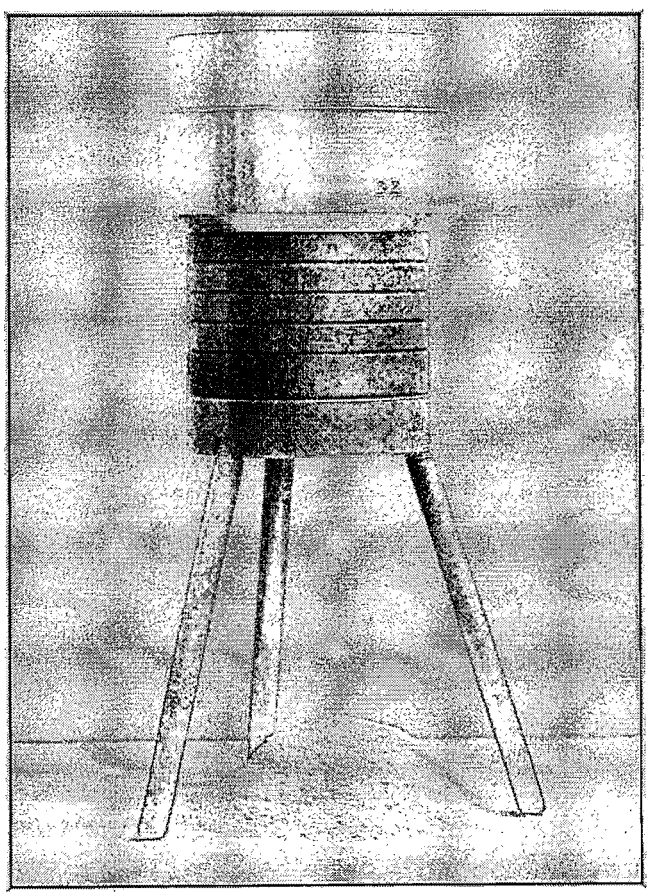

Figure 2.2: *Critical orifice diameter apparatus.*

2.3.3 Flow rate

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

2.3.4 Density

Density is universally defined as weight per unit volume. Several parameters are used to define powder densities, including bulk density, tapped density and porosity.

2.3.4.1 Bulk density (ρ_b)

Bulk density is defined as the weight of powder that occupies a volume. This volume consists of particle volume and the pores between the particles. Approximately 100 ml of powder was gently poured into a graduated cylinder and the initial volume and weight of the material were recorded. The bulk density was calculated according to equation 2.2. This procedure was repeated in triplicate and the mean value was calculated.

$$\rho_b = \frac{w}{v_b} \qquad [2.2]$$

Where:

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

2.3.4.2 Tapped density (ρ_t)

The tapped density is defined exactly the same as the bulk density except for the volume consisting only of particle volume. Tapped density was determined by placing the graduated cylinder with the powder from the bulk density on a vibrating surface (Fritsh® analysette) set at an amplitude of 5 ampere and vibrated for 5 minutes intervals (up to 20 minutes). Repetitions of the procedure were performed until the powder volume reached a constant

level (after 10 minutes) (De Kock, 2005:66). The mean value of the tapped density was calculated according to equation 2.3.

$$\rho_t = \frac{w}{v_t} \qquad [2.3]$$

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

2.3.4.3 Porosity (Є)

Porosity (Є) of a powder is defined as the proportion of a powder bed that is occupied by pores. Therefore, the porosity could be considered as the packing efficiency of a powder (Martin *et al.*, 1993:442-444). Equation 2.4 was used to calculate the porosity of the powder.

$$\epsilon = \left(1 - \frac{\rho_b}{\rho_T}\right) \times 100 \qquad [2.4]$$

Where:

Є is porosity expressed in percentage (%), ρ_b is the bulk density (g.cm^{-3}) and ρ_T is the true density (g.cm^{-3}).

2.3.5 Carr's index

Carr's index, also known as "percentage compressibility", is calculated from the bulk and tapped densities. Using equation 2.5 Carr's index can be calculated, this provides a better understanding of the flowability of powders.

$$Carr's\ index\,(\%) = \frac{\rho_t - \rho_b}{\rho_t} \times 100 \qquad [2.5]$$

Where:

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

The index shown in Table 2.2 was used to characterize powder flow.

Table 2.2: *Indication of powder flow by means of Carr's index (Wells, 2002:134).*

CARR'S INDEX (%)	TYPE OF FLOW
5-15	EXCELLENT
12-16	GOOD
18-21	FAIR TO PASSABLE
23-35	POOR
33-38	VERY POOR
>40	EXTREMELY POOR

2.3.6 Composite index

Taylor *et al.* (2000:3) introduced a composite index as a new parameter to describe powder flow. They used data from the COD, angle of repose and Carr's index of a powder to construct a new, more comprehensive flow index (called the composite flow index) for various pharmaceutical powders. According to the authors powder can be classified in 3 basic categories based on their respective composite flow index scores (a value between 0 and 100), namely poor (<60); average (60-70) and good (>70). The composite index of the various powders used in this study was calculated using the equations from Taylor *et al.* (2000:3) (equations 2.6-2.9) and the data from the various flow parameters determined as described in sections 2.3.1 (angle of repose), 2.3.2 (critical orifice diameter) and 2.3.5 (Carr's index).

$$\textit{Critical orifice diameter: Point value (A)} = -1\frac{1}{9} \times \textit{COD result} + 37\frac{7}{9} \qquad [2.6]$$

$$\textit{\% Compressibility: Point value (B)} = -\frac{2}{3} \times \textit{\% compressibility result} + 36\frac{2}{3} \qquad [2.7]$$

$$\textit{Angle of repose: Point value (C)} = -\frac{2}{3} \times \textit{AoR result} + 50 \qquad [2.8]$$

$$\textit{Composite index} = A + B + C \qquad [2.9]$$

2.4 INFRARED (IR) ANALYSIS

The stretching and bending vibrations of different groups on a molecule can be analysed and identified with the use of infrared spectrometry. These spectra may also be used to identify compounds, as they are unique to those compounds (De Kock, 2005:60). The IR-spectra was used do determine if the two batches of chitosan was the same powder. IR-spectra were recorded on a Nicolet Nexus 470 FT IR ESP spectrometer (Madison, USA) over a range of 400-4000 cm^{-1} using the KBr reference technique. Samples weighing approximately 2 mg were collected after drying for 1 hour at 40 °C and mixed with 200 mg of KBr (Merck, Germany) before analysis.

2.5 PARTICLE MORPHOLOGY

The morphology (*the study of the shape of things*) of a powder can shed light on the behaviour of the powder during processes like flow and compression. Scanning electron microscopy was used to identify particle shape and surface structure of the chitosan particles, whilst standard sieving and laser diffraction were used to determined particle size and particle size distribution of the different chitosan batches used in this study.

2.5.1 Scanning Electron Microscopy (SEM)

A scanning electron microscope was employed to observe the shape and surface structure of the particles in the different chitosan batches. SEM analysis provides information on a microscopic level to better understand the behaviour of the powder. SEM photos of the two different batches and their various size fractions were taken. The powders were affixed on double-sided conductive carbon tape to a sampling tray and dusted with an inert gas. Samples 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 better than 0.06 Torr. Samples were studied using a Philips®XL 30 DX 4i SEM microscope (Eindhoven, The Netherlands). The SEM was also used to determine the outside diameter (length diameter) of a number of particles in each sieve fraction of both batches. From this data the mean, minimum and maximum diameter, standard deviation (SD) and percentage relative standard deviation (%RSD) were calculated.

2.5.2 Determination of particle size and particle size distribution

The particle size and size distribution of the two chitosan batches were determined using a standard sieve apparatus and laser diffraction according to the methods described in section 2.5.2.

2.5.2.1 Sieve analysis

A sieve analysis was performed on both batches. Several stainless steel sieves (Labotec test sieve, Industria, Johannesburg, South Africa) ranging from 45 μm – 355 μm with a woven mesh were stacked on top of each other on a collector tray. The stack of sieves (ranging from the smallest mesh at the bottom on the collector tray to the coarsest mesh at the top) was placed on a vibrating plane (Fritsh® analysette, Germany, TYPE 03.502). Each sieve was first individually weighed. A certain quantity of powder (approximately 100 ml) was weighed and placed on the coarsest sieve at the top of the stack. The apparatus was set at an amplitude of 6 ampere and vibrating was continued until the powder mass on each sieve remained constant. Each sieve with the remaining powder on it was weighed and recorded. The amount and percentage of powder on each sieve were then calculated.

2.5.2.2 Laser diffraction using a Malvern Mastersizer 2000

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

A volume of 600 ml of ethanol was used as dispersant in a glass beaker (capacity 1000 ml). 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% where after the particle size measurement was made. Two measurements 20 seconds apart consisting of 12000 sweeps each were taken. Samples were analyzed in triplicate.

2.6 COMPRESSION STUDIES

Previous studies by Aucamp (2004) showed poor compression characteristics for the pure chitosan raw material on an eccentric tablet press. The unsuccessful attempt to produce tablets from pure chitosan raw material (chitosan batch 021010 with an average particle size in the range of 215.6 μm) was attributed to its poor compressibility and flow properties. This study, however, showed that combination with microcrystalline cellulose (Avicel® PH200) in a

ratio of at least 30/70% (MCC/chitosan) could produce tablets with a crushing strength in the 150-180 N range, although mixing time played an important role in the efficiency of the tabletting process (Aucamp, 2004:45). The addition of dry binders (Kollidon® VA-64 or Methocel® K100M between 4 and 20% w/w) contributed little in improving the compressibility of chitosan, whilst the wet granulation of chitosan with Kollidon® VA-64 and/or HPMC didn't improve the compressibility of the raw material.

From the results of a study done by Buys (2006:75) it was be concluded that the poor compressibility of chitosan (resulting in tablets with low crushing strength and relative high friability) on eccentric tablet presses (single stroke) could probably contribute to the high porosity (high volume to mass ratio) of the raw material. Therefore, the mass of chitosan filling the die was relative low (compared to its volume), and during compression the tablet press (operating on a single die fill during each compression cycle) could not sufficiently accommodate the volume reduction of the material even at the highest compression setting.

The compression characteristics of chitosan in this study were initially done on batch 30912 using a Manesty® eccentric tablet press (Manesty Machines, Liverpool, England). These preliminary compression studies were done to confirm previous compression results obtained by Aucamp (2004), de Kock (2005) and Buys (2006) as well as to set a baseline for the chitosan batches used in this study (namely batches 021010 and 030912). Chitosan tablets of varying weight (100, 150 and 200 mg respectively) were prepared in an 8 mm die using flat-faced punches.

2.6.1 Tablet compression using a standard eccentric tablet press

In order to produce 100 mg tablets the lower punch was set to a depth of 6.80 mm (from the top of the die). The setting on the upper punch (on a scale from 0 to 50) determined the strike depth of the upper punch (i.e. the distance the upper punch moved into the die during compression) and thus determined the force exerted on the powder during compression. The press was set on the lowest upper punch setting able to produce an intact compact (tablet) when removed from the die after compression. One hundred tablets were compressed at this setting and then the upper punch setting was increased on setting (interval) and the process repeated. One hundred tablets were compressed at each setting up to the maximum upper punch setting that could still compress the powder volume in the die. In order to produce tablets at 150 and 200 mg, the lower punch setting was adjusted to 10.38 mm and 13.56 mm respectively and the process repeated. The first 20 tablets produced at each weight and upper punch setting were discarded. The tablets were transferred to glass containers, sealed with Parafilm® and then closed with a screw cap. The

containers were stored in a cabinet at room temperature for at least 24 hours before analysis.

2.6.2 Tablet compression on a modified tablet press

During the second phase of the compression studies both chitosan bathes (021010 and 030912) were used and compression was done on a modified Manesty eccentric tablet press which could provide a double (or more) fill of the die during each complete compression cycle developed by Buys (2007:78-85).

2.6.2.1 Press modifications

The modification of a standard Manesty® eccentric tablet press involved replacing the motor with a stepper motor which could be stopped and reversed after each filling and compression of the powder in the die. This allowed for subsequent fillings of the die with additional powder before the compression cycle was completed and the tablet ejected. The stepper motor was operated from an embedded controller with a human machine interface for controlling the compression cycle. A presentation of the modified press is shown in figure 2.3.

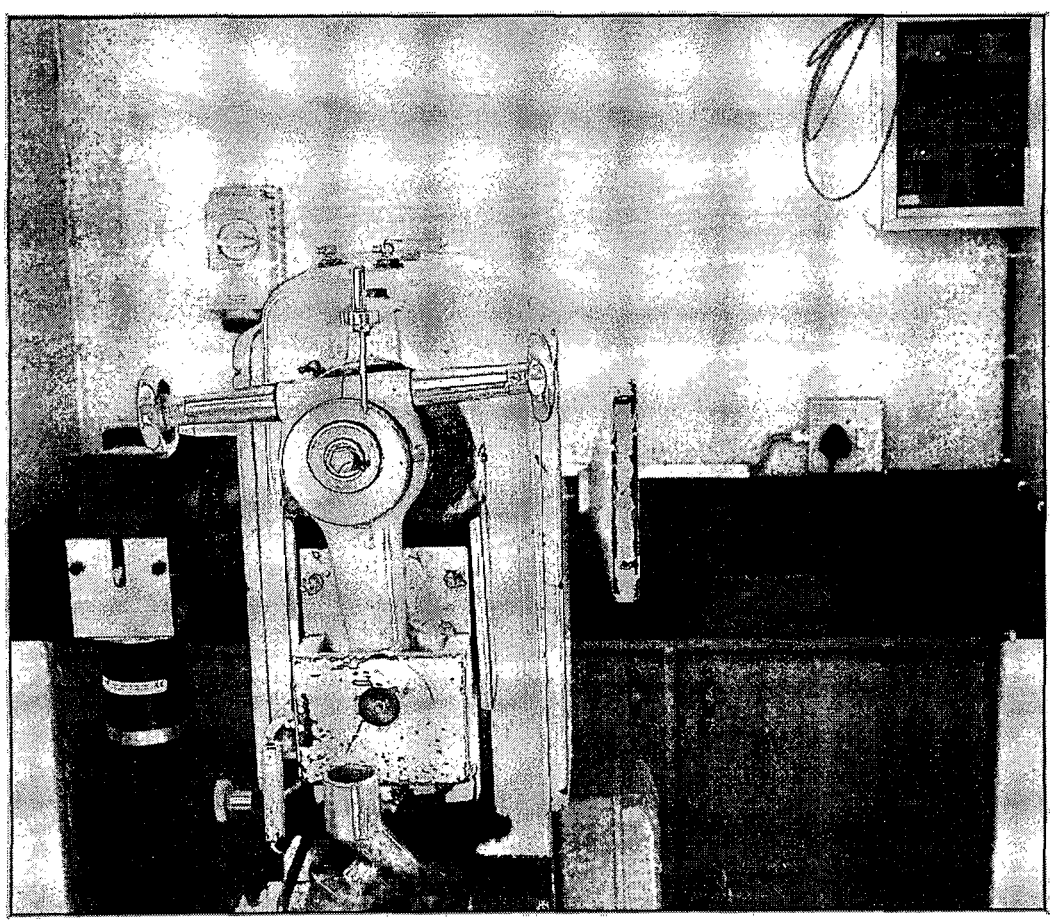

Figure 2.3: *The modified Manesty® tablet press and controller.*

Control over the first compression cycle allowed for changing the stroke length of the upper punch into the die through a manual input into the computerized system prior to starting the press. The amount of compression of the powder after the first fill cycle (called the percentage compression) could be varied manually between 0 and 80% at any upper punch setting (ranging between 0 and 50 units). Other parameters which could be set are the machine speed and the number of tablets to be produced.

The compression cycle on the modified press progresses as follows (read with the sketch in figure 2.4)

The lower punch is adjusted to accommodate the volume of powder required for a specific weight (for example 200 mg). The volume available in the die for powder is given in equation 2.10.

$$Die\ volume = \pi.r^2.h \qquad [2.10]$$

Where:

h is the distance (in cm) from the top of the lower punch to the top edge of the die and ***r*** is the radius of the die opening (in cm).

The weight of the tablet to be produced is determined by the relationship between the volume in the die cavity and the density of the powder.

In the case of the standard eccentric press, the distance the upper punch descents into the die is determined only by adjustment of the upper punch setting (UPS) on a scale between 0 and 50. On the modified version, the depth is determined by the UPS on the press **and** the percentage compression setting on the interface connected to the press. Therefore, at a percentage compression setting of 60% at a UPS of 17, the upper punch will only descend 60% of the total distance the upper punch displaces (determined by the UPS).

Explanation:

Say for instance the UPS setting is set at 17, at the maximum descent (displacement) the upper punch will have travelled 4.255 mm into the die. However, at a percentage compression setting of 60% the upper punch will only descent (60% x 4.255 mm) 2.553 mm into the die cavity.

After partial compaction of the powder during this first compression cycle the stepper motor will change into reverse and the upper punch will be withdrawn from the die cavity (without the lower punch moving). The hopper will once again discharge powder into the die and then the upper punch will move into the die again (now to its full extend as determined by the UPS). The powder will be compressed again (100%) and then the lower punch will move upwards to eject the tablet.

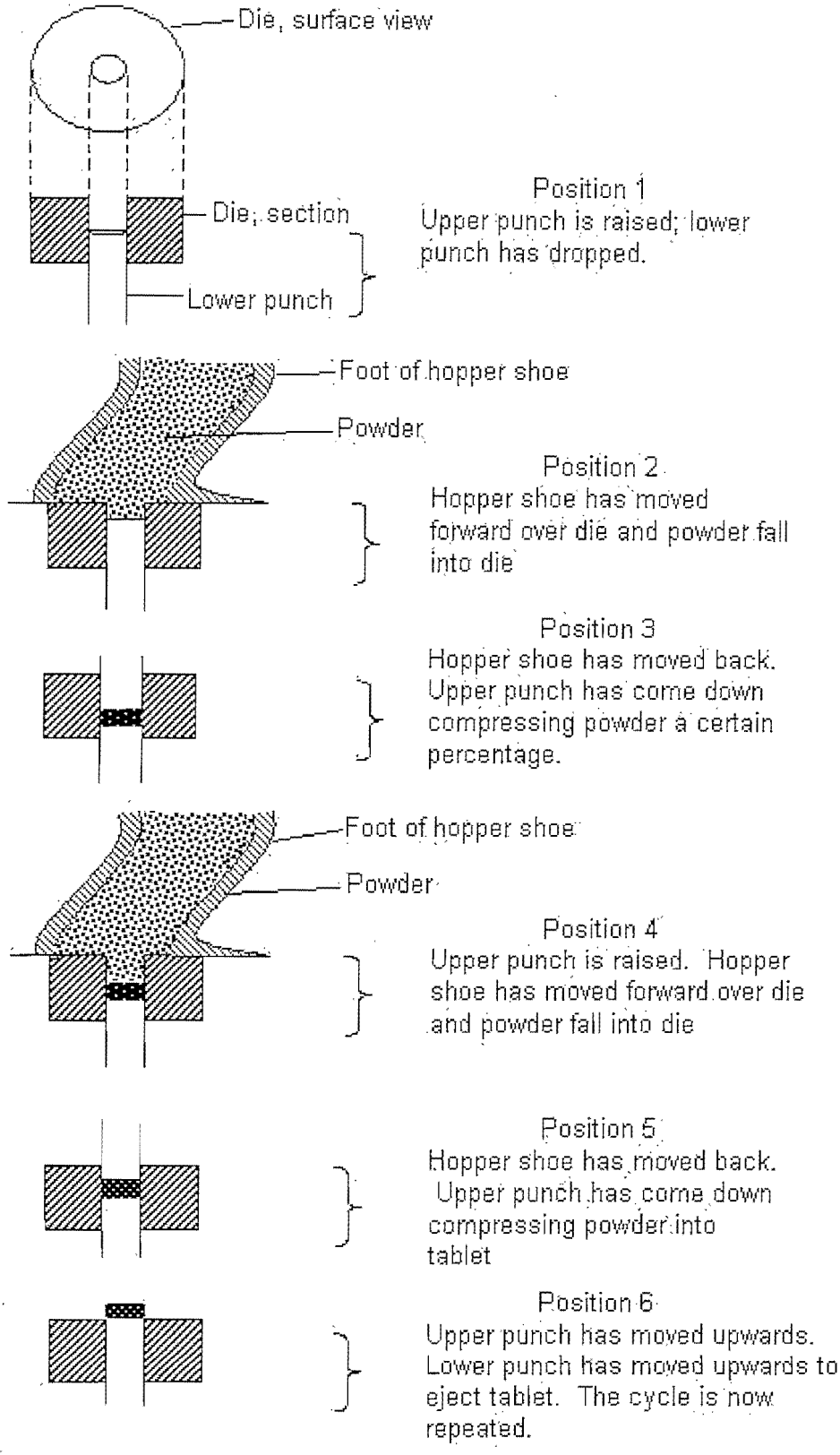

Figure 2.4: *The sequence of events involved in the formation of tablet using a double cycle press (Alderborn, 2002:399).*

The major advantage of the modified press's mechanism is that it could produce heavier tablets using the same punch and die sets available for the standard eccentric press due to the additional powder discharged into the die after a percentage compression of the first volume has been done, thus enabling the direct compression of powders with poorly compressible characteristics.

2.6.2.2 Compression studies

The same punch and die set as before was used (i.e. die with an opening of 8 mm in diameter and flat-faced punches). The depth of the lower punch was set at 13.56 mm to produce a tablet of 200 mg after the first fill cycle. The upper punch strike length was set at 30 for chitosan batch 03912 and at 33 for batch 021010 then the percentage compression setting on the controller was initially set at 10% and increased with 10% intervals to the maximum of 80% for each chitosan batch. For each batch 100 tablets at each percentage compression were produced of which the first 20 were discarded. Tablets were once again transferred to glass containers, sealed with Parafilm® and closed with a screw cap. The tablets were stored in a cabinet at room temperature (20±5 °C) for at least 24 hours before analysis.

Environmental conditions were monitored and all tabletting was done below 50% RH and at 17±3 °C.

2.6.3 Analysis of tablets

Each batch of tablets was analyzed for the following physical properties and according to the methods described below: individual tablet; crushing strength; diameter; thickness and friability. In addition the weight variation (%RSD) and tensile strength of each batch were calculated.

2.6.3.1 Weight variation

Twenty tablets from each batch of tablets were randomly selected. Each tablet was individually weighed on a Precisa® analytical balance (model 240A, PAG OERLIKON AG, Zurich, Switzerland) and the reading was recorded. The average of the 20 tablets, the standard deviation and the percentage relative standard deviation were calculated.

2.6.3.2 Crushing strength, diameter and thickness

The crushing strength, diameter and thickness were determined with the use of a Pharma Test® (model PTB-311, Switzerland) tablet test unit. Ten tablets selected randomly from each

batch were used. The readings were recorded and the average of 10 tablets, the standard deviation, and the percentage relative standard deviation were calculated.

2.6.3.3 Friability

Ten tablets of each batch were selected randomly and lightly dusted. The ten tablets were weighed on a Precisa® analytical balance (model 240A, PAG OERLIKON AG, Zurich, Switzerland) and the reading recorded. The ten tablets were placed in a Roche® friabilitor for 4 minutes at 25 revolutions per minute; lightly dusted and weighed again and the reading recorded. Equation 2.11 was used to calculate the percentage friability.

$$\%F = 100 \times \frac{W_B - W_A}{W_B} \qquad [2.11]$$

Where:

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

2.6.3.4 Tensile strength

Tablet tensile strength was determined from the force required to fracture tablets by diametral compression on a motorized tablet hardness tester (David & Augsburger, 1977:155). The tensile strength was calculated (Fell & Newton, 1968:658) using equation 2.12.

$$T = \frac{2P}{\pi D t} \qquad [2.12]$$

Where:

T is the tensile strength (N/mm^2); ***P*** is the crushing strength (N); ***D*** is the diameter (mm) and ***t*** is the thickness (mm)

2.7 CALCULATIONS

All the calculations were computed with Microsoft® Excel™ XP for Windows™ (Microsoft®, Seattle, Washington, USA). The statistical analysis was done using Microsoft® Excel™ XP for Windows™ with the ANOVA, single factor analysis.

CHAPTER 3

CHARACTERIZATION OF THE POWDER FLOWABILITY OF CHITOSAN

3.1 INTRODUCTION

The term powder flowability is used loosely and has generally been more closely associated to the test method used to measure it than the significance to the process. To the formulator, flowability is linked to the product. To the engineer, flowability relates to the process. Relating powder flowability results to actual behaviour in the production process is the true reason flowability is measured. A simple definition of powder flowability is the ability of a powder to flow without a great amount of energy input. By this definition, flowability is sometimes thought of as a one-dimensional characteristic of a powder, whereby powders can be ranked on a sliding scale from free-flowing to nonflowing. Unfortunately, this simplistic view lacks the science and sufficient understanding to address common problems encountered by the formulator and equipment designer. Powder flow is complex; flow behaviour is multidimensional and does in fact depend on many powder characteristics. For this reason, no one test could ever quantify flowability. The flowability of the powdered materials used in a tablet formulation is a major consideration in the production of this popular dosage form (Gioia, 1980:1; Freeman, 2000:3; Prescott & Barnum, 2000:60).

The two major problems identified in terms of the use of chitosan as directly compressible filler in tablet formulations is its poor flow and compressibility properties (Aucamp, 2004; Buys, 2006; De Kock, 2005). However, another possible reason in the difference in the characteristics may be found in the difference in the morphology of different batches of the raw material. Chitosan is obtained from chitin (a polysaccharide in the exoskeleton of crustaceous water animals) through a chemical process called alkaline deacetylation. A series of chitosan polymers exist which differ in molecular weight, viscosity and degree of acetylation. Variations in the various process factors during the manufacturing of chitosan may lead to major differences in the morphology of the raw material, such as particle shape, particle size, size distribution and porosity.

During the first phase of characterization of chitosan the aim was to determine to which extend its physical properties affects the flow of the material and to compare its flow properties to that of other commonly used tablet fillers. Two chitosan batches (021010 and 030912) were examined in order to determine the effect of differences in morphology on their

physical properties.

3.2 INFRARED (IR) ANALYSIS

Infrared analysis was performed on the two chitosan batches to establish that both products indeed represent the same material. The analysis done on both batches of chitosan confirm that these two powders were indeed the same excipient. The infrared analysis was done as described in section 2.4. Figure 3.1 (and annexure A.4) shows that the two excipients are the same product and both depict the IR-spectra of chitosan.

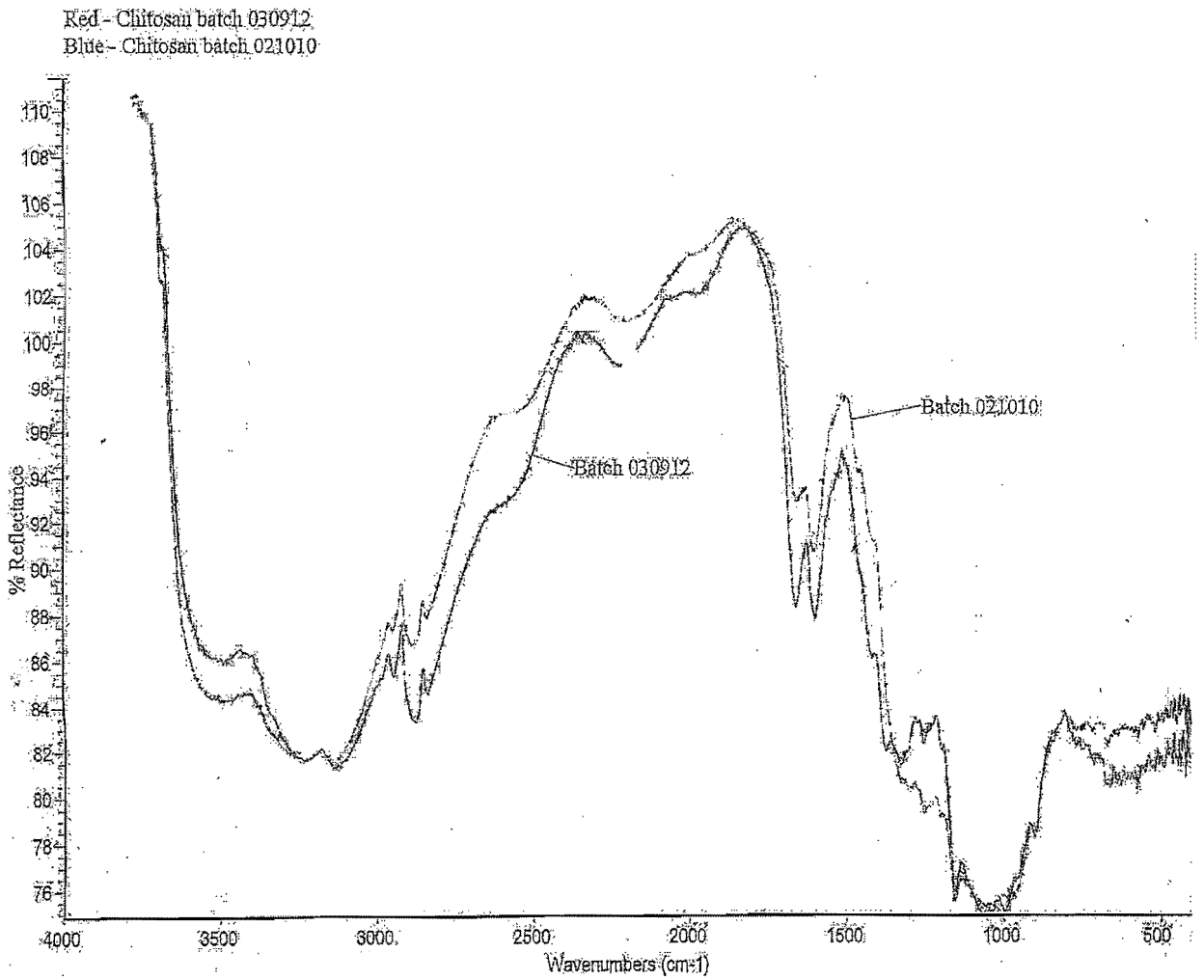

Figure 3.1: *Infrared analysis. Overlay of chitosan batch 021010 and chitosan batch 030912.*

The IR-spectrum of chitosan showed a weak band of C-H stretching at 2874.1 cm^{-1} for batch 030912 and 2886.6 cm^{-1} for batch 021010. The absorption band of the carbonyl (C=O) stretching of the secondary amide (amide I band) at 1660 cm^{-1} representing the structure of *N*-acetylglucosamine as well as the NH_2 stretching peak at 1600 cm^{-1}. The peaks at 1420 cm^{-1} and 1320 cm^{-1} belong to the N-H stretching of the amide and ether bonds and N-H

stretching (amide III band),respectively. The bridge oxygen (C-O-C, cyclic ether) stretching bands at 1066 cm-1 and 989.2 cm^{-1} were also observed. The strong peaks in the range 3400-3200 cm^{-1} correspond to combined peaks of hydroxyl and intramolecular hydrogen bonding (Nunthanid *et al.*, 2004:22; Ghaffari *et al.*, 2007:12; Banerjee *et al.*, 2002:100; Sankalia *et al.*, 2007:25).

3.3 MORPHOLOGY

Particle shape, particle size and particle size distribution of the two chitosan batches were determined in order to evaluate the effects of these properties on the flow characteristics of the material.

3.3.1 Particle shape

The particle shape of powders plays an important role in the flowability of the material and in general the more the shape deviates from spherical the more flow is impeded. The particle shape was observed by scanning electron microscopy (SEM) as described in section 2.5 and the results are shown in figure 3.2 and 3.3 (and Annexure A.3). These figures clearly showed that the shape of the two batches differ markedly, with the particles from batch 021010 being oblong in shape and rather curled (almost like dried leaves), whilst particles from batch 031912 were more consistent in shape, with a disk-like form. These differences might suggest significant differences in flow and possibly also compression behaviour.

Figure 3.2: *SEM photo of chitosan 021010: fraction 125-150 µm.*

Figure 3.3: *SEM photo of chitosan 030912: fraction 125-150 µm.*

Both batches were divided into four sieve fractions (obtained as described in section 2.5.2), namely <90 μm; 90-125 μm; 125-250 μm and >250 μm. In order to determine the consistency of the particle shape of the material, the outside diameter of a number of particles in the unsieved material and sieved fractions were measured using the SEM. The results are tabulated in table 3.1.

Table 3.1: *The outside diameters of particles in two chitosan batches.*

Batch	Fraction(μm)	Total particles measured	Mean (μm)	Min (μm)	Max (μm)	SD	%RSD
021010	*UNSIEVED*	13	358.13	75.04	625.00	180.26	50.33
	<90	16	187.10	70.71	325.90	79.37	42.42
	90-125	16	276.01	120.75	391.04	70.94	25.70
	125-150	18	348.16	191.34	803.65	161.23	46.31
	>150	17	352.14	188.56	826.81	142.63	40.50
030912	*UNSIEVED*	20	287.40	164.41	372.51	46.18	16.07
	<90	26	163.45	97.08	247.82	36.08	22.07
	90-125	27	252.74	145.09	362.64	50.15	19.84
	125-150	25	254.92	159.55	353.31	46.77	18.37
	>150	24	313.69	195.58	561.81	77.05	24.56

The results from measurements of the outside diameters of the particles showed marked differences in the two batches. Particles of batch 030912 (for the unsieved material and sieved fractions) showed consistently lower variation in particle size (as indicated by lower values for %RSD) compared to that of batch 021010.

3.3.2 Surface structure

The surface structure of the two batches showed marked differences. The surface structure of batch 030912 is rugged and uneven, whereas the surface structure of batch 021010 is smoother. The particles of batch 030912 were flat whilst those of batch 021010 were puffy. These findings point towards a difference in the flowability of the powder and/or in the compressibility of the powder.

3.3.3 Particle size and size distribution of chitosan

The SEM micrographs (figures 3.2 and 3.3) clearly indicated marked differences in the particle shape and size of the two chitosan batches, despite the fact that both were manufactured by the same chemical process and obtained from the same company (Warren Chemicals Ltd., Durban, South Africa). Since cohesion and adhesion are surface forces, differences in particle size and size distribution will affect their flow and compression properties.

The particle size and size distribution of both chitosan batches were determined by two methods, namely a sieve analysis and laser diffraction as described in section 2.5.2. The results of the sieve analysis are presented in figure 3.4 to 3.6 and the data in annexure A.1.

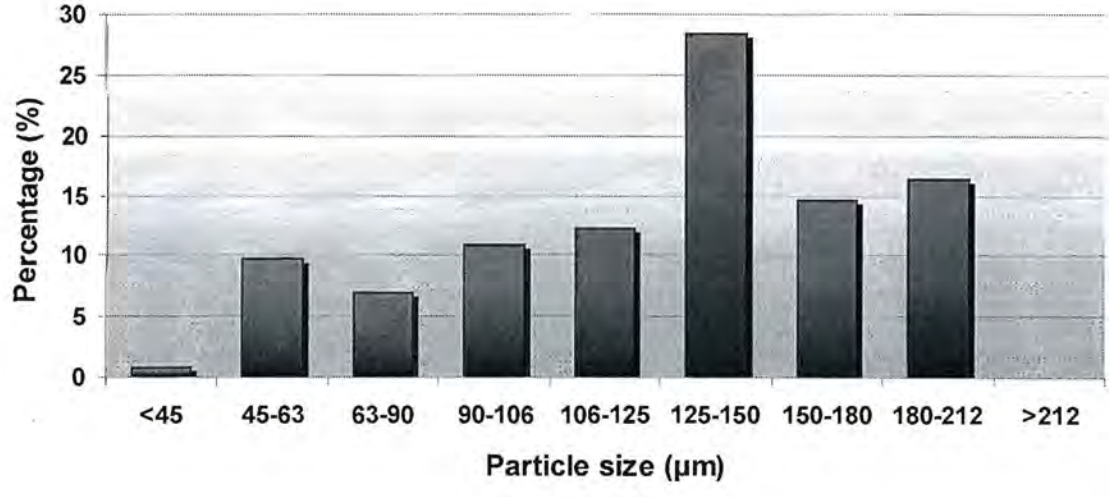

***Figure 3.4**: Sieve analysis of chitosan batch 030912.*

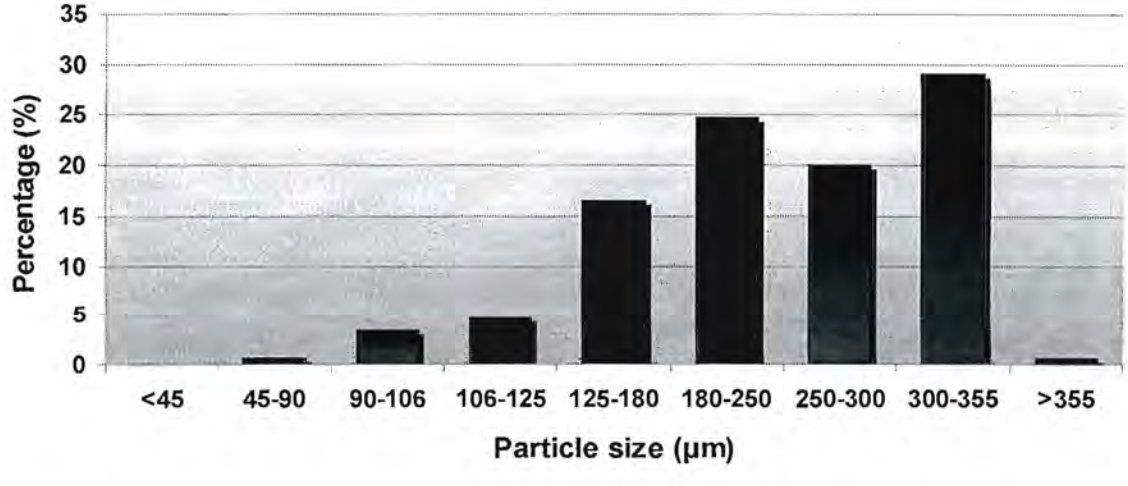

***Figure 3.5**: Sieve analysis of chitosan batch 021010.*

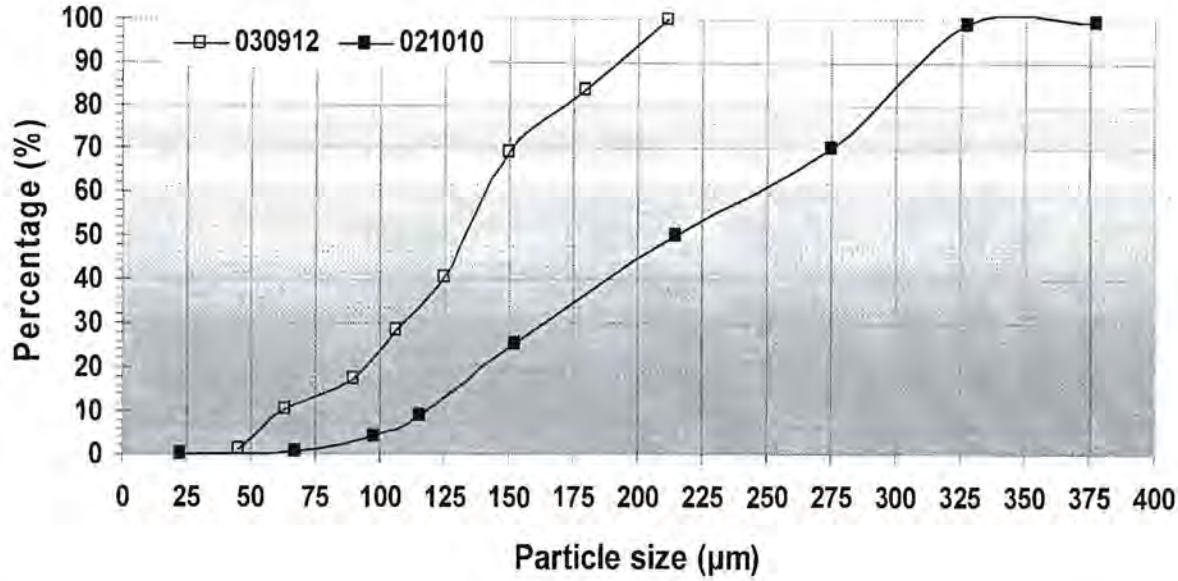

Figure 3.6: *Percentage cumulative particle size distribution of chitosan batch 021010 and 030912.*

The calculated average particle size of the batches was approximately 130.84 µm (batch 030912) and 240.74 µm (batch 021010), respectively (as obtained from the sieve analysis), whilst batch 030912 exhibited a much wider particle size range (45 – 355 µm) compared to 45 – 212 µm for batch 021010. Particles larger than 250 µm are considered to be relative free flowing, whilst particles below 100 µm exhibits a cohesive tendency resulting in decreased flowability (Staniforth, 2002:200), due to their higher surface area to weight ratio which increases frictional forces (negative in terms of flow). The presence of a fraction of particles smaller than the average particle size of the powder, however, may enhance powder flow due to their adherence to the surfaces of larger particles, thus smoothing these surfaces and reducing frictional forces. From the percentage cumulative distribution plot (figure 3.6) it could be seen that batch 030912 contained a much higher percentage of particles below 100 µm (±30%) compared to batch 021010 (±5%) which could either contribute to or reduce powder flow.

Although a sieve analysis is a relative cheap and easy method to determine particle size and size distribution properties, it lacks accuracy especially in powders with particle shapes which deviates much from a spherical form. In order to obtain a more accurate prediction for the average particle size and size distribution, laser diffraction was used to analyze the two chitosan batches (described in section 2.5.2.2). The results are presented in table 3.2 and the data in annexure A.2.

Table 3.2: *Results from the particle size analysis of chitosan batches 030912 and 021010 by means of laser diffraction.*

Excipients	10% particles smaller (µm)	Median (µm)	90% particles smaller (µm)	Geometric mean particle size (µm)
Chitosan 021010	77.863 ± 3.527	188.277 ±4.300	365.97 ±8.564	206.855 ±5.286
Chitosan 030912	56.261 ±0.926	153.188 ±1.502	297.686 ±1.640	166.659 ±1.103

The results once again confirmed the larger average particle size of batch 021010 (206.855 µm ±5.286) compared to that of batch 030912 (166.659 µm ±1.103), although much closer than suggested by the results from the sieve analysis.

The results from morphology studies clearly demonstrated significant differences between the particles in the two chitosan batches, but prediction about flow and compression characteristics at this time would be mere speculation. The obtained results could, however, be valuable in terms of explaining observed differences (if any) in the flow of the raw materials. The following section provides the results from the various flow tests that have been conducted.

3.4 POWDER FLOW STUDIES

The various flow parameters commonly used to describe powder flow were conducted on both chitosan batches and some commonly used pharmaceutical fillers. These methods have been described in section 2.3. The results are presented in table 3.3 and the data in annexure A.5.

The results are also presented graphically in figure 3.7 and 3.8. In both figures the y-axis used is an arbitrary scale resulting from setting the value of the filler with the highest value for each individual parameter to 1, and then expressing the values of the other fillers as a ratio thereof. The values obtained for the angle of repose confirmed the general believe that this parameter is less discriminative in terms of indicating differences in flow between different materials. No significant differences ($p>0.05$) were observed between the Angle of Repose of the various fillers examined, whilst both the other two flow parameters (Carr's index and the critical orifice diameter) indicated significant differences ($p<0.05$) between the two chitosan batches and all the other fillers, with chitosan performing significantly poorer than the other fillers. The composite flow index (CFI), as determined according to the method suggested by Taylor *et al.* (2000), confirmed this poor flow (for materials with a value

below 60) of the chitosan batches compared to the other fillers. Table 3.4 presents a rank order of the various fillers for each of the flow parameters, with a value of 1 for the filler with the best performance and 6 for the poorest flow properties. From the results it can clearly be observed that both chitosan batches rank the poorest in terms of almost all the flow parameters.

Table 3.3: *Flow parameters for chitosan (batches 021010 and 030912) and some commonly used tablet fillers.*

Excipient	CI* (%)	AoR* (°)	COD (mm)	Density ($g.cm^{-3}$)		Porosity (%)	CFI*
				Bulk	Tapped		
Chitosan (021010)	37.94 ±0.0399	39,71 ±6.719	11	0.157 ±0.002	0.253 ±0.003	88.58 ±0.0148	59.04
Chitosan (030912)	38.98 ±1.0613	37,44 ±2.118	13	0.302 ±0.007	0.496 ±0.004	78.04 ±0.2741	60.41
Emcompress®	17.20 ±1.9089	38,46 ±1.787	2	0.757 ±0.011	0.914 ±0.022	68.31 ±0.2008	85.91
Ludipress®	18.50 ±0.2489	34,75 ±1.350	2	0.583 ±0.003	0.715 ±0.001	62.27 ±0.0332	86.72
Tablettose®	23.67 ±0.3664	37.11 ±1.303	6	0.594 ±0.003	0.778 ±0.007	61.55 ±0.0329	77.26
Avicel®PH200	18.03 ±3.8522	32.49 ±0.573	1.5	0.368 ±0.002	0.449 ±0.009	76.86 ±0.0136	89.10

*CI = Carr's index, AoR = angle of repose, COD = critical orifice diameter, CFI = Composite index

Table 3.4: *Rank order of two chitosan batches and various other commonly used tablet fillers for various flow parameters.*

Excipient	CI	AoR	COD	CFI
Chitosan (021010)	6	5	5	6
Chitosan (030912)	4	6	6	6
Emcompress®	5	1	2	3
Ludipress®	2	3	2	2
Tablettose®	3	4	4	4
Avicel®PH200	1	2	1	1

*CI = Carr's index, AoR = angle of repose, COD = critical orifice diameter, CFI = Composite index

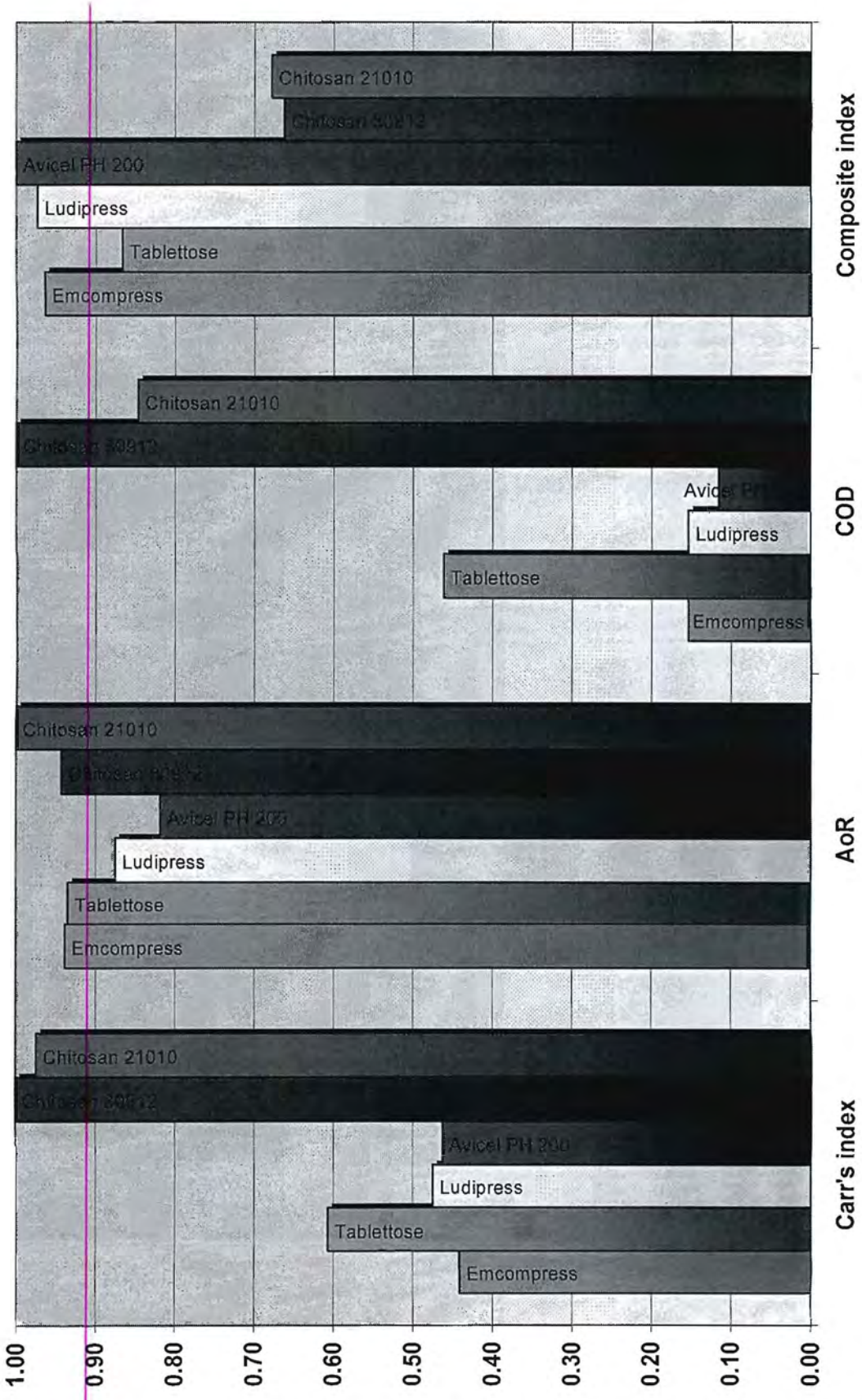

***Figure 3.7**: Flow properties of excipients (Carr's index, angle of repose, critical orifice diameter and composite index).*

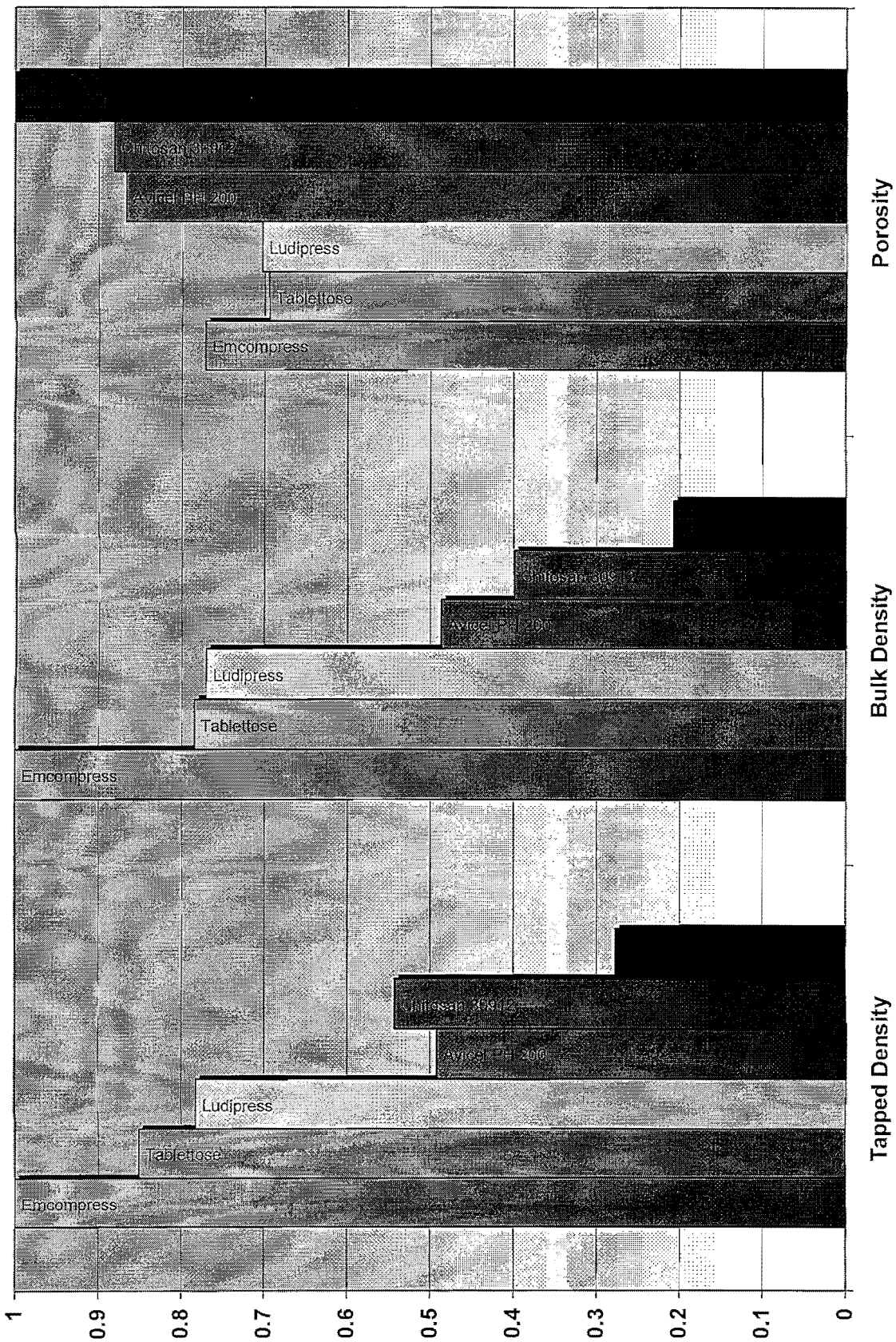

Figure 3.8: *Flow properties of excipients (tapped density, bulk density and porosity).*

From the density and porosity data of the various fillers examined (table 3.3 and figure 3.8) it was clear that both chitosan batches differed significantly from the other fillers as well as from each other. The bulk and tapped density of both chitosan batches were markedly lower than most of the other fillers. Only chitosan (batch 030912) and Avicel®PH-200 showed a comparison. These differences between the densities of the two chitosan batches could probably be ascribed to the variation between the particle size, particle size distribution and particle shape of the two batches resulting in a difference in the packing geometry of the particles in each powder. The larger average particle size of batch 021010 and the presence of more large (>250 μm) and less small particles (<100 μm) in this batch contributed to the lower bulk and tapped densities (almost 50% lower) and higher porosity (approximately 10%) of this batch compared to that of batch 030912. This high porosity of chitosan (>75%) could be responsible for the previously observed poor compression characteristics of the material. Since 75% of the volume occupied by the material consists of voids (intra- and interparticulate spaces, which converts to almost 38% of void space between particles in the tablet die), the conversion of upper punch force to effective compression force might be largely neutralized during compression due to applied pressure been wasted mainly on particle consolidation (volume reduction) and rearrangement of particles rather than bond formation. This hypothesis will, however, be tested in the following chapter during compression studies on chitosan raw material.

One of the most discriminating flow parameters proved to be the critical orifice diameter. Compared to COD's varying form 1.5 mm for Avicel® PH200 to 6 mm for Tablettose®, the chitosan batches produced flow through orifices with diameters in excess of 10 mm (11 mm and 13 mm for batches 021010 and 030912 respectively), indicating significant poorer natural flow than the other materials. This could either be due to cohesive forces (forces between like surfaces, like interparticulate forces and particle interlocking) or the low density of the material. Comparison of the flow rate of the two chitosan batches (determined using a recording flow apparatus – see section 2.3.3, data given in table 3.5 and annexure A.5) through a funnel with an orifice of 13 mm, showed a markedly higher flow rate for batch 030912 (4.394 $g.sec^{-1}$) than for batch 021010 (2.785 $g.sec^{-1}$). This difference in flow rate might be attributed to the differences in the particle shape and surface structure of the particles (discussed in section 3.3.1 and 3.3.2) and/or the differences in the average particle size of the two batches (indicated in section 3.3.3).

Table 3.5: *Flow rate of excipients using a recording flowmeter. Percentage standard deviation is given in brackets.*

Excipient	Opening size (mm)	Average mass (g) powder per second
Chitosan 30912	13	4.394 (13.48)
	14	7.240 (21.49)
	15	7.856 (6.32)
Chitosan 21010	11	1.795(1.50)
	12	1.892 (8.2)
	13	2.785 (2.42)
Emcompress®	2	0.108 (6.75)
	3	0.597 (0.72)
	4	0.680 (5.97)

In order to further examine the properties of chitosan raw material, the density, porosity, and flow properties of various sieve fractions of the two chitosan batches were determined (obtained as described in section 2.5.2.1). The results are presented in table 3.6 and the data in annexure A.5.

Table 3.6: *Properties and flow parameters of different sieve fraction of two chitosan batches.*

Parameters	Sieve fraction (μm)							
	Batch 030912				Batch 021010			
	<90	90-125	125-150	>150	<90	90-125	125-150	>150
COD (mm)	26	11	6	5	30	16	6	6
AoR (°)	19.60 ±1.475	23.21 ±4.235	41.85 ±2.565	41.71 ±1.650	37.53 ±3.917	31.48 ±1.955	46.91 ±2.001	44.45 ±1.814
CI (%)	38.67 ±1.528	34.67 ±0.577	32.33 ±0.577	35 ±1	39.33 ±0.577	37 ±1	31 ±1	28.67 ±1.155
CFI*	56.71	73.64	68.33	67.75	39.87	61.02	65.84	69.03
Tapped Density (g/cm^3)	0.472 ±0.013	0.466 ±0.004	0.487 ±0.001	0.427 ±0.003	0.281 ±0.003	0.250 ±0.007	0.232 ±0.002	0.232 ±0.006
Bulk Density (g/cm^3)	0.290 ±0.002	0.305 ±0.000 2	0.330 ±0.002	0.278 ±0.002	0.170 ±0.000 5	0.158 ±0.002	0.160 ±0.0008	0.165 ±0.004
Porosity (%)	78.91 ±0.134	77.82 ±0.011	76 ±0.175	79.78 ±0.167	87.64 ±0.038	88.51 ±0.166	88.36 ±0.055	88 ±0.289

* COD = Critical orifice diameter, AoR = angle of repose, CI = Carr's index, CFI = Composite index

Considerable differences were observed between most of the flow properties of the various sieve fractions compared to the matching unsieved chitosan batches.

For the unsieved chitosan batches, batch 030912 showed densities (both bulk and tapped) almost twice as high as that of batch 021010 (table 3.3). Comparison of the tapped and bulk densities of the various sieve fractions of the two batches, revealed the same tendency. The speculated reason for this is that the particle size and shape influence the packing geometry. Sieving changed the porosity of the material to a minimal, suggesting that compression problems might still occur during tabletting of the sieved fractions. The porosity of batch 021010 is ±10% higher than batch 030912, suggesting that the particles of batch 021010 pack poorer and therefore have weaker bonds between the particles which could result in poor compression characteristics.

Significant differences ($p<0.05$) were observed for flow through an orifice (as measured by the COD) for sieve fractions of both batches containing particles <90 μm compared to the unsieved chitosan. The relative large orifice diameters (30 and 26 mm for batches 021010 and 030912, respectively) needed to induce flow; proved the negative effect of small particle sizes on efficient powder flow. Sieve fraction of both batches containing particles in the range of 120-150 μm and >150 μm produced flow properties comparable with that of Tablettose® and confirmed the theory that larger particles are more free flowing due to less contact between particles resulting in less interparticular cohesive forces. The AoR seemed to be a less reliable parameter to judge powder flow. The results of AoR indicated that the particles in the range <90 μm and 90 – 125 μm showed good flowability: This contradicts all the other parameters.

The observed better flow of the sieve fractions containing larger particles were also visible in the composite flow index (CFI) with values that matched or even exceeded that of the unsieved material. The better flow of the particles in these sieve fractions (125–150 μm and >150 μm) compared to the unsieved materials confirmed that the presence of smaller particles (which were present in the unsieved chitosan batches) might reduce powder flow in some instances. Then again, it is possible that the small particles can increase the compressibility of the powder because it fills the spaces between the larger particles that could contribute towards effective bonding during compression. The flow properties of particles of batch 030912 in the range of <90 μm and 90–125 μm were markedly better than that of the same sieve fractions of batch 021010 as indicated by a lower angle of repose, smaller critical orifice diameter and higher composite flow index.

3.5 CONCLUSION

Characterization of the two chitosan batches used in this study revealed significant differences in the morphology of the particles of the different batches, especially in terms of average particle size, particle shape and particle size distribution. These differences could probably relate to poor control of the various steps involved in the manufacturing process. As could be expected, these variations also affected the flow characteristics of the two batches, since particle flow is to a large extend depended on particle-related properties such as size, shape, surface structure and density.

The flow properties of both chitosan batches compared rather poorly to other pharmaceutical fillers examined. With the exception of the angle of repose, which proved less accurate in discriminating between free-flowing and cohesive powders or materials; all the other flow parameters clearly confirmed the poor inherent flow properties of chitosan. The flow parameters also revealed, as expected, significant differences between the two chitosan batches in both the unsieved materials and the various sieve fraction. These results clearly demonstrated the relationship between particle properties and flow characteristics.

From the particle characterization in chitosan it could be concluded that the previously observed poor compression characteristics (as indicated by De Kock, 2005; Aucamp, 2004 and Buys, 2006), could be attributed to the low density and high porosity of the material which could impair effective compression on eccentric tablet presses. This hypothesis, however, will be studied and tested in the following section concerning the compression behaviour and characteristics of chitosan.

CHAPTER 4

CHARACTERIZATION OF THE COMPRESSION PROPERTIES OF CHITOSAN

4.1 INTRODUCTION

Considering the chemical structure of chitosan (section 1.4.1), good compression for this material should be expected due to the possibility of the formation of hydrogen bonds (H-bonds), which are considered the strongest of the intermolecular attraction forces available for bonding of powder particles under pressure. However, results from studies by De Kock (2005), Aucamp (2004) and Buys (2006) all emphasized the poor compression profiles of chitosan on eccentric tablet presses. Attempts to improve the compression behaviour of this material by wet granulation (Aucamp, 2004; De Kock 2005), addition of dry binders and combination with other fillers (Aucamp, 2004) were at best only partially successful and rather disappointing. The results of Buys (2006), however, was promising for the material when changing the compression cycle from a single fill to a double die fill for each compression cycle.

Results from the physical characterization of chitosan during this study (as presented and discussed in chapter 3) might shed some light on its poor, and sometimes variable, compression behaviour. The high porosity (>75%) of chitosan powder – resulting in a low mass to volume ratio – results in low powder volumes filling the die during compression on a standard tablet press. Chitosan also has large inter-batch variations with respect to the physical properties of the different batches even when manufactured by the same company via the same method.

The postulate that has been formulated, and which will be tested in this section of the study is that: *"volume reduction and particle rearrangement during the compression cycle wastes most of the movement of the upper punch into the die without effective bonding of particles due to the large voids within the powder bed."* H-bonding, like other intermolecular attraction forces, is a distant force – thus the closer the particles, the stronger the bond. Furthermore, particle contact and fragmentation, to produce new surfaces, are a prerequisite for effective bonding and strong tablet structures (Morrison & Boyd, 1973:10)

The following sections deal with compression studies on the two chitosan batches using an eccentric tablet press to determine the effect of differences in the physical properties of the

material on its compression characteristics and the compression behaviour of the material using a modified tablet press which allows double compression (and a higher powder volume to be contained within the die cavity).

4.2 COMPRESSION STUDIES ON CHITOSAN USING AN ECCENTRIC TABLET PRESS

Chitosan tablets (batch 03091), of varying weight, were compressed on an eccentric tablet press (Manesty) at varying upper punch settings as described in section 2.6.1. This was done to set a baseline for the compression behaviour of the material during a single fill compression cycle. The tablets were analyzed in terms of weight variation, thickness, diameter, crushing strength and friability using the methods described in section 2.6.3. The results are presented in tables 4.1 – 4.3 (data in annexure B).

Table 4.1: *Physical properties of* ***100 mg*** *chitosan tablets (batch 030912) produced on a Manesty eccentric tablet press at different upper punch settings. %RSD indicated in brackets.*

Physical property	Upper punch setting (UPS)			
	17	18	19	20
Weight variation (mg)	101.54 (1.57)	101.96 (1.43)	102.10 (1.59)	102.28 (1.43)
Thickness (mm)	2.33 (0.61)	1.91 (.56)	1.62 (1.16)	1.54 (1.37)
Diameter (mm)	7.98 (0.24)	8.00 (0.13)	7.94 (0.07)	8.04 (0.17)
Crushing strength (N)	8.31 (13.45)	28.81 (11.98)	89.45 (9.82)	103.75 (2.65)
Friability (%)	11.46	1.80	0.56	0.24

Table 4.2: *Physical properties of* ***150 mg*** *chitosan tablets (batch 030912) produced on a Manesty eccentric tablet press at different upper punch settings. %RSD indicated in brackets.*

Physical property	Upper punch setting (UPS)			
	24	25	26	27
Weight variation (mg)	151.79 (1.19)	151.36 (1.72)	151.63 (1.83)	152.81 (1.99)
Thickness (mm)	3.43 (0.52)	2.88 (0.43)	2.48 (0.64)	2.29 (2.51)
Diameter (mm)	7.98 (0.12)	7.95 (0.21)	7.91 (0.09)	7.90 (0.17)
Crushing strength (N)	12.87 (13.56)	34.76 (10.74)	91.49 (8.99)	162.27 (6.57)
Friability (%)	12.67	2.77	0.88	0.23

Table 4.3: *Physical properties of* ***200 mg*** *chitosan tablets (batch 030912) produced on a Manesty eccentric tablet press at different upper punch settings. %RSD indicated in brackets.*

Physical property	Upper punch setting (UPS)				
	30	31	32	33	34
Weight variation (mg)	196.31 (1.47)	196.63 (1.41)	196.77 (1.43)	198.48 (1.94)	196.20 (1.24)
Thickness (mm)	4.47 (1.03)	3.93 (0.80)	3.49 (0.35)	3.14 (0.40)	3.01 (0.89)
Diameter (mm)	8.01 (0.25)	7.97 (0.15)	7.96 (0.08)	7.93 (0.15)	7.94 (0.18)
Crushing strength (N)	16.10 (20.13)	29.98 (19.51)	80.75 (7.45)	136.76 (7.73)	202.07 (6.31)
Friability (%)	18.08	3.97	1.29	0.47	0.18

The range of the upper punch settings used for each tablet weight were the minimum and maximum setting at which tablets of sufficient hardness (to be tested) could be produced.

The data from the compression studies revealed that none of the upper punch ranges overlapped between the different tablet weights. In each case the higher the tablet weight, the higher the upper punch setting (UPS) needed to produce tablets of sufficient hardness. This could probably be explained in terms of the mechanics of the press used to produce the tablets. On eccentric tablet presses the lower punch setting determines the available volume in the die cavity. Since the lower punch stays stationary during the filling and compression stages (and only moves upwards after compression to eject the tablet) the volume available in the die for powder is given by equation 2.10

Theoretically, the descent (displacement) of the upper punch into the die for a specific tablet weight could be calculated using the density of chitosan (0.302 $g.cm^{-3}$ for batch 030912) and the tablet weight required (for example 0.1 gram). From these values the powder volume can be determined (0.331 cm^3). Using equation 2.10, and taking the die radius as 0.4 cm (diameter = 8 mm), it relates to a setting of the lower punch to 6.58 mm from the top edge of the die. Lowering of the lower punch to 9.88 mm and 13.17 mm (measured from the top of the die) would accommodate 150 and 200 mg of this material respectively. In practice, however, the descent of the upper punch was determined manually to produce tablets of 100 mg. For this weight the displacement of the upper punch was determined to be 6.8 mm. Increasing the upper punch displacement to 10.38 mm and 13.56 mm produced tablet weights of 150 and 200 mg respectively (using the same 8 mm die).

The UPS determines the distance the upper punch descents into the die, resulting in reduction of the volume between the upper and lower punch which is occupied by the powder in the die. This volume reaches a minimum (V_{min}) when the upper punch reaches its

lowest level (determined by the setting), at which stage it would have compressed the powder and reduces its volume to V_{min}. Using the values of the known variables in the press set-up (i.e. the available die volume for a desired tablet weight, die depth, die diameter, upper punch setting and distance of upper punch into the die) and the tablet dimensions produced at this particular set-up (tablet weight, tablet thickness and tablet diameter which were obtained from the results of the tablet testing as described in section 2.6.3.2), data can be calculated which could be helpful to explain the compression characteristics of the powder. These values are presented in table 4.4.

Table 4.4: *Data pertaining to the machine setting for each chitosan tablet weight.*

Tablet weight (mg)	Upper punch setting	Maximum distance of descent of upper punch into die (mm)	Initial die volume[(1)] (cm^3)	Final die volume[(2)] (cm^3)	Volume reduction (%)
100	17	4.467	0.342	0.117	65.72
	18	4.887		0.096	71.90
	19	5.187		0.081	76.31
	20	5.257		0.077	77.34
150	24	6.946	0.522	0.172	66.94
	25	7.946		0.145	72.24
	26	7.896		0.125	76.10
	27	8.086		0.115	77.93
200	30	9.087	0.682	0.225	67.03
	31	9.627		0.198	71.01
	32	10..067		0.175	74.26
	33	10.417		0.158	76.84
	34	10.547		0.151	77.80

[1] = *determined by the setting of the lower punch.*

[2] = *determined by the distance the upper punch descents into the die (dependant on the upper punch setting).*

For an increase in the tablet weight from 100 to 150 mg, the lower punch was adjusted (lowered) to increase the depth of the die cavity from 6.8 mm to 10.38 mm (an increase of 3.58 mm) which resulted in an increase in the available die volume for powder from 0.342 to 0.522 cm^3. At an UPS of 17 the compression of 150 mg of chitosan only resulted in a volume decrease of approximately 43%, which was insufficient to produce tablets which could be tested. Only at an upper punch setting of at least 24, the volume reduction were sufficient (approximately 67%) to produce tablets. The same tendency was observed with an increase in the tablet weight from 150 to 200 mg – where tablets were only produced at a volume reduction of 67%.

For every tablet weight (i.e. 100; 150 and 200 mg) the lowest upper punch setting which produced tablets of sufficient strength to be handled and tested, resulted in tablets with poor / low crushing strength (8-16 N) and high friability (11-18%). This was mainly due to the low volume reduction which occurred in the die cavity at these settings (between 65-67%). From the data in tables 4.1 – 4.3 it is clear that sufficiently strong tablets, with hardness in the order of 80 N and higher and friability lower than 1%, were only obtained at upper punch settings of at least 2 units above the lowest setting which produced tablets (for each of the selected tablet weights). In all these cases, the approximate volume reduction was between 74 and 76%, which seems to be the minimum volume reduction required to produce tablets of sufficient strength and low friability (i.e. between 81 – 91 N and less than 1% friability).

Figure 4.1 clearly indicates that a volume reduction of approximately 65-67% was required to produce tablets of sufficient hardness at each selected tablet weight, i.e. tablets that could be handled and thus tested. This was accomplished at the lowest UPS for each weight, namely 17 for 100 mg; 24 for 150 mg and 30 for 200 mg tablets. For this reason, no tablets of weight 150 mg could be produced at an UPS below 24, and none at an UPS below 30 for 200 mg tablets.

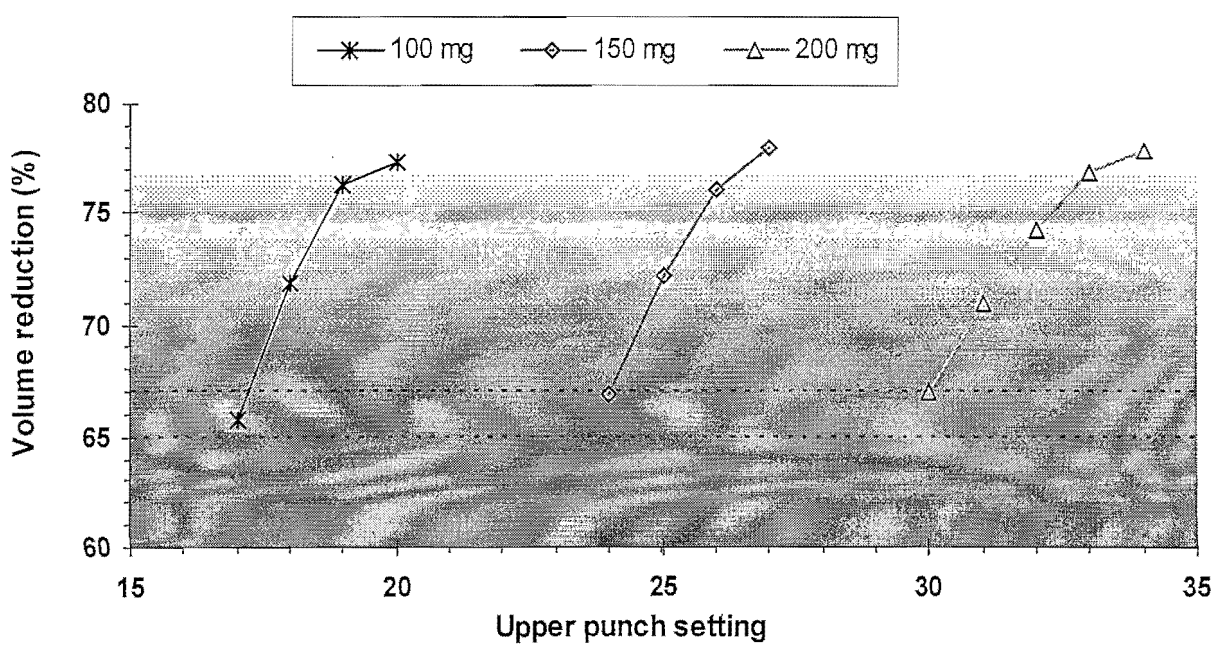

Figure 4.1: *Effect of upper punch setting on the volume reduction in the die cavity (8 mm in diameter) for various weights of chitosan tablets (batch 030912).*

The maximum UPS possible at each tablet weight related to a percentage volume reduction of approximately 76-78%. The tablet press failed to compress the powder with an increase in the UPS by one unit or more (on a scale between 0 and 50). These results confirmed that

chitosan has a very narrow compression range (in terms of volume reduction). The reaction of the material under compression is quite stern as indicated by the rapid increase in crushing strength with an increase of 1 unit in the UPS at every tablet weight (tables 4-1 – 4.3). An increase of 1 unit in the UPS at every tablet weight resulted in a significant increase in the crushing strength of the tablets (from 8 to 28 N [±250%] for an increase in the UPS from 17 to 18 for the 100 mg tablets; 12 to 34 N [±180%] from 24 to 25 for the 150 mg and 16 to 29 N [±80%] from 30 to 31 for the 200 mg tablets). This narrow range for compression force adjustment (a maximum of 3-4 units at each weight) is not considered advantageous in the case of fillers, especially in the case of direct compression processes.

The tensile strength is a parameter incorporating both the crushing strength and tablet dimensions (thickness and diameter), thus providing a better indication of the effect of compression force on tablet properties. The higher the tensile strength, the better the strength of the compaction, which would indicate effective particle bonding. The tensile strength (σ_T) at each tablet weight was calculated from equation 2.12.

Figure 4.2 shows the effect of UPS on the tensile strength of the tablets. Each selected tablet weight exhibited a sharp increase in tensile strength with an increase in UPS, which could primarily contribute to the significant increase in tablet hardness.

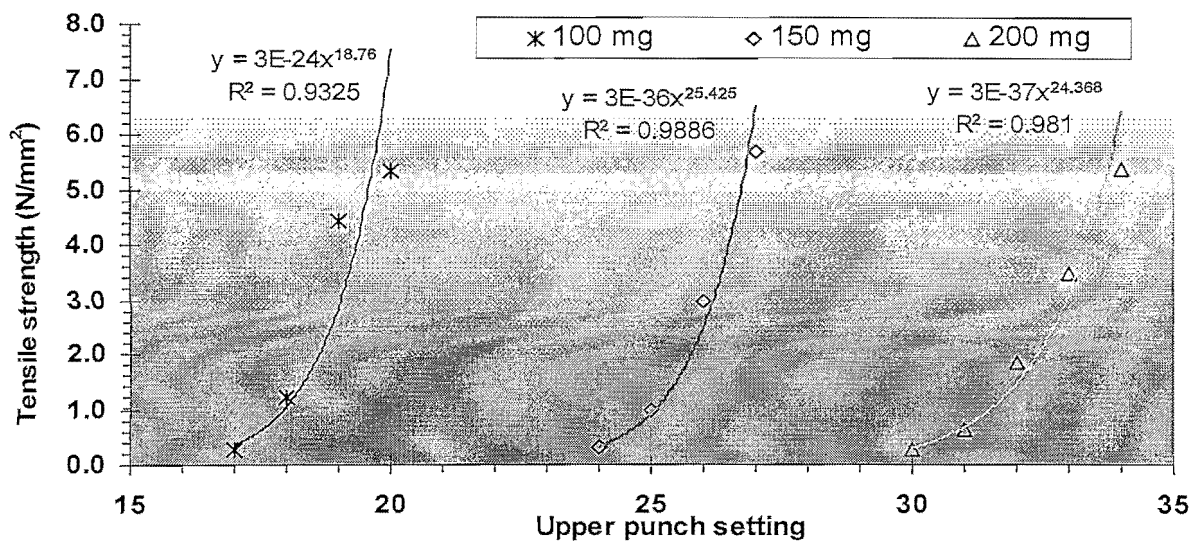

Figure 4.2: *Effect of upper punch setting on the crushing strength of chitosan tablets at various weights.*

The relationship of percentage friability to crushing strength for the 100 mg tablets is shown in figure 4.3. Both the other two tablet weights exhibited the same tendency, with regression lines ($y = ax^{-b}$) showing r^2-value higher than 0.92. At the lowest UPS the friability for each

weight was in the excess of 10%, but declined sharply to about 1% with an increase of 1 unit on the UPS-scale.

The high crushing strength (>100 N) and low percentage friability (<0.24%) of chitosan at the top of the UPS range for each tablet weigh, indicated fair to good compressibility characteristics, although over a very small compression force range. The main problem using an eccentric (single stroke) tablet press, however, seemed to be the relative low tablet weights that could be achieved due to the high porosity of the material, especially when considering the available die volume. This problem could be resolved using a die with a larger diameter which could contain larger powder volumes, but this would result in tablets with a low height to diameter ratio, which would be rather unappealing.

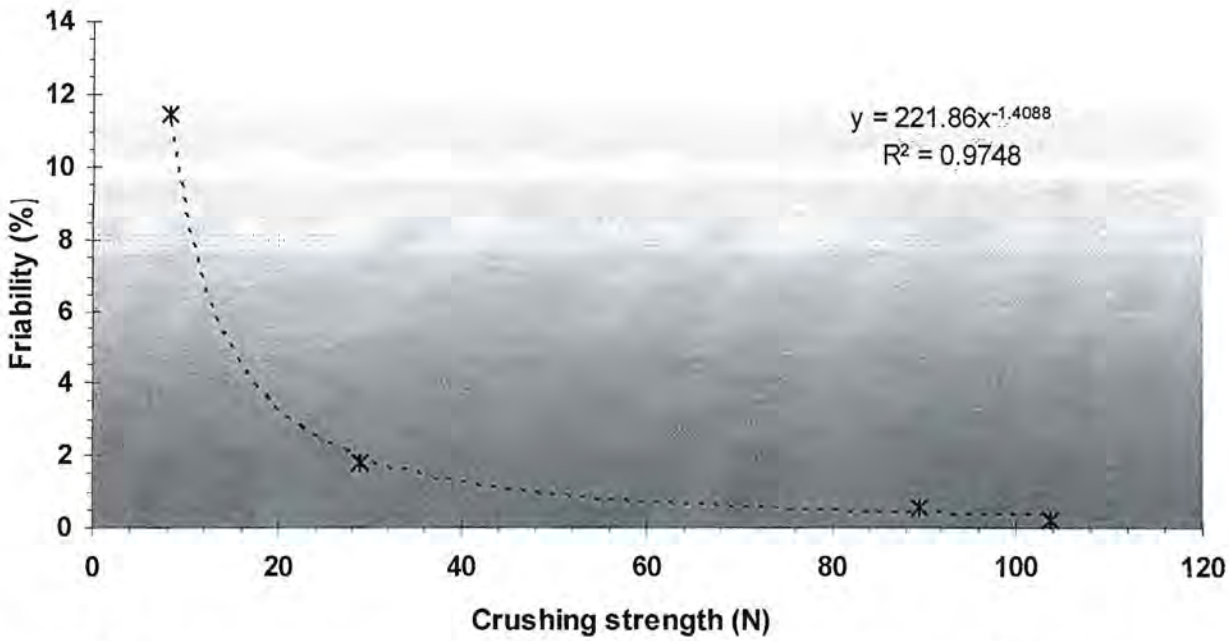

Figure 4.3: *Relationship between crushing strength and percentage friability of 100 mg chitosan tablet produced at various upper punch settings. The dotted line represents the best powder fitt regression line through the data points.*

Another parameter which is used to express the compression characteristics of powder is the hardness-friability index (HFI). The steeper the incline (slope) of the line, the better the material reacts towards compression force, which is a result of an increase in the crushing strength accompanied by a sharp decrease in the percentage friability (figure 4.4).

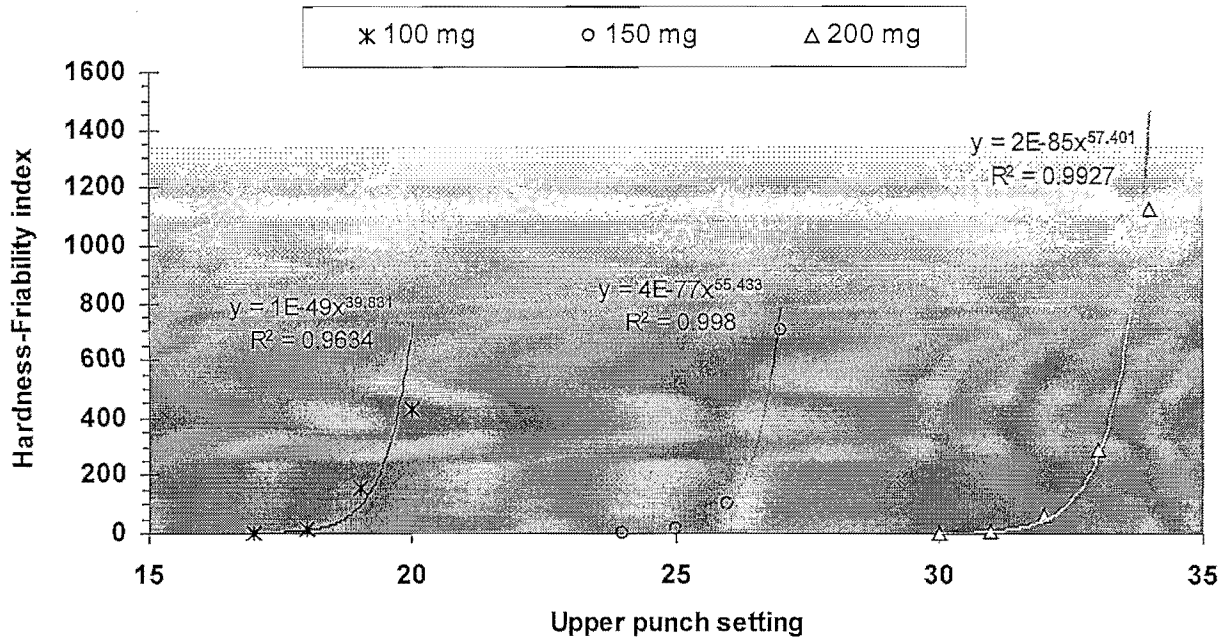

Figure 4.4: *Hardness-friability index (HFI) as function of the UPS of chitosan (batch 030912) tablets of varying weight.*

4.3 CONCLUSION

Chitosan raw material showed promising compression characteristics at specific (carefully chosen) machine settings, with good crushing strength and low friability at the top of the compression range of each tablet weight selected. The main drawbacks of the compression properties of the material on a standard eccentric tablet press, however, may be summarized as follows:

- Relative low tablet weights and/or a small weight range available for a specific die size;
- Narrow range of upper punch settings available to achieve a suitable tablet hardness and friability; and
- Very limited (small) range between minimum and maximum upper punch settings which produce tablets of sufficient hardness and friability (not very large margin for adjustments available).

These characteristics may render the material rather ineffective as a direct compressible filler where it would be the major constituent in the formulation, when considering that in these formulations its major function is to impart good flow and compression properties in the mixture.

4.4 COMPRESSION OF CHITOSAN USING THE DOUBLE FILL CYCLE

The standard eccentric press has one die filling per compression cycle. In order to increase the amount of powder in the die, an eccentric tablet press was modified using a stepper motor which allows for multiple fillings per cycle, and changing the amount of compression (percentage compression) per cycle. The modifications and press setup was discussed in section 2.6.2. The limitation of the standard eccentric press and the physical properties of batch 021010 prevented this batch to be effectively compressed on an eccentric press, whilst batch 030912 produced tablets although at relatively low weights (maximum 200 mg in an 8 mm die) and restricted UPS ranges at each weight selected. This failure of batch 021010 to produce tablets could be ascribed to the differences observed in the physical properties of the material, especially the density, particle size and particle structure, compared to that of batch 030912 (section 3.3 and 3.4).

Since 200 mg tablets of batch 030912 provided the widest range for upper punch settings (30-34), this weight was selected as the target weight of the tablets to be produced on the modified eccentric press. Both batches of chitosan (021010 and 030912) were used in order to evaluate and compare their physical tablet properties. The press was initially setup to accommodate 200 mg of chitosan (batch 030912) and a UPS of 30 was selected. The percentage compression setting on the controller was varied between 0% and 80%, and 50 tablets were compressed at each setting. For batch 021010 the volume in the die cavity was kept equal to that being used for batch 030912 (which produced 200 mg tablets), and the UPS setting was increased to 33. This UPS was the lowest setting that produced tablets of sufficient hardness for batch 021010. The percentage compression was varied between 30% and 80% and 50 tablets were compressed at each setting. Tablets of an average weight of approximately 118 mg could be produced at the lowest percentage compression setting (i.e. 30%). The data of the physical properties of the tablets from the two batches are presented in tables 4.5 and 4.6. The raw data is presented in annexure B.2

Table 4.5: *Tablet properties of chitosan (batch 030912) tablets (initial weight 200 mg) at various percentage compression settings using double compression. The percentage relative standard deviation (% RSD) is shown in brackets.*

% compression	Upper punch setting = 30				
	Weight (mg)	Height (mm)	Diameter (mm)	Crushing strength (N)	Percentage friability (%)
0	196.31 (1.47)	4.47 (1.03)	8.01 (0.25)	16.10 (20.13)	18.08
10	210.16 (1.32)	4.67 (0.69)	8.07 (0.12)	22.72 (18.73)	13.76
20	223.97 (1.57)	4.59 (0.41)	8.06 (0.10)	35.91 (9.17)	5.64
30	233.22 (1.44)	4.54 (0.39)	8.05 (0.10)	59.02 (17.71)	3.31
40	246.20 (1.05)	4.52 (0.24)	8.04 (0.11)	78.05 (9.49)	2.19
50	259.17 (1.55)	4.49 (0.14)	8.02 (0.06)	127.52 (7.48)	1.53
60	270.02 (1.68)	4.51 (0.28)	8.02 (0.08)	169.82 (6.71)	0.94
70	288.06 (0.84)	4.58 (0.56)	8.00 (0.09)	241.50 (10.24)	0.64
80	301.31 (1.47)	4.73 (1.05)	8.01 (0.12)	291.34 (5.54)	0.54

Table 4.6: *Tablet properties of chitosan (batch 021010) tablets (initial weight ±118 mg) at various percentage compression settings using double compression. The percentage relative standard deviation (% RSD) is shown in brackets.*

% compression	Upper punch setting = 33				
	Weight (mg)	Height (mm)	Diameter (mm)	Crushing strength (N)	Percentage friability (%)
30	118.11 (3.06)	3.54 (1.09)	8.01 (0.27)	11.12 (29.32)	10.31
40	121.66 (5.30)	3.51 (1.26)	8.03 (0.18)	13.55 (21.98)	13.19
50	130.55 (3.81)	3.52 (2.19)	8.03 (0.25)	15.89 (44.09)	4.10
60	136.99 (5.14)	3.38 (3.15)	8.04 (0.14)	35.71 (44.88)	1.59
70	152.46 (5.35)	3.21 (0.52)	8.02 (0.08)	70.32 (12.25)	0.62
80	170.39 (5.38)	3.20 (0.69)	8.01 (0.20)	116.30 (30.61)	0.45

The results from the compression studies revealed the significant effect of the differences in the physical properties of the particles from the 2 batches on the compaction behaviour of the powders, and thus on the properties of the tablets that were produced. Although tablets from both batches showed the same tendency in terms of compaction behaviour with an increase in tablet hardness and a decrease in friability with an increase in compression force (as obtained from an increase in the UPS), tablets from batch 030912 exhibited superior compression characteristics. The structural (size and shape) and density differences between particles of the two batches (see section 3.3 and 3.4) could be the determinant cause for these observed differences. Chitosan from batch 021010 could not be compressed on an eccentric tablet press probably because of the low density of the powder (0.157 g/cm^3), due to the fact that the amount of powder which occupied the die (after filling) was insufficient to produce proper compacts upon compaction. This could probably be ascribed to insufficient volume reduction of the powder during compression as a result of the high porosity of the powder (low bulk density). The higher porosity of batch 021010 (88%) compared to the 78% of batch 030912 could possibly be the main reason why the former batch could only be compressed successfully at an UPS of 33 and a compression of 30% compared to an UPS of 30 and 0% compression for batch 030912.

The available volume in the die cavity of the modified press is also determined by the lower punch setting which was the same as for the standard press (discussed in section 4.2). The modification of the standard eccentric press was discussed in section 2.6.2.1.

The advantage of the modified press in terms of improvement of the compactibility of low density materials was clearly demonstrated by the results from the compression studies of both chitosan batches. On the standard eccentric tablet press batch 021010 could not be compressed into compacts solid enough to be tested. The use of the modified press alleviate this problem due to an increase in the powder weight in the die (that occurred after the first partial compression) which caused an increase in powder volume and a subsequent reduction in powder porosity. Thus, at an UPS of 33 and with a percentage compression setting of 30%, and with an increase in the powder mass inside the die from 104 to 118 mg, the powder volume during the second (final) compression stage could be reduced to approximately 73% which seemed to be the minimum required volume necessary for this batch to produce tablets of sufficient hardness. The higher powder volume within the die cavity during the final compression stage (when the upper punch completed its full descent into the die) resulted in closer proximity of the particles inside the die which would naturally lead to stronger bonds being formed in the case where attraction forces is the major bonding mechanism (as is the case for H-bonding). The same results were obtained with batch 030912, but due to the favourable physical characteristics of the powder bed (especially

higher density) and its particles exhibiting better flow and superior shape and texture, the improvement in compression characteristics were even better.

Due to the superior compactibility of batch 030912, probably due to more sufficient particle rearrangement: possible fragmentation and particle deformation under pressure, a weight increase of approximately 53% could be achieved within an 8 mm die at a constant UPS through variation of the percentage compression. In comparison, batch 021010 could only produce an increase in tablet weight of approximately 44% (figure 4.5).

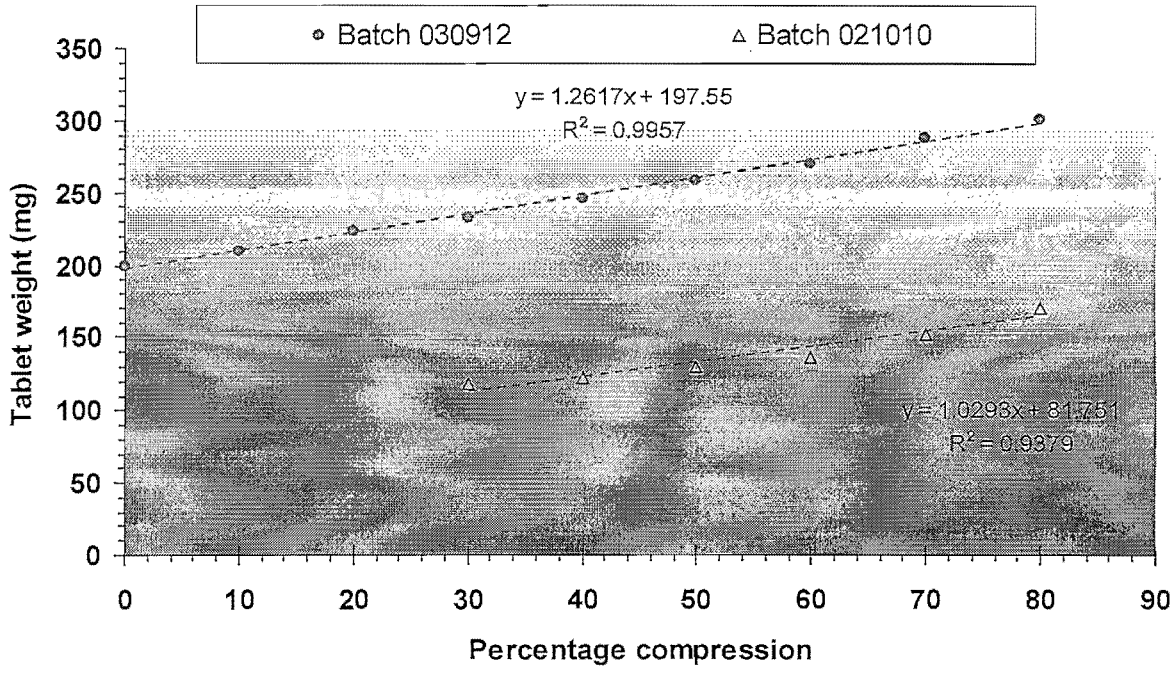

Figure 4.5: *Tablet weight of chitosan batch 030912 (at UPS = 30) and batch 021010 (at UPS = 33).*

Noteworthy from figure 4.5, is the linearity (for both batches) of the increase in tablet weight with and increase in percentage compression for both chitosan batches; and the poorer compression characteristics of batch 021010 compared to batch 030912. This poorer compression behaviour is deducted from the fact that this batch (021010):

- produced significantly lower tablet hardness at a higher UPS (33) compared to that of batch 030912 (UPS = 30); and
- could be compressed over a smaller percentage compression range (30 – 80%) compared to batch 030912 (0 – 80%).

This increase in the tablet weight for both batches resulted in an improved tablet structure with markedly higher hardness and lower friability. Although the crushing strength of batch

021010 (116.3 N) at the highest percentage compression setting possible (i.e. 80%) was acceptable, it was still poor compared to tablets from batch 030912 which exhibited similar hardness values at approximately 50% compression and a maximum hardness of 291 N at 80% compression.

The hardness friability-index as a function of percentage compression for the two batches is presented in figure 4.6.

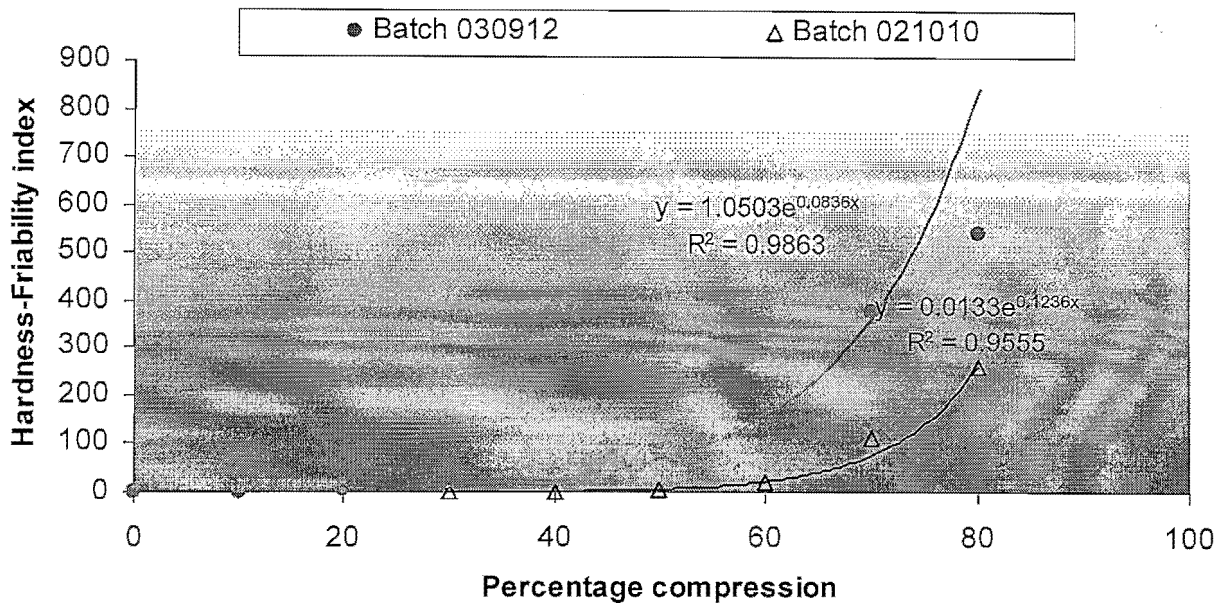

Figure 4.6: *HF-index of chitosan batches produced on a modified eccentric tablet press at different percentage compression settings.*

Both batches exhibited excellent HF-indexes as a function of compression force, with the tablets of batch 030912 once again outperforming those of batch 021010. The difference in results could once again be ascribed to the better compaction properties of batch 030912 which resulted in better tablet hardness and lower friability at each percentage compression setting.

It is, therefore, concluded that the superior compaction and compression characteristics of batch 030912 compared to that of batch 021010 were primarily due to the higher tablet weight (which is directly related to the higher powder volume that could be accommodated in the die cavity) which could be achieved for the first mentioned batch.

For a comparison of the differences in the results obtained from the two tablet presses employed in this study, the tablet properties of batch 030192 were used. Figures 4.7 and 4.8 present a comparison of the crushing strength and friability (respectively) for tablets from this

particular chitosan batch as a function for the percentage compression settings obtained from the two tablet presses used.

On the standard single fill eccentric tablet press, tablets with a maximum weight of 200 mg (in an 8 mm die), with a hardness of approximately 200 N were obtained, but only at an UPS of 34. Conversely, on the modified press with a double compression cycle, a maximum tablet weight of approximately 300 mg (in an 8 mm die) could be obtained whilst the tablet hardness increased to a maximum of ±290 N (an increase of 44%). This was obtained at an UPS of only 30 (figure 4.7).

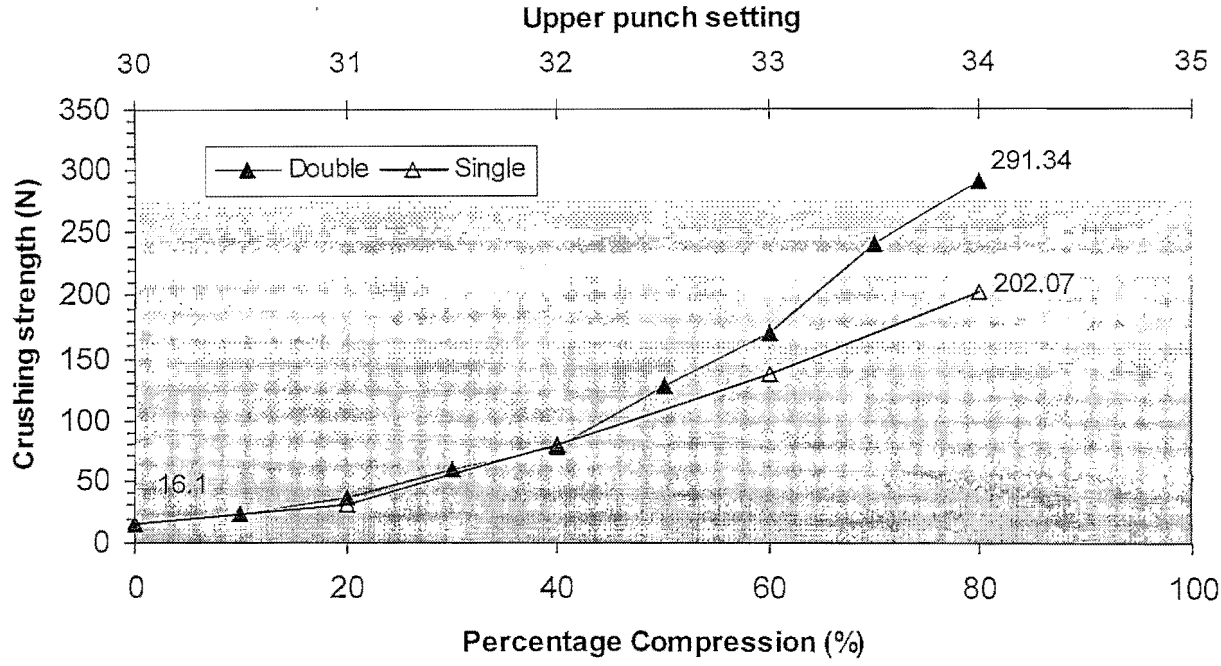

Figure 4.7: *Comparison of the crushing strength of chitosan tablets (batch 030912) produced on a single and double fill eccentric tablet press. Data from the standard press (open triangles) was obtained at UPS 30-34, whilst data from the modified press (solid triangles) was obtained at UPS = 30 at different percentage compression settings (0-80%).*

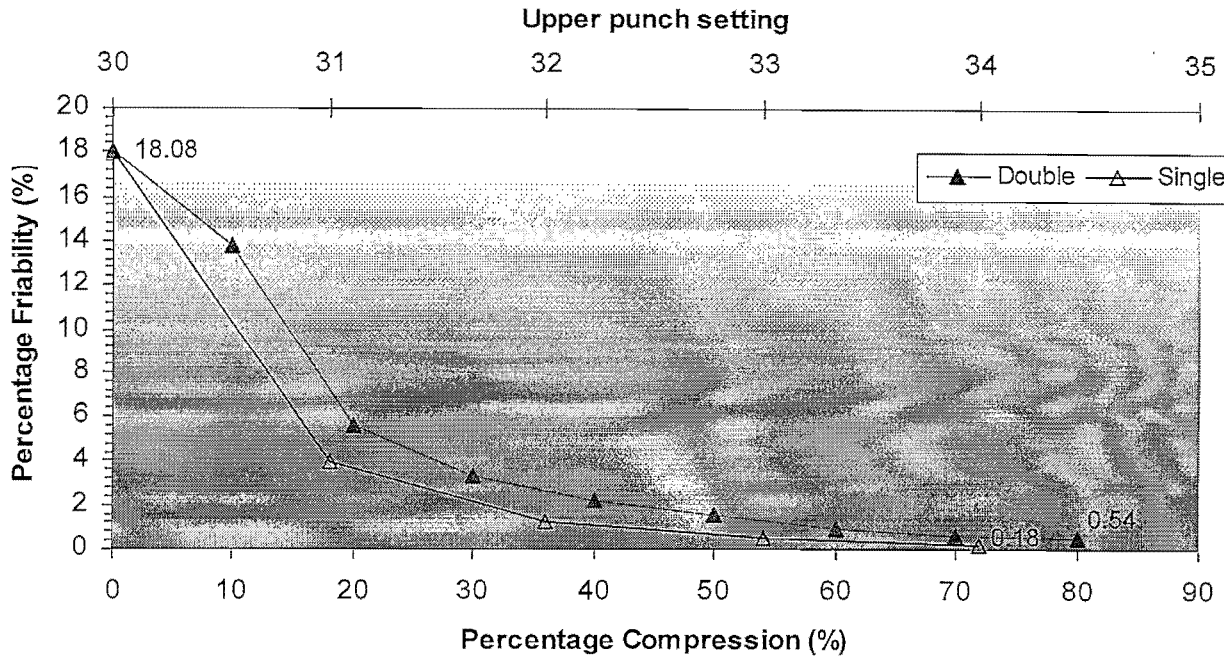

Figure 4.8: *Comparison of the friability of chitosan tablets (batch 030912) produced on a single and double fill eccentric tablet press. Data from the standard press (open triangles) was obtained at UPS 30-34, whilst data from the modified press (solid triangles) was obtained at UPS = 30 at different percentage compression settings (0-80%).*

The minimum UPS that chitosan (batch 030912) could be compressed at gave poor results in regard to the compressibility of the powder (table 4.5). The percentage volume reduction at an UPS of 30 was 67.027% (table 4.4). The percentage volume reduction remained the same for each compression although the amount of powder that filled the die increased. This could be explained by the illustration in figure 2.4; with a percentage setting of 10% at an UPS of 30 the volume available for extra powder in the die was 0.046 cm^3 and for every 10% increase the volume increased by 0.046 cm^3. The extra volume was calculated using equation 2.10 and taking the distance the upper punch descented into the die as 10% of 9.087 mm at an UPS of 30.

By only increasing the amount of powder in the die, the crushing strength of the tablets increased whereas the friability decreased. On the modified eccentric press it was possible to produce a tablet that was approximately 100 mg heavier than the original tablet weight at an UPS of 30. The crushing strength was also approximately 18 times higher than that of the tablets produced at an UPS of 30 (on a standard tablet press), whilst the friability of the tablets also decreased approximately 30 times. It was therefore possible to produce tablets with markedly higher weights (with good crushing strength and friability) on the modified eccentric tablet press at a lower UPS.

4.4 CONCLUSION

Chitosan raw material has the ability to compress into tablets with high crushing strength and low friability which makes it a powder with good compressibility characteristics. It was possible to produce heavier tablets with good compressibility characteristics with the double cycle on a standard press. The narrow range of upper punch settings available to achieve a suitable tablet hardness and friability on the standard eccentric tablet press has been increased on the modified tablet press; lower UPS with increasing percentage compression settings can be used to produce heavier tablets than that of higher UPS on a standard eccentric tablet press. A batch of chitosan, which could not be compressed on an eccentric tablet press when using an 8 mm die, was compressed with the modification of the tablet press at that setting.

The structure of chitosan (figure 1.8) suggests that the bonding mechanism for chitosan is most likely H-bonding which is dependent on the distance between the particles. With the double fill cycle of the modified press it was possible to fill the die with enough powder so that when the upper punch descents into the die, the voids between the particles were already reduced during the first cycle. Therefore, the particles were close enough to bond, which was confirmed by the high crushing strength that was obtained at the higher compression settings.

The percentage compression setting on the modified tablet press made it possible to predict more or less the tablet weight that we could expect at that specific UPS and die setting. Heavier tablets can now be compressed on the modified tablet press at the same UPS used on the standard eccentric tablet press.

Preformulation studies on chitosan raw material are necessary to determine the physical properties of the specific material. The physical characteristics of the raw material differ from batch to batch even when manufactured by the same company. As seen from the results in chapter 3 and 4 it is clear that the particle shape and size, and the roughness of the powder play an important role in the flowability and compressibility of chitosan.

REFERENCES

ADOLFSSON, Å., OLSSON, H. & NYSTRÖM, C. 1997. Effect of particle size and compaction load on interparticulate bonding structure for some pharmaceutical materials studied by compaction and strength characterisation in butanol. *European Journal of Pharmaceutics and Biopharmaceutics*, 44:243-251.

ALDERBORN, G. & NYSTRÖM, C. 1982. Studies on direct compression of tablets. IV. The effect of particle size on the mechanical strength of tablets. *Acta Pharmaceutica Suecica*, 19:381-390.

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

ALDERBORN, G. 2003. A Novel Approach to Derive a Compression Parameter Indicating Effective Particle Deformability. *Pharmaceutical Development and Technology*, 8(4):367-377.

ANDRÈS, C., NDIAYE, A., THOMAS, C., TROMELIN, A., CHAILLOT, B. & POURCELOT, Y. 1995. Influence of the parameters molecular structure and granularity on the compactibility of a powder. *Drug Development and Industrial Pharmacy*, 21(16):1875-1885.

ARAI, K., KINUMAKI, T. & FUJITA, T. 1968. Toxicity of Chitosan. *Bulletin of Tokai Regional Fisheries Research Laboratory*, 5689-94.

ARMSTRONG, T. 1982. Causes of tablet compression problems. *Manufacturing Chemist*, 64-65.

ASADA, M., TAKAHASHI, H., OKAMOTO, H., TANINO, H. & DANJO, K. 2004. Theophylline particle design using chitosan by the spray drying. *International Journal of Pharmaceutics*, 270(1-2):167-174.

AUCAMP, M.E. 2004. Assessment of the tabletting properties of chitosan through wet granulation and direct compression formulations. Potchefstroom: North-West University. (M.Sc) 174p.

BANERJEE, T., MITRA, S., SINGH, A.K., SHARMA, R.K. & MAITRA, A. 2002. Preparation, characterization and biodistribution of ultrafine chitosan nanoparticles. *International Journal of Pharmaceutics*, 243(1-2):93-105.

BERGER, J., REIST, M., MAYER, J.M., FELT, O. & GURNY, R. 2004. Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications. *European Journal of Pharmaceutics and Biopharmaceutics*, 57(1):35-52.

BODHMAGE, A. 2006. Correlation between physical properties and flowability indicators for fine powders. Saskatchewan: University of Saskatchewan. (M.Sc) 122p.

BOLHUIS, G.K. & LERK, C.F. 1973. Comparative evaluation of excipients for direct compression. *Pharmaceutisch Weekblad*, 469-481.

BOLHUIS, G.K. & CHOWHA, Z.T. 1996. Materials for direct compaction. (*In* Alderborn, G. & Nyström, C., *eds.* Pharmaceutical Powder Compaction Technology. New York: Marcel Dekker Inc. p. 419-500.)

BRUGNEROTTO, J., LIZARDI, J., GOYCOOLEA, F.M., ARGÜELLES-MONAL, W., DESBRIÈRES, J. & RINAUDO, M. 2001. An infrared investigation in relation with chitin and chitosan characterization. *Polymer*, 42:3569-3580.

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

CARLESS, J.E. & LEIGH, S. 1974. Compression characteristics of powders: radial die wall pressure transmission and density changes. *Journal of Pharmacy and Pharmacology*, 26:289-297.

CARR, R.L. 1965. Evaluating Flow Properties of Solids. *Chemical Engineering*, 163-168.

CELIK, M. 1992. Overview of compaction data analysis techniques. *Drug Development and Industrial Pharmacy*, 18(6 & 7):767-810.

CEVHER, E., ORHAN, Z., MULAZIMOGLU, L., SENSOY, D., ALPER, M., YILDIZ, A. & OZSOY, Y. 2006. Characterization of biodegradable chitosan microspheres containing vancomycin and treatment of experimental osteomyelitis caused by methicillin-resistant Staphylococcus aureaus with prepared microspheres. *International Journal of Pharmaceutics*, 317(2):127-135.

CHOWHAN, Z.T. & YANG, I.C. 1983. Powder flow studies. IV. Tensile strength and orifice flow rate relationships of binary mixtures. *International Journal of Pharmaceutics*, 14:231-242.

CLARK, N.N. 1986. Three Techniques for Implementing Digital Fractal Analysis of Particle Shape. *Powder Technology*, 46:45-52.

COFFIN-BEACH, D.P. & HOLLENBECK, R.G. 1983. Determination of the energy of tablet formation during compression of selected pharmaceutical powders. *International Journal of Pharmaceutics*, 17:313-324.

DANISH, F.Q. & PARROTT, E.L. 1971. Flow Rates of Solid Particulate Pharmaceuticals. *Journal of Pharmaceutical Sciences*, 60(4):548-553.

DAVID, S.T. & AUGSBURGER, L.L. 1977. Plastic Flow during Compression of Directly Compressible Fillers and Its Effect on Tablet Strength. *Journal of Pharmaceutical Sciences*, 66(2):155-159.

DAVIS, S.S. & ILLUM, L. 2000. Chitosan for oral delivery of drugs. (*In* Muzzarelli, R.A.A., *ed.* Chitosan per os. Grottammare: Atec. p. 137-164.)

DE KOCK, J.M. 2005. Chitosan as a multipurpose excipient in directly compressed minitablets. Potchefstroom: North-West University. (Ph.D.) 225p.

DODANE, V. & VILIVALAM, V.D. 1998. Pharmaceutical applications of chitosan. *Pharmaceutical Science & Technology Today*, 1(6):246-253.

FELL, J.T. & NEWTON, J.M. 1968. The tensile strength of lactose tablets. *Journal of Pharmacy and Pharmacology*, 20:657-658.

FREEMAN, R. 2000. The Classification of Powders in relation to Flowability. *Freeman Technology*, 1-10. www.freemantech.co.uk Date of access: 6 Dec. 2007.

GELDART, D., ABDULLAH, E.C., HASSANPOUR, A., NWOKE, L.C. & WOUTERS, I. 2006. Characterization of powder flowability using measurement of angle of repose. *China Particuology*, 4(3-4):104-107.

GHAFFARI, A., NAVAEE, K., OSKOUI, M., BAYATI, K. & RAIFIEE-TEHRANI, M. 2007. Preparation and characterization of free mixed-film of pectin/chitosan/Eudragit®RS intended for sigmoidal drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics*, 65(1):1-20.

GIOIA, A. 1980. Intrinsic flowability: a new technology for powder-flowability classification. *Pharmaceutical technology uniformity*, 1-4.

GOCHO, H., SHIMIZU, H., TANIOKA, A., CHOU, T.-J. & NAKAJIMA, T. 2000. Effect of plumer chain end on sorption isotherm of water by chitosan. *Carbohydrate Polymers*, 41:87-90.

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

GRAF, E., GHANEM, A.H. & MAHMOUD, H. 1984. Studies on the Direct Compression of Pharmaceuticals. *Pharmaceutical Industry*, 46(3):279-284.

GSCHAIDER, M.E., DEBBAUDT, A. & AGULLO, E. 2002. metal ion chelation with chitosan calcium pectinate pellets. (*In* Muzzarelli, R.A.A. & Muzzarelli, C., *eds.* Chitosan in Pharmacy and Chemistry. Italy: Atec. p. 347-348.)

GUERIN, E., TCHORELOFF, P., LECLERC, B., TANGUY, D., DELEUIL, M. & COUARRAZE, G. 1999. Rheological characterization of pharmaceutical powders using tap testing, shear cell and mercury porosimeter. *International Journal of Pharmaceutics*, 189(1):91-103.

HAMMAN, J.H. & KOTZÉ, A.F. 2002. Paracellular absorption enhancement across intestinal epithelia by N-trimethyl chiosan chloride. (*In* Muzzarelli, R.A.A. & Muzzarelli, C., *eds.* Chitosan in Pharmacy and Chemistry. Italy: Atec. p. 41-50.)

HANCOCK, B.C., VUKOVINSKY, K.E., BROLLEY, B., GRIMSEY, I., HEDDEN, D., OLSOFSKY, A. & DOHERTY, R.A. 2004. Development of a robust procedure for assessing powder flow using a commercial avalanche testing instrument. *Journal of Pharmaceutical and Biomedical Analysis*, 35:979-990.

HECKEL, R.W. 1961. An Analysis of Powder Compaction Phenomena. *Transactions of the metallurgical society of aime*, 221:1001-1008.

HIESTAND, E.N. 1997. Principles, tenets and notions of tablet bonding and measurements of strength. *European Journal of Pharmaceutics and Biopharmaceutics*, 44:229-242.

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

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

JONES, D.S. & MAWHINNEY, H.J. 2005. Monograph: Chitosan. *The handbook of pharmaceutical excipients*, www.medicinescomplete.com/mc/excipients Date of access: 12 Jun. 2008.

KADIRI, M.S., MICHRAFY, A. & DODDS, J.A. 2005. Pharmaceutical powders compaction: Experimental and numerical analysis of the density distribution. *Powder Technology*, 157(1-3):176-182.

KAMATH, S., PURI, V.M., MANBECK, H.B. & HOGG, R. 1993. Flow properties of powders using four testers - measurement, comparison and assessment. *Powder Technology*, 76:277-289.

KAWASHIMA, Y., IMAI, M., TAKEUCHI, H., YAMAMOTO, H., KAMIYA, K. & HINO, T. 2003. Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tableting designed by spherical crystallization process. *Powder Technology*, 130:283-289.

KENINGLEY, S.T., KNIGHT P.C & MARSON, A.D. 1997. An investigation into the effects of binder viscosity on agglomeration behaviour. *Powder Technology*, 91(2):95-103.

KHAN, K.A. & RHODES, C.T. 1975. Effect of Compaction on Particle Size. *Journal of Pharmaceutical Sciences*, 64(3):444-446.

KHAN, K.A. & RHODES, C.T. 1976. Effects of Variation in Compaction Force on Properties of Six Direct Compression Tablet Formulations. *Journal of Pharmaceutical Sciences*, 66(12):1835-1837.

KIM, T.H., PARK, Y.H., KIM, K.J. & CHO, C.S. 2003. Release of albumin from chitosan-coated pectin beads in vitro. *International Journal of Pharmaceutics*, 250:371-383.

KOTZÉ, A.F., DE LEEUW, B.J., LUEBEN, H.L., DE BOER, A.G., VERHOEF, J.C. & JUNGINGER, H.E. 1997a. Chitosans for enhaced delivery of therapeutic peptides across intestinal epithelia: in vitro evaluation in Caco-2 cell monolayers. *International Journal of Pharmaceutics*, 159:243-253.

KOTZÉ, A.F., LUEBEN, H.L., DE LEEUW, B.J., DE BOER, A.G., VERHOEF, J.C. & JUNGINGER, H.E. 1997b. N-Trimethyl chitosan Chloride as a Potential Absorption Enhancer Across Mucosal Surfaces: In vitro Evaluation in Intestinal Epithelial Cells (Caco-2). *Pharmaceutical Research*, 14(9):1197-1202.

KOTZÉ, A.F., HAMMAN, J.H., SNYMAN, D., JONKER, C. & STANDER, M. 2002. Mucoadhesive and absorption enhancing properties of N-trimethyl chitosan chloride. (*In* Muzzarelli, R.A.A. & Muzzarelli, C., *eds.* Chitosan in Pharmacy and Chemistry. Italy: Atec. p. 31-39.)

KRAULAND, A.H., GUGGI, D. & BERNKOP-SCHNÜRCH, A. 2004. Oral insulin delivery: the potential of thiolated chitosan-insulin tablets on non-diabetic rats. *Journal of controlled release*, 95(3):547-555.

KUENTZ, M. & LEUENBERGER, H. 2000. A new theoretical approach to tablet strength of a binary mixture consisting of a well and a poorly compactable substance. *European Journal of Pharmaceutics and Biopharmaceutics*, 49:151-159.

KUMAR, M.N.V.R. 2000. A review of chitin and chitosan applications. *Reactive and Functional Polymers*, 46(1):1-27.

LAHDENPÄÄ, E., ANTIKAINEN, O. & YLIRUUSI, J. 2001. Direct compression with silicified and non-silicified microcrystalline cellulose: study of some properties of powders and tablets. *S.T.P.Pharma Sciences* , 11(2):129-135.

LAVOIE, F., CARTILIER, L. & THIBERT, R. 2002. New Methods Characterizing Avalanche Behavior to Determine Powder Flow. *Pharmaceutical Research*, 19(6):887-893.

LEUENBERGER, H. & ROHERA, B.D. 1986. Fundamentals of Powder Compression. I. The Compactibility and Compressibility of Pharmaceutical Powders. *Pharmaceutical Research*, 3(1):12-22.

LEVIN, M. 2000. Changing Tableting Machines in Scale-Up and Production: Ramifications for SUPAC. (*In* FDA CDER DPQR Seminar. Pharmaceutical Systems. P.1-11)

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

LINDBERG, N.-O., BERDAL, A., ENSTAD, G., SEIFERT, E. & LUNDSTEDT, T. 2002. Investigation of Flow Properties of Powders by Means of a Uniaxial Tester, in Relation to Direct Tablet Compression. *Drug Development and Industrial Pharmacy*, 28(1):15-28.

LINDBERG, N.-O., PALSSON, M., PIHL, A., FREEMAN, R., FREEMAN, T., ZETZENER, H. & ENSTAD, G. 2004. Flowability Measurements of Pharmaceutical Powder Mixtures with Poor Flow Using Five Different Techniques. *Drug Development and Industrial Pharmacy*, 30(7):785-791.

LIU, H., YANG, X., NIE, S., WEI, L., ZHOU, L., LIU, H., TANG, R. & PAN, W. 2007. Chitosan-based controlled porosity osmotic pump for colon-specific delivery system: Screening of formulation variables and in vitro investigation. *International Journal of Pharmaceutics*, 332(1-2):115-124.

LUANGTANA-ANAN, M. & FELL, J.T. 1990. Bonding mechanisms in tabletting. *International Journal of Pharmaceutics*, 60:197-202.

MARTIN, A., BUSTAMANTE, P. & CHUN, A.H.C. 1993. Physical Pharmacy : Physical chemical principles in the pharmaceutical sciences. 4 ed. Philadelphia: Lippincott Williams & Wilkins. 622p.

MI, F., WU, Y., SHYU, S. & SCHOUNG, J. 2002. Asymmetric chitosan membrane wound dressing. (*In* Muzzarelli, R.A.A. & Muzzarelli, C., *eds.* Chitosan in Pharmacy and Chemistry. Italy: Atec. p. 139-144.)

MICHRAFY, A., RINGENBACHER, D. & TCHORELOFF, P. 2002. Modelling the compaction behaviour of powders: application to pharmaceutical powders. *Powder Technology*, 127:257-266.

MOHAMMED, H., BRISCOE, B.J. & PITT, K.G. 2005. The interrelationship between the compaction behaviour and the mechanical strength of pure pharmaceutical tablets. *Chemical Engineering Science*, 60(14):3941-3947.

MORRISON, R.T. & BOYD, R.N. 1973. Structures and Properties. 3 ed. (*In* Morrison, R.T. & Boyd, R.N., *eds.* Organic Chemistry. Boston: Allyn and Bacon, Inc. p. 1-39.)

MURATA, J., OHYA, Y. & OUCHI, T. 1997. Design of quaternary chitosan conjugate having antennary galactose residues as a gene delivery tool. *Carbohydrate Polymers*, 32(2):105-109.

MUZZARELLI, R.A.A. 2000. Recent results in the oral administration of chitosan. (*In* Muzzarelli, R.A.A., *ed.* Chitosan per os: from dietary supplement to drug carrier. Grottammare: Atec. p. 3-40.)

MUZZARELLI, R.A.A. 2002. Chitosan in Pharmacy and Chemistry. Italy: Atec Edizioni. 524p.

MUZZIO, F.J., SHINBROT, T. & GLASSER, B.J. 2002. Powder technology in the pharmaceutical industry: the need to catch up fast. *Powder Technology*, 124:1-7.

NARAYAN, P. & HANCOCK, B.C. 2003. The relationship between the particle properties, mechanical behavior, and surface roughness of some pharmaceutical excipient compacts. *Materials Science and Engineering*, A355:24-36.

NUNTHANID, J., LAUNGRANA-ANAN, M., SRIAMORNSAK, P., LIMMATVAPIRAT, S., PUTTIPIPATKHACHORN, S., LIM, L.Y. & KHOR, E. 2004. Characterization of chitosan acetate as a binder for sustained release tablets. *Journal of controlled release*, 99(1):15-26.

OLSSON, H. & NYSTRÖM, C. 2001. Assessing Tablet Bond Types from Structural Features that Affect Tablet Tensile Strength. *Pharmaceutical Research*, 18(2):203-210.

ORIENTI, I., CERCHIARA, B., LUPPI, B. & ZECCHI, V. 2002. Chitosan salts as supporting materials for colon-specific drug delivery. (*In* Muzzarelli, R.A.A. & Muzzarelli, C., *eds.* Chitosan in Pharmacy and Chemistry. Italy: Atec. p. 57-64.)

PODCZECK, F. & YASMIN, M. 1996. The influence of particle size and shape on the angle of internal friction and the flow factor of unlubricated and lubricated powders. *International Journal of Pharmaceutics*, 144:187-194.

PODCZECK, F. & WOOD, A.V. 2003. The relationship between granule growth mechanism, amount of liquid binder added and properties of the wet powder mass determined using a split bed shear tester. *International Journal of Pharmaceutics*, 257(1-2):57-67.

PORTERO, A., ALONSO, M.J. & REMUNAN-LOPEZ, C. 2002. Chitosan bilayered devices for buccal administration of insulin. (*In* Muzzarelli, R.A.A. & Muzzarelli, C., *eds.* Chitosan in Pharmacy and Chemistry. Italy: Atec. p. 21-29.)

PRESCOTT, J.K. & BARNUM, R.G. 2000. On Powder Flowability. *Pharmaceutical Technology*, 24(10):60-85.

REGE, P.R., SHUKLA, D.J. & BLOCK, L.H. 1999. Chitinosans as tableting excipients for modified release delivery systems. *International Journal of Pharmaceutics*, 181(1):49-60.

RIIPPI, M., ANTIKAINEN, O., NISKANEN, T. & YLIRUUSI, J. 1998. The effect of compression force on surface structure, crushing strength, friability and disintegration time of erythromycin acistrate tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, 46(3):339-345.

SANKALIA, M.G., MASHRU, R.C., SANKALIA, J.M. & SUTARIYA, V.B. 2007. Reversed chitosan-alginate polyelectrolyte complex for stability improvement of alpha-amylase:

Optimization and physicochemical characterization. *European Journal of Pharmaceutics and Biopharmaceutics*, 65(2):215-232.

SANTOS, H., VEIGA, F., PINA, M., PODCZECK, F. & SOUSA, J. 2002. Physical properties of chitosan pellets produced by extrusion-spheronisation: influence of formulation variables. *International Journal of Pharmaceutics*, 246(1-2):153-169.

SEBHATU, T. & ALDERBORN, G. 1999. Relationships between the effective interparticulate contact area and the tensile strength of tablets of amorphous and crystalline lactose of varying particle size. *European Journal of Pharmaceutical Sciences*, 8:235-242.

SENEL, S., KAS, S. & SQUIER, C.A. 2000. Applications of chitosan in dental drug delivery and therapy. (*In* Muzzarelli, R.A.A., *ed*. Chitosan per os: from dietary supplement to drug carrier. Grottammare: Atec. p. 241-256.)

SENEL, S., KREMER, M.J., WERTZ, P.W., HILL, J.R., KAS, S., HINCAL, A.A. & SQUIER, C.A. 2002. Chitosan for intraoral peptide delivery. (*In* Muzzarelli, R.A.A. & Muzzarelli, C., *eds*. Chitosan in Pharmacy and Chemistry. Italy: Atec. p. 77-84.)

SHAGRAW, R.F. & DEMAREST, D.A. 1993. A Survey of Current Industrial Practices in the Formulation and Manufacture of Tablets and Capsules. *Pharmaceutical Technology*, 17(1):32

SHOTTON, E. 1972. The Compression of Powders. *Pharmaceutical Industry*, 34(4):256-262.

SINGLA, A.K. & CHAWLA, M. 2001. Chitosan: some pharmaceutical and biological aspects -an update. *Journal of Pharmacy and Pharmacology*, 53:1047-1067.

SINHA, V.R., SINGLA, A.K., WADHAWAN, S., KAUSHIK, R., KUMRIA, R., BANSAL, K. & DHAWAN, S. 2004. Chitosan microspheres as a potential carrier for drugs. *International Journal of Pharmaceutics*, 274(1-2):1-33.

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

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

TAKEUCHI, H., NAGIRA, S., YAMAMOTO, H. & KAWAHIMA, Y. 2004. Die wall pressure measurement for evaluation of compaction property of pharmaceutical materials. *International Journal of Pharmaceutics*, 274(1-2):131-138.

TAWASHI, R. 1970. Particulate Solids: Flow properties and mixing. *D & CI*, 46-52 & 148-150.

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

VAN DER MERWE, S.M., VERHOEF, J.C., KOTZÉ, A.F. & JUNGINGER, H.E. 2004. N-Trimethyl chitosan chloride as absorption enhancer in oral peptide drug delivery. Development and characterization of minitablet and granule formulations. *European Journal of Pharmaceutics and Biopharmaceutics*, 57(1):85-91.

VELASCO, M.V., MUÑOZ-RUIZ, A., MONEDERO, M.C. & JIMÉNEZ-CASTELLANOS, M.R. 1995. Study of flowability of powders, effect of the addition of lubricants. *Drug Development and Industrial Pharmacy*, 21(20):2385-2391.

VERHOEF, J.C., THANOU, M., VERHEIJDEN, J.H.M. & JUNGINGER, H.E. 2002. Chitosan derivatives as age and effective absorption enhancers for oral delivery of macromolecular drugs. (*In* Muzzarelli, R.A.A. & Muzzarelli, C., *eds.* Chitosan in Pharmacy and Chemistry. Italy: Atec. p. 51-56.)

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

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

YAMASHIRO, M. & YUASA, Y. 1983. An Experimental Study on the Relationships between compressibility, Fluidity and Cohesion of Powder Solids at Small Tapping Numbers. *Powder Technology*, 34:225-231.

(Poster presentation at the 66th International Congress of FIP held in Salvador, Brazil, 2006)

A NEW FLOW METER FOR THE MEASUREMENT OF POWDER FLOW BY MEANS OF THE CRITICAL ORIFICE DIAMETER.

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BACKGROUND

The critical orifice diameter (COD) is one of the well known parameters used in quantifying powder flow. This parameter can be defined as "*the smallest orifice diameter through which a powder can flow freely under the influence of gravity.*" Taylor *et al.* (2000) included this parameter in their composite index (CI) for a variety of pharmaceutical powders with different flow properties.

Many flow apparatuses used to determine the COD show inherent problems including (i) static powder regions in the corners between the cylinder wall and the cylinder floor, (ii) static regions between the floor and the shutter, (iii) formation of "rat holes" or "pipes" in the powder bed through which powders fall rather than flow and (iv) adhesion phenomena due to the material from which these apparatuses are manufactured (Staniforth, 2002:202-205). These factors affect spontaneous powder flow and result in inaccurate results, especially in powders exhibiting poor to extremely poor flow.

The results obtained with the new flow meter indicate:

- a more accurate determination of actual powder flow ;
- a higher scale of scrutiny for distinguishing between the flow of commonly used pharmaceutical powders (especially those with good and poor flow) and
- the value of the COD as indicator of powder flow (compared to the angle of repose [AOR] and Carr's index or the % compressibility (%C).

Other advantages of this apparatus fall in the field of education. It is relatively cheap, easy for students to set-up and use, strong and rigid with low maintenance and "student proof".

MATERIALS

Excipients used in this study were obtained from commercial suppliers and included Avicel® PH-200, Chitosan, Emcocell® 50M & 90M, Emcompress®, Ludipress®, Prosolv® SMCC50 & SMCC90, and Tablettose®.

APPARATUS AND METHODS

Flow meter for measuring critical orifice diameter

The new flow meter comprises of a number of brass cylinders (8 to 15 mm thick) which can be stacked on top of each other to form a funnel (figures 1 and 2 and sketches under "Technical drawings"). Each cylinder has a circular bore which pass through the centre of the cylinder with an inlet and an outlet (orifice diameter), the latter being smaller than the inlet. The passage is thus in the form of a cone. The arrangement is such that the bore of each cylinder tapers from the inlet to the outlet at an angle of approximately 30° (corresponding with the angle in industrial tablet press hoppers). The bores of the cylinders are aligned with one another with the outlet of the bore of any cylinder the same as the inlet of the cylinder directly below it. The orifice diameters range from 1 mm tot 24 mm. The apparatus further includes:

- a hopper for containing the powder and an additional cylindrically shaped container for containing more powder, which fits onto the hopper. The diameter of the hopper and the container are the same;

- a stand defining an opening with a shutter for opening and closing the opening. Supports are provided at the bottom of the stand to support the apparatus in an upright position and away from the surface on which it is positioned.

The apparatus was set up as shown in figure 3, and filled with a sample of the powder, whilst the shutter was closed. The shutter was opened and the powder allowed to flow through the passage towards the outlet. If the passage outlet was too small, the powder would not be able to flow through the said passage outlet. The lower most cylinder was then removed so that the passage had a larger diameter. The bottom cylinder was removed from the lower end of the apparatus until the smallest bore through which the powder could flow freely was determined. This bore opening was taken as the critical orifice diameter of the powder. A smaller critical orifice diameter value indicated better flow. The critical orifice diameter of

each excipient was determined as the average (of 3 successive runs) of the smallest orifice through which the powder flowed freely on.

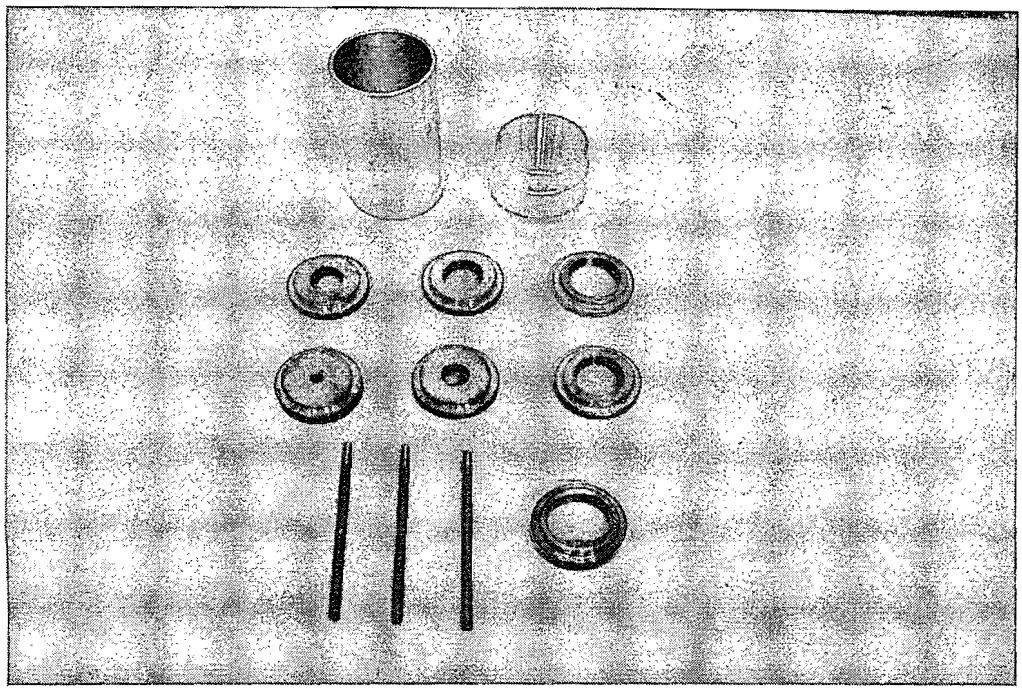


Figure 1: The various components of the flow meter.

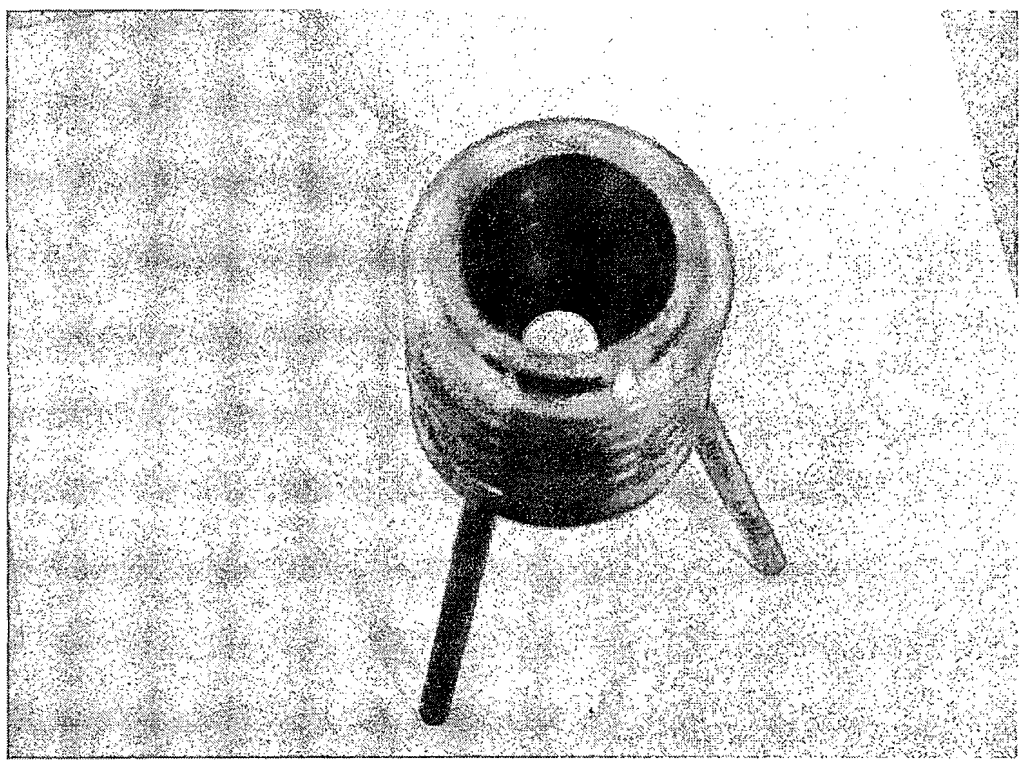


Figure 2: Set-up showing the funnel formed by the cylinders when stacked correctly.

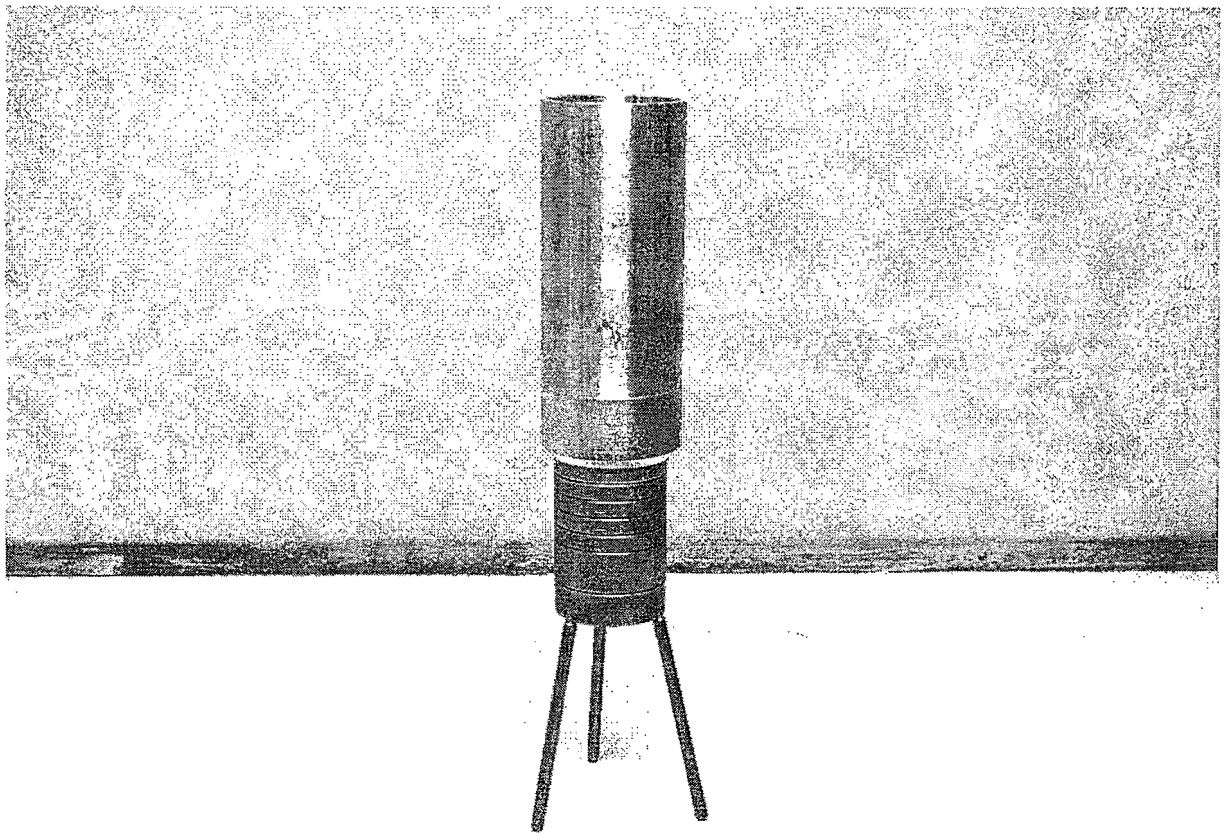


Figure 3: *A picture showing the set-up of the flow meter.*

Angle of repose

Approximately 200 ml of powder was poured through a funnel from a height of 8 cm onto a leveled glass plate. The angle of repose (θ) was determined from the angle that the side of the conical powder heap made with the horizontal plane. Lower angles of repose represent better flow.

Carr's Index (Percent compressibility index)

Approximately 100 ml of powder was gently poured into a tared graduated cylinder and the initial volume and weight of the material was noted. The cylinder was vibrated until the volume remained constant and the final volume was noted. Lower percent compressibility values represent better flow (see equation below)

Composite Index

The composite index (CI) of each powder was calculated using the integrated equations supplied by Taylor *et al.* (2000).

RESULTS AND DISCUSSION

Results

The results of the tests are presented in table 1, whilst figure 4 provides a graphical view of the data.

Table 1: ***The COD, AOR, %C and composite index (CI) of the various excipients.***

EXCIPIENT	COD (MM)	AOR (DEGREES)	% C	CI
AVICEL® PH-200	**1.5**	**32.5**	**18.0**	**89.1**
CHITOSAN	**12.0**	**45.8**	**34.7**	**57.4**
EMCOCELL® 50M	**24.0**	**41.7**	**28.3**	**51.1**
EMCOCELL® 90M	**11.0**	**37.5**	**25.0**	**70.6**
EMCOMPRESS®	**1.5**	**36.8**	**16.0**	**87.6**
LUDIPRESS®	**2.0**	**34.1**	**17.3**	**88.0**
TABLETTOSE®	**6.0**	**34.1**	**17.3**	**77.3**
PROSOLV®SMCC50	**16.0**	**39.2**	**30.3**	**60.3**
PROSOLV®SMCC90	**9.0**	**38.0**	**25.3**	**72.2**

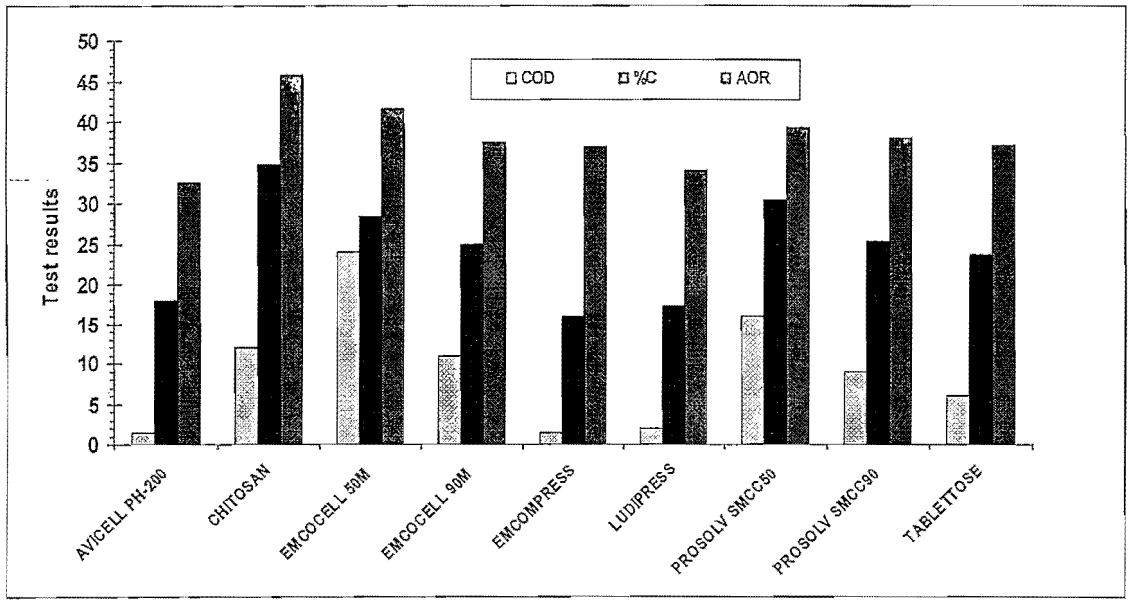


Figure 4: ***Graphical presentation of the results of different flow tests on various pharmaceutical excipients.***

Figure 5 shows the relationship between the test results (COD, %C and AOR) of the excipients and the composite index for that particular excipient.

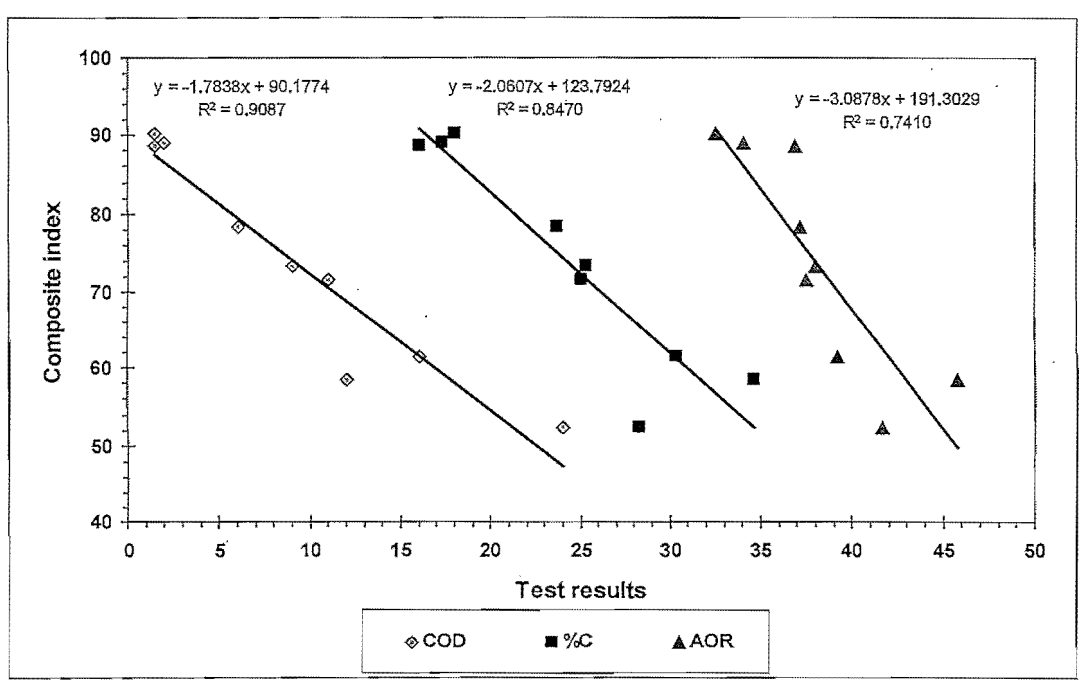


Figure 5: ***Relationship between the composite index and the COD, %C and AOR of the various pharmaceutical excipients.***

Discussion

All three tests could distinguish between the flow properties of the excipients that were tested. The difference between the results for a particular test however varied from 16x for the COD, 2.2x for the %C and 1.4x for the AOR, indicating a much higher degree of sensitivity for differences in powder flow obtained with the test for COD than for the other two tests (table 1 and figure 4). These results could possible be contributed to the specific design of the flow meter used to determine the COD, especially the material used, the angle of the tapered funnel and the absence of static areas in the apparatus.

The low COD's (1.5 to 2.0 mm) measured for Avicel® PH200, Ludipress® and Emcompress® clearly demonstrated the ability of the flow meter to identify (recognize) excellent flow properties and its ability to distinguish / discriminate between powders with subtle differences in flow.

The relationship between the COD and the composite index showed a much higher correlation over the entire range of excipients tested ($r^2 > 0.91$), compared to values of $r^2 > 0.84$ for the %C and $r^2 > 0.74$ for the AOR, which emphasized the accuracy of the COD (and the apparatus used) as an indicator of powder flow (figure 5).

Interestingly, although maybe not significant, there was a higher correlation between the results from the tests for %C and the COD ($r^2 \approx 0.598$) than between the AOR and the COD ($r^2 \approx 0.484$), whilst the highest correlation was obtained between the results from the tests for AOR and %C ($r^2 \approx 0.774$).

CONCLUSIONS

- All three tests could separate between the various powders according to their inherent flowability. From figure 5 it is clear that the selected excipients could be divided into three categories, namely those with CI values:

  - between 80 and 90, namely Avicel® pH200; Emcompress® and Ludipress® (indicating excellent flow);
  - between 70 and 80, namely Tablettose®, Emcocell® 90M and Prosolv® SMCC90 (good to fair flow) and

- below 70, namely chitosan, Emcocell® 50M; Prosolv® SMCC50 (poor to extremely poor flow)..

- Whilst both the test for COD and %C could accurately distinguish between powders with fair/good to good/excellent flow (concluded form the deviation of the individual scores from the straight lines drawn through the scores), all three tests somewhat fall short in accurately measuring the flow properties of the powders with poor to extremely poor flow (indicated by a much larger deviation from the respective lines).

- The composite index, as constructed by Taylor *et al.* (2000), provides an extremely accurate estimate of the flowability of powders. However, due to the apparent higher accuracy or sensitivity of the COD test (compared to the other two tests used in determining the CI), this model can perhaps be refined by increasing the weight assigned to this parameter in the determination of the composite index. Furthermore, the inclusion of the flow rate of powders (which is an important factor in high-speed tablet production) could also be introduced into this model.

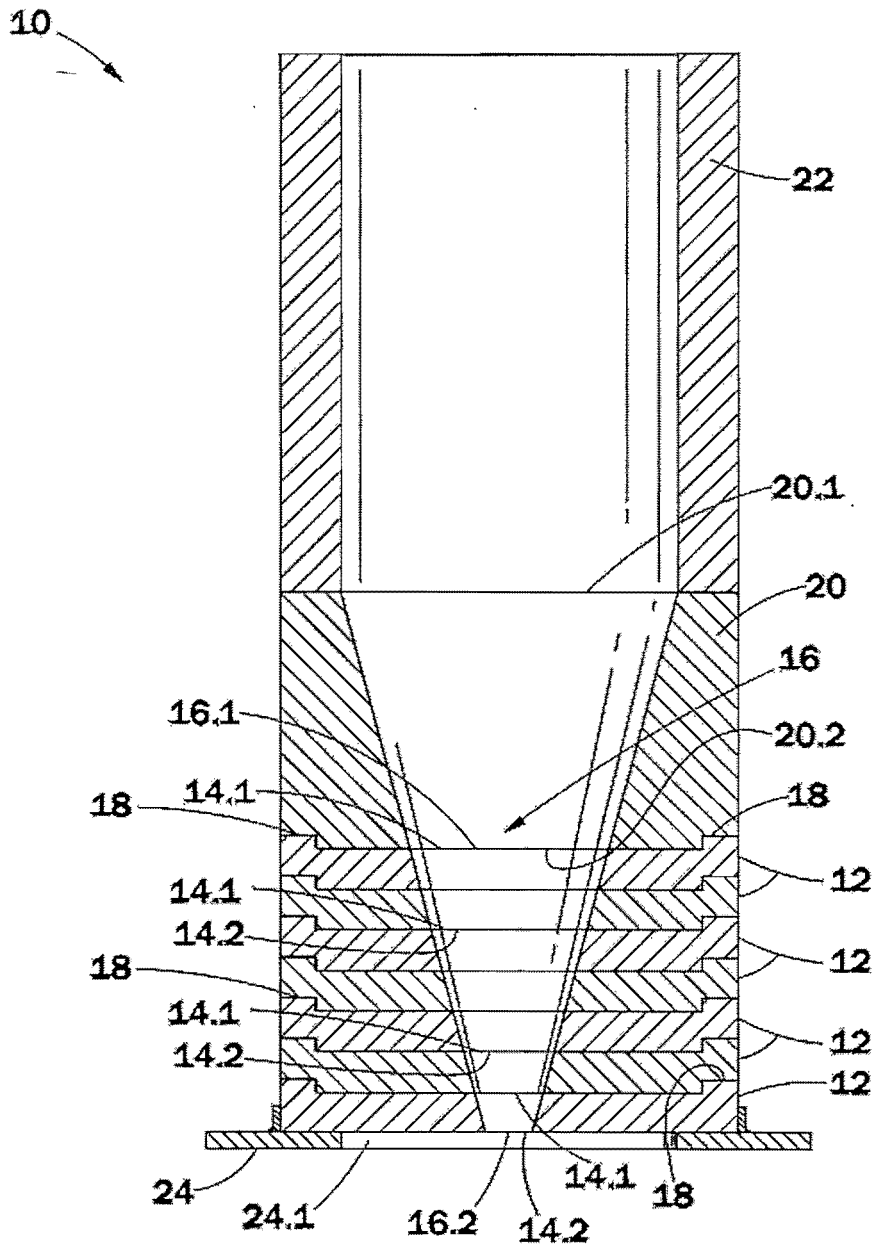
- The flow meter can also be used to accurately determine the flow rate of pharmaceutical powders through the critical orifice diameter for each powder.

REFERENCES

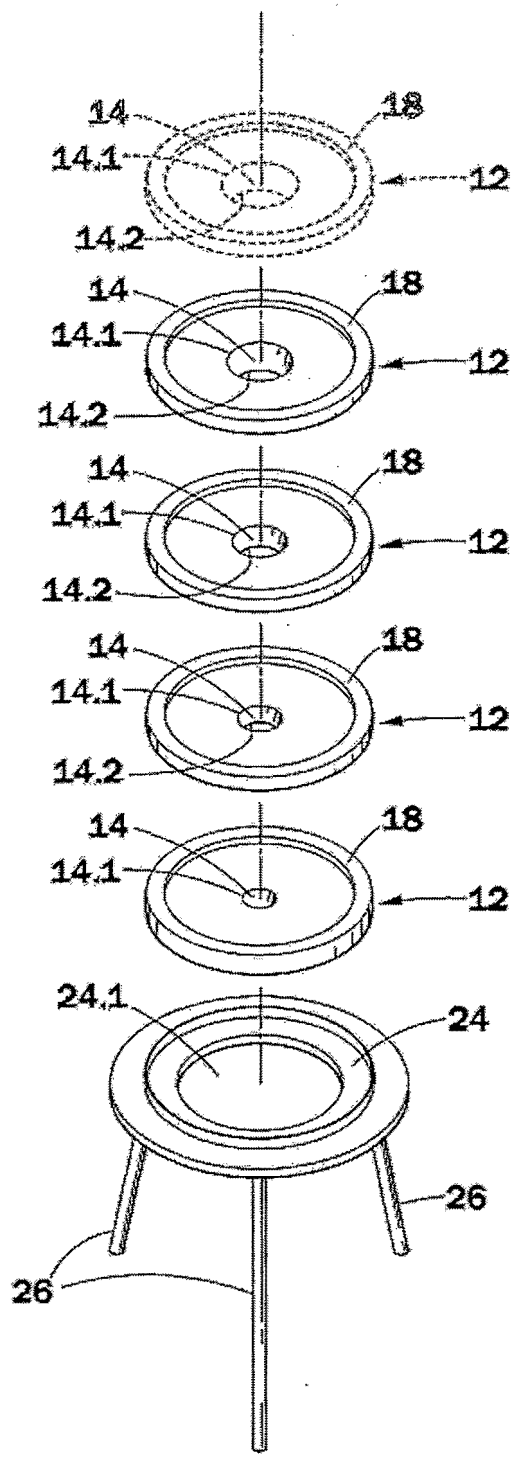
- **TAYLOR, M.K., GINSBURG, J., HICKEY, A.J. & GHEYAS, F.** 2000. Composite method to quantify powder flow as a screening method in early tablet and capsule formulation development. AAPS PharmSciTech., 1(3), article 18.

- **STANIFORH, J.** 2002. Powder flow. (***In*** Aulton, M.E. ***ed***. Pharmaceutics: the science of dosage form design. 2nd ed. Edinburgh : Churchill Livingstone. p.202-205)

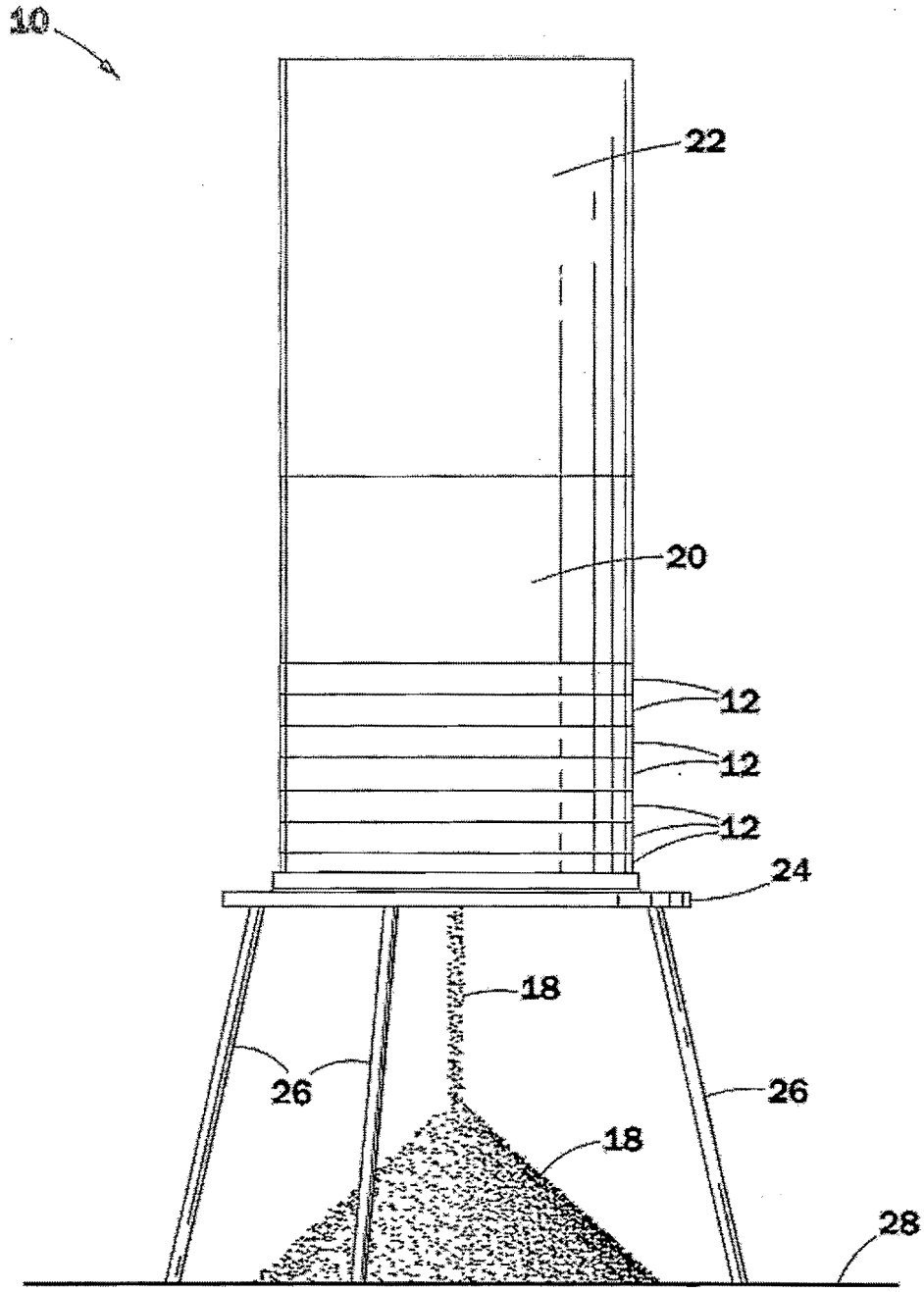
TECHNICAL DRAWINGS



Drawing 1: *Longitudinal sectional side view*



Drawing 2: *Exploded perspective view*



Drawing 3: *Side view of the apparatus*

ANNEXURE A

CHARACTERIZATION OF THE FLOWABILITY OF CHITOSAN POWDER

A.1: SIEVE ANALYSIS

Table A.1.1: *Sieve analysis of chitosan 030912.*

Chitosan 030912		
Size (µm)	**Average size (µm)**	**% Powder**
>212	212	0
180-212	196	16.44
150-180	165	14.65
125-150	137.5	28.32
106-125	115.5	12.19
90-106	98	10.87
63-90	76.5	6.97
45-63	54	9.73
<45	22.5	0.83

Table A.1.2: *Sieve analysis of chitosan 021010.*

Chitosan 021010		
Size (µm)	**Average size (µm)**	**% Powder**
>355	355	0.51
300-355	327.5	29.06
250-300	275	20.06
180-250	215	24.71
125-180	152.5	16.45
106-125	115.5	4.72
90-106	98	3.83
45-90	67.5	0.59
<45	22.5	0.07

A.2: PARTICLE SIZE ANALYSIS

Table A.2.1: *Particle size analysis for chitosan 021010. Sample 1; Run number 1.*

MASTERSIZER 2000

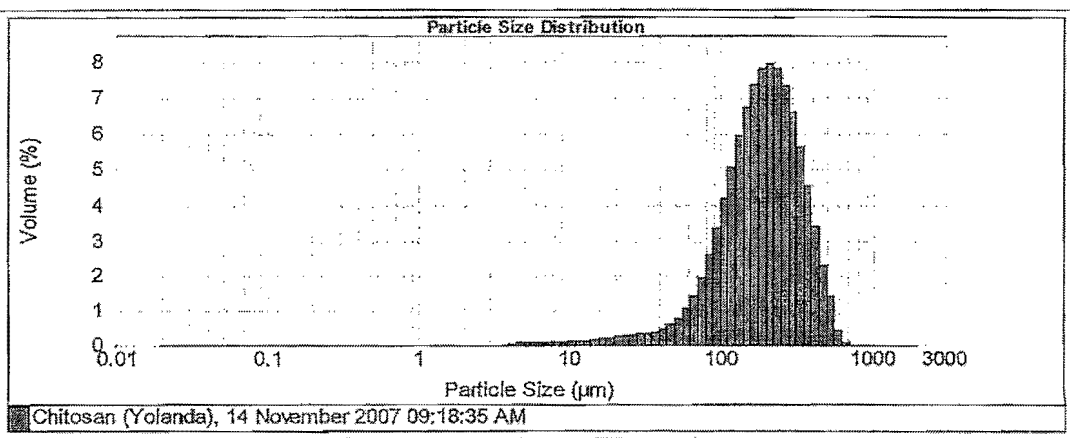
Result Analysis Report

Sample Name: Chitosan (Yolanda)	**SOP Name:** Chitosan	**Measured:** 14 November 2007 09:18:35 AM
Sample Source & type:	**Measured by:** Micron Scientific	**Analysed:** 14 November 2007 09:18:36 AM
Sample bulk lot ref: 21010 Y	**Result Source:** Measurement	

Particle Name: Talc	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 1.589	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 10.74 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 1.368 %	**Result Emulation:** Off

Concentration: 0.2005 %Vol	**Span :** 1.518	**Uniformity:** 0.469	**Result units:** Volume
Specific Surface Area: 0.0475 m²/g	**Surface Weighted Mean D[3,2]:** 126.370 um	**Vol. Weighted Mean D[4,3]:** 212.227 um	

d(0.1): 81.555 um **d(0.5):** 192.819 um **d(0.9):** 374.238 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 %
0.020	0.00	0.142	0.00	1.002	0.00	7.096	0.05	50.238	0.77	355.656	4.55
0.022	0.00	0.159	0.00	1.125	0.00	7.962	0.07	56.368	1.05	399.052	3.40
0.025	0.00	0.178	0.00	1.262	0.00	8.934	0.09	63.246	1.45	447.744	2.02
0.028	0.00	0.200	0.00	1.416	0.00	10.024	0.09	70.963	1.96	502.377	1.42
0.032	0.00	0.224	0.00	1.589	0.00	11.247	0.09	79.621	2.59	563.677	0.40
0.036	0.00	0.252	0.00	1.783	0.00	12.619	0.11	89.337	3.34	632.456	0.07
0.040	0.00	0.283	0.00	2.000	0.00	14.159	0.13	100.237	4.17	709.527	0.00
0.045	0.00	0.317	0.00	2.244	0.00	15.887	0.16	112.468	5.05	796.214	0.00
0.050	0.00	0.356	0.00	2.518	0.00	17.825	0.19	126.191	5.92	893.367	0.00
0.056	0.00	0.399	0.00	2.825	0.00	20.000	0.22	141.589	6.73	1002.374	0.00
0.063	0.00	0.448	0.00	3.170	0.00	22.440	0.25	158.865	7.37	1124.693	0.00
0.071	0.00	0.502	0.00	3.557	0.00	25.179	0.28	178.250	7.81	1261.915	0.00
0.080	0.00	0.564	0.00	3.991	0.04	28.251	0.30	200.000	7.97	1415.862	0.00
0.090	0.00	0.632	0.00	4.477	0.05	31.698	0.32	224.404	7.81	1588.655	0.00
0.100	0.00	0.710	0.00	5.024	0.05	35.569	0.35	251.785	7.34	1782.502	0.00
0.112	0.00	0.796	0.00	5.637	0.03	39.905	0.39	282.508	6.60	2000.000	0.00
0.126	0.00	0.893	0.00	6.325	0.05	44.774	0.46	316.979	5.62		
0.142	0.00	1.002	0.00	7.096	0.05	50.238	0.58	355.656	4.55		

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
Tel: +[44] (0) 1684-892456 Fax +[44] (0) 1684-892789

Mastersizer 2000 Ver. 5.31
Serial Number : MAL1007548

File name: Chitosan (Yolanda).sop
Record Number: 2
14 Nov 2007 11:50:15 AM

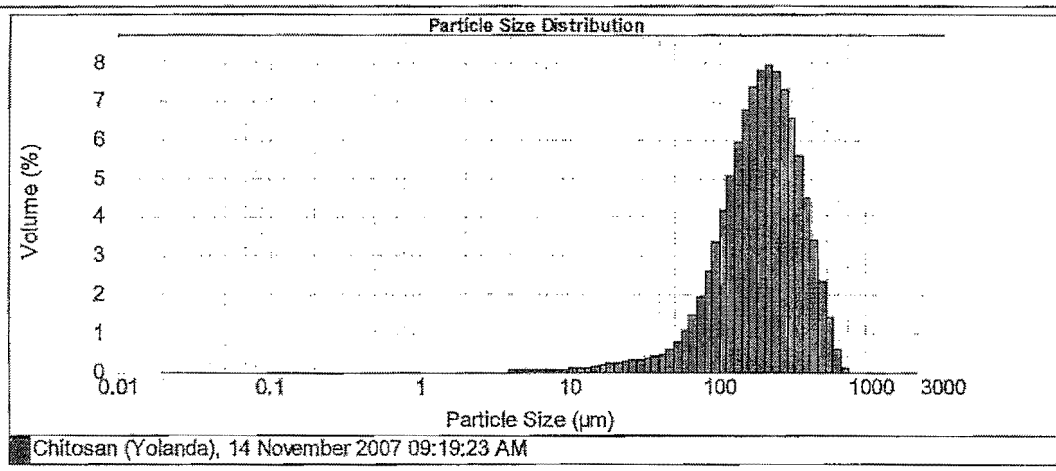
Table A.2.2: *Particle size analysis for chitosan 021010. Sample 1; Run number 2.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Chitosan (Yolanda)	**SOP Name:** Chitosan	**Measured:** 14 November 2007 09:19:23 AM	
Sample Source & type:	**Measured by:** Micron Scientific	**Analysed:** 14 November 2007 09:19:24 AM	
Sample bulk lot ref: 21010 Y	**Result Source:** Measurement		
Particle Name: Talc	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 1.589	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 13.23 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 1.323 %	**Result Emulation:** Off
Concentration: 0.2488 %Vol	**Span :** 1.529	**Uniformity:** 0.473	**Result units:** Volume
Specific Surface Area: 0.0478 m²/g	**Surface Weighted Mean D[3,2]:** 125.549 um	**Vol. Weighted Mean D[4,3]:** 212.565 um	

d(0.1): 81.155 um **d(0.5):** 192.550 um **d(0.9):** 375.671 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 %
0.020	0.00	0.142	0.00	1.002	0.00	7.096	0.05	50.238	0.78	355.656	1.49
0.022	0.00	0.159	0.00	1.125	0.00	7.962	0.07	56.368	1.05	399.052	3.37
0.025	0.00	0.178	0.00	1.262	0.00	8.934	0.07	63.246	1.44	447.744	2.32
0.028	0.00	0.200	0.00	1.416	0.00	10.024	0.09	70.963	1.95	502.377	1.40
0.032	0.00	0.224	0.00	1.589	0.00	11.247	0.09	79.621	2.59	563.677	0.60
0.036	0.00	0.252	0.00	1.783	0.00	12.619	0.11	89.337	3.34	632.466	0.09
0.040	0.00	0.283	0.00	2.000	0.00	14.159	0.13	100.237	4.17	709.627	0.00
0.045	0.00	0.317	0.00	2.244	0.00	15.887	0.16	112.468	5.05	796.214	0.00
0.050	0.00	0.356	0.00	2.518	0.00	17.825	0.19	126.191	5.93	893.367	0.00
0.056	0.00	0.399	0.00	2.825	0.00	20.000	0.22	141.569	6.73	1002.374	0.00
0.063	0.00	0.449	0.00	3.170	0.00	22.440	0.25	158.866	7.37	1124.893	0.00
0.071	0.00	0.502	0.00	3.557	0.00	25.179	0.28	178.250	7.80	1261.915	0.00
0.080	0.00	0.564	0.00	3.991	0.00	28.251	0.31	200.000	7.95	1415.692	0.00
0.089	0.00	0.632	0.00	4.477	0.04	31.696	0.33	224.404	7.78	1588.653	0.00
0.100	0.00	0.710	0.00	5.024	0.05	35.566	0.36	251.785	7.29	1782.502	0.00
0.112	0.00	0.795	0.00	5.637	0.05	39.905	0.40	282.509	6.54	2000.000	0.00
0.126	0.00	0.893	0.00	6.325	0.05	44.774	0.47	316.979	5.57		
0.142	0.00	1.002	0.00	7.096	0.05	50.238	0.59	355.656	4.57		

Operator notes:

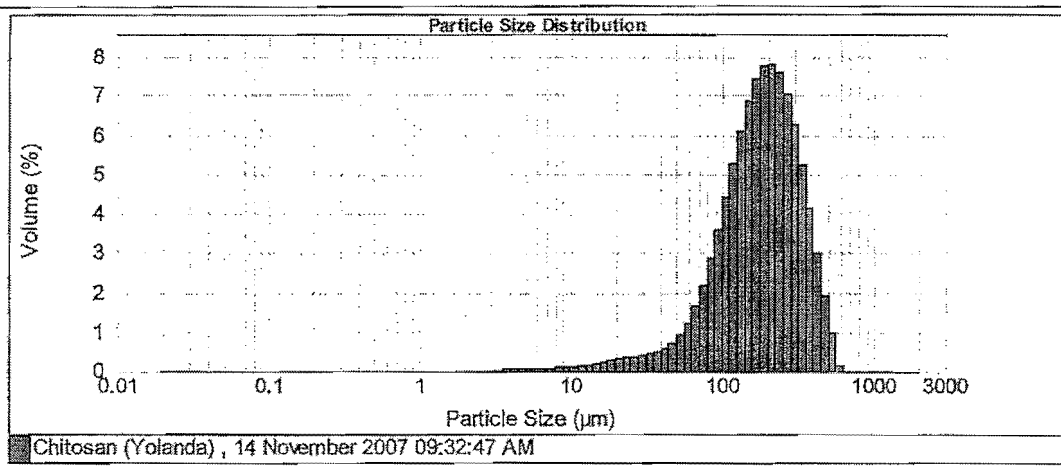
Table A.2.3: *Particle size analysis for chitosan 021010. Sample 2; Run number 1.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Chitosan (Yolanda)	**SOP Name:** Chitosan		**Measured:** 14 November 2007 09:32:47 AM
Sample Source & type: 2nd SAMPLE	**Measured by:** Micron Scientific		**Analysed:** 14 November 2007 09:32:48 AM
Sample bulk lot ref: 21010 Y	**Result Source:** Measurement		
Particle Name: Talc	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 1.589	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 16.61 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 1.653 %	**Result Emulation:** Off
Concentration: 0.2809 %Vol	**Span :** 1.546	**Uniformity:** 0.479	**Result units:** Volume
Specific Surface Area: 0.0539 m^2/g	**Surface Weighted Mean D[3,2]:** 111.269 um	**Vol. Weighted Mean D[4,3]:** 201.118 um	

d(0.1): 73.636 um **d(0.5):** 183.415 um **d(0.9):** 357.256 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 %
0.020	0.00	0.142	0.00	1.002	0.00	7.096	0.09	50.238	0.93	355.656	4.15
0.022	0.00	0.159	0.00	1.125	0.00	7.962	0.09	56.368	1.23	399.052	3.00
0.025	0.00	0.178	0.00	1.262	0.00	8.934	0.10	63.246	1.66	447.744	1.92
0.028	0.00	0.200	0.00	1.416	0.00	10.024	0.12	70.963	2.19	502.377	0.98
0.032	0.00	0.224	0.00	1.589	0.00	11.247	0.14	79.621	2.85	563.677	0.14
0.036	0.00	0.252	0.00	1.783	0.00	12.619	0.17	89.337	3.61	632.456	0.00
0.040	0.00	0.283	0.00	2.000	0.00	14.159	0.20	100.237	4.43	709.627	0.00
0.045	0.00	0.317	0.00	2.244	0.00	15.887	0.24	112.468	5.29	796.214	0.00
0.050	0.00	0.356	0.00	2.518	0.00	17.825	0.28	126.191	6.11	893.357	0.00
0.056	0.00	0.399	0.00	2.825	0.00	20.000	0.31	141.589	6.85	1002.374	0.00
0.063	0.00	0.448	0.00	3.170	0.01	22.440	0.35	158.866	7.42	1124.583	0.00
0.071	0.00	0.502	0.00	3.557	0.07	25.179	0.37	178.250	7.76	1261.915	0.00
0.080	0.00	0.564	0.00	3.991	0.07	28.251	0.40	200.000	7.83	1415.892	0.00
0.089	0.00	0.632	0.00	4.477	0.07	31.699	0.44	224.404	7.59	1588.655	0.00
0.100	0.00	0.710	0.00	5.024	0.06	35.566	0.49	251.785	7.06	1782.502	0.00
0.112	0.00	0.796	0.00	5.637	0.06	39.905	0.58	282.508	6.26	2000.000	0.00
0.126	0.00	0.893	0.00	6.325	0.06	44.774	0.71	316.979	5.29		
0.142	0.00	1.002	0.00	7.096	0.06	50.238	0.71	355.656	5.29		

Operator notes:

Table A.2.4: *Particle size analysis for chitosan 021010. Sample 2; Run number 2.*

MASTERSIZER 2000

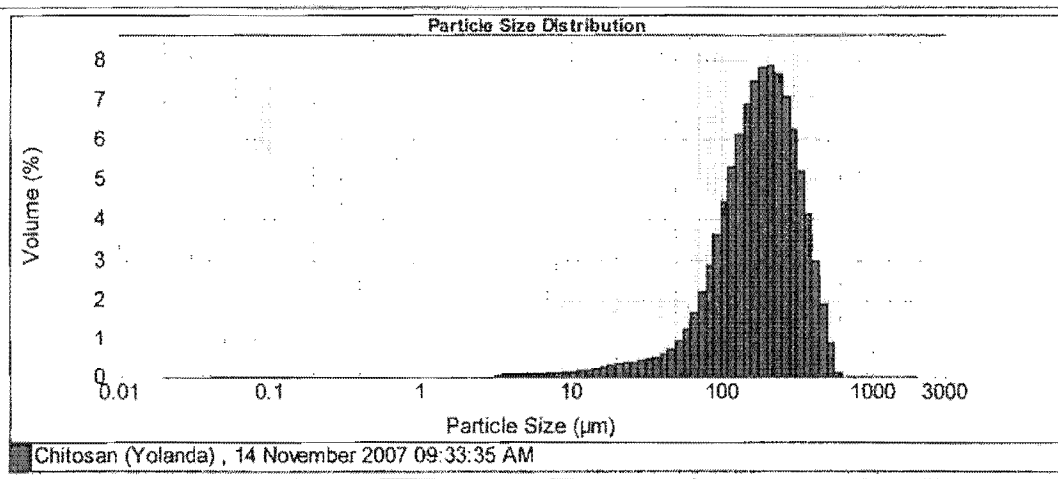
Result Analysis Report

Sample Name: Chitosan (Yolanda)	**SOP Name:** Chitosan	**Measured:** 14 November 2007 09:33:35 AM
Sample Source & type: 2nd SAMPLE	**Measured by:** Micron Scientific	**Analysed:** 14 November 2007 09:33:36 AM
Sample bulk lot ref: 21010 Y	**Result Source:** Measurement	

Particle Name: Talc	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 1.589	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 16.60 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 1.773 %	**Result Emulation:** Off

Concentration: 0.2793 %Vol	**Span :** 1.539	**Uniformity:** 0.477	**Result units:** Volume
Specific Surface Area: 0.0542 m²/g	**Surface Weighted Mean D[3,2]:** 110.761 um	**Vol. Weighted Mean D[4,3]:** 200.292 um	

d(0.1): 73.558 um d(0.5): 182.937 um d(0.9): 355.169 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 %
0.020	0.00	0.142	0.00	1.002	0.00	7.096	0.09	50.238	0.93	355.656	4.11
0.022	0.00	0.159	0.00	1.125	0.00	7.962	0.09	56.368	1.23	399.052	2.95
0.025	0.00	0.178	0.00	1.262	0.00	8.934	0.11	63.246	1.55	447.744	1.87
0.028	0.00	0.200	0.00	1.416	0.00	10.024	0.12	70.963	2.19	502.377	0.90
0.032	0.00	0.224	0.00	1.589	0.00	11.247	0.14	79.621	2.86	563.677	0.12
0.036	0.00	0.252	0.00	1.783	0.00	12.619	0.17	89.337	3.61	632.459	0.00
0.040	0.00	0.283	0.00	2.000	0.00	14.159	0.21	100.237	4.44	709.627	0.00
0.045	0.00	0.317	0.00	2.244	0.00	15.887	0.24	112.468	5.31	796.214	0.00
0.050	0.00	0.356	0.00	2.518	0.00	17.825	0.28	126.191	6.14	893.397	0.00
0.056	0.00	0.399	0.00	2.825	0.00	20.000	0.31	141.589	6.89	1002.374	0.00
0.063	0.00	0.448	0.00	3.170	0.01	22.440	0.35	158.866	7.45	1124.683	0.00
0.071	0.00	0.502	0.00	3.557	0.07	25.179	0.38	178.250	7.80	1261.915	0.00
0.080	0.00	0.564	0.00	3.991	0.07	28.251	0.40	200.000	7.88	1415.892	0.00
0.089	0.00	0.632	0.00	4.477	0.08	31.698	0.44	224.404	7.51	1588.606	0.00
0.100	0.00	0.710	0.00	5.024	0.08	35.565	0.49	251.785	7.05	1782.502	0.00
0.112	0.00	0.796	0.00	5.637	0.08	39.905	0.57	282.508	6.24	2000.000	0.00
0.126	0.00	0.893	0.00	6.325	0.08	44.774	0.71	316.979	5.22		
0.142	0.00	1.002	0.00	7.096	0.08	50.238	0.71	355.656	5.22		

Operator notes:

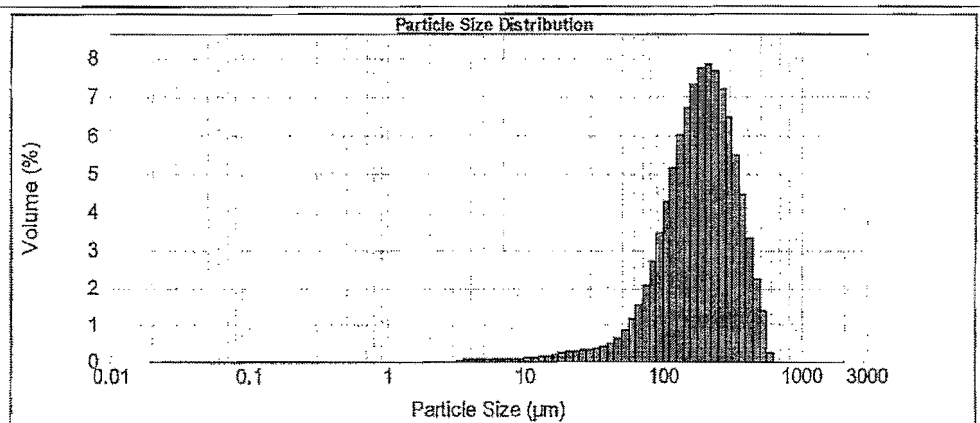
Table A.2.5: *Particle size analysis for chitosan 021010. Sample 3; Run number 1.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Chitosan (Yolanda)	**SOP Name:** Chitosan		**Measured:** 14 November 2007 09:42:25 AM
Sample Source & type: 3rd SAMPLE	**Measured by:** Micron Scientific		**Analysed:** 14 November 2007 09:42:26 AM
Sample bulk lot ref: 21010 Y	**Result Source:** Measurement		
Particle Name: Talc	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 1.589	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 15.02 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 1.637 %	**Result Emulation:** Off
Concentration: 0.2732 %Vol	**Span :** 1.532	**Uniformity:** 0.472	**Result units:** Volume
Specific Surface Area: 0.0498 m²/g	**Surface Weighted Mean D[3,2]:** 120.511 um	**Vol. Weighted Mean D[4,3]:** 208.334 um	

d(0.1): 78.799 um **d(0.5):** 189.435 um **d(0.9):** 369.039 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 %
0.020	0.00	0.142	0.00	1.002	0.00	7.095	0.07	50.238	0.83	355.656	4.44
0.022	0.00	0.159	0.00	1.125	0.00	7.962	0.07	56.368	1.13	399.052	3.30
0.025	0.00	0.178	0.00	1.262	0.00	8.934	0.08	63.249	1.54	447.744	2.23
0.028	0.00	0.200	0.00	1.416	0.00	10.024	0.10	70.993	2.07	502.377	1.35
0.032	0.00	0.224	0.00	1.589	0.00	11.247	0.12	79.621	2.71	563.677	0.72
0.036	0.00	0.252	0.00	1.783	0.00	12.618	0.12	89.337	3.46	632.456	0.00
0.040	0.00	0.283	0.00	2.000	0.00	14.159	0.14	100.237	4.28	709.627	0.00
0.045	0.00	0.317	0.00	2.244	0.00	15.887	0.17	112.466	5.15	796.214	0.00
0.050	0.00	0.356	0.00	2.519	0.00	17.825	0.20	126.191	5.99	893.367	0.00
0.056	0.00	0.399	0.00	2.825	0.00	20.000	0.23	141.599	6.78	1002.374	0.00
0.063	0.00	0.448	0.00	3.170	0.00	22.440	0.26	158.809	7.56	1124.683	0.00
0.071	0.00	0.502	0.00	3.557	0.01	25.179	0.29	178.250	7.76	1261.915	0.00
0.080	0.00	0.564	0.00	3.991	0.05	28.251	0.31	200.000	7.66	1415.992	0.00
0.089	0.00	0.632	0.00	4.477	0.05	31.698	0.34	224.404	7.70	1588.656	0.00
0.100	0.00	0.710	0.00	5.024	0.06	35.568	0.37	251.785	7.21	1782.532	0.00
0.112	0.00	0.796	0.00	5.637	0.06	39.905	0.42	282.509	6.47	2000.000	0.00
0.126	0.00	0.893	0.00	6.325	0.06	44.774	0.50	316.979	5.50		
0.142	0.00	1.002	0.00	7.095	0.06	50.238	0.63	355.656	4.50		

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
Tel: +[illegible] Fax +[illegible]

Mastersizer 2000 Ver. 5.31
Serial Number : MAL1007548

File name: Chitosan (Yolanda).sop
Record Number: 6
14 Nov 2007 11:58:37 AM

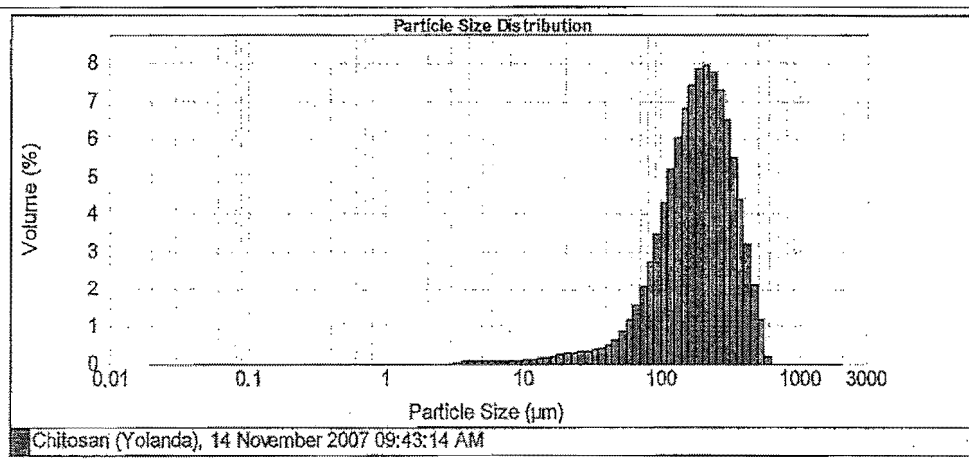
Table A.2.6: *Particle size analysis for chitosan 021010. Sample 3; Run number 2.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Chitosan (Yolanda)	**SOP Name:** Chitosan		**Measured:** 14 November 2007 09:43:14 AM
Sample Source & type: 3rd SAMPLE	**Measured by:** Micron Scientific		**Analysed:** 14 November 2007 09:43:15 AM
Sample bulk lot ref: 21010 Y	**Result Source:** Measurement		
Particle Name: Talc	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 1.589	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 15.07 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 1.711 %	**Result Emulation:** Off
Concentration: 0.2723 %Vol	**Span :** 1.517	**Uniformity:** 0.468	**Result units:** Volume
Specific Surface Area: 0.0501 m^2/g	**Surface Weighted Mean D[3,2]:** 119.659 um	**Vol. Weighted Mean D[4,3]:** 206.596 um	

d(0.1): 78.462 um **d(0.5):** 188.503 um **d(0.9):** 364.470 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 %
0.020	0.00	0.142	0.00	1.002	0.00	7.095	0.07	50.238	0.84	355.656	4.36
0.022	0.00	0.159	0.00	1.125	0.00	7.962	0.07	56.368	1.14	399.052	3.21
0.025	0.00	0.178	0.00	1.262	0.00	8.934	0.09	63.246	1.55	447.744	2.10
0.028	0.00	0.200	0.00	1.416	0.00	10.024	0.10	70.963	2.09	502.377	1.16
0.032	0.00	0.224	0.00	1.589	0.00	11.247	0.12	79.621	2.72	563.677	0.18
0.036	0.00	0.252	0.00	1.783	0.00	12.619	0.14	89.337	3.48	632.456	0.00
0.040	0.00	0.283	0.00	2.000	0.00	14.159	0.17	100.237	4.30	709.627	0.00
0.045	0.00	0.317	0.00	2.244	0.00	15.887	0.20	112.468	5.19	796.214	0.00
0.050	0.00	0.356	0.00	2.518	0.00	17.825	0.24	126.191	6.03	893.367	0.00
0.056	0.00	0.399	0.00	2.825	0.00	20.000	0.27	141.569	6.60	1002.374	0.00
0.063	0.00	0.448	0.00	3.170	0.01	22.440	0.29	158.868	7.42	1124.583	0.00
0.071	0.00	0.502	0.00	3.557	0.03	25.179	0.32	178.250	7.82	1261.915	0.00
0.080	0.00	0.564	0.00	3.991	0.05	28.251	0.34	200.000	7.94	1415.892	0.00
0.089	0.00	0.632	0.00	4.477	0.06	31.698	0.37	224.404	7.76	1588.855	0.00
0.100	0.00	0.710	0.00	5.024	0.06	35.566	0.42	251.785	7.25	1782.602	0.00
0.112	0.00	0.796	0.00	5.637	0.05	39.905	0.50	282.508	6.48	2000.000	
0.126	0.00	0.893	0.00	6.325	0.05	44.774	0.63	316.979	5.48		
0.142	0.00	1.002	0.00	7.096	0.06	50.238	0.83	355.656			

Operator notes:

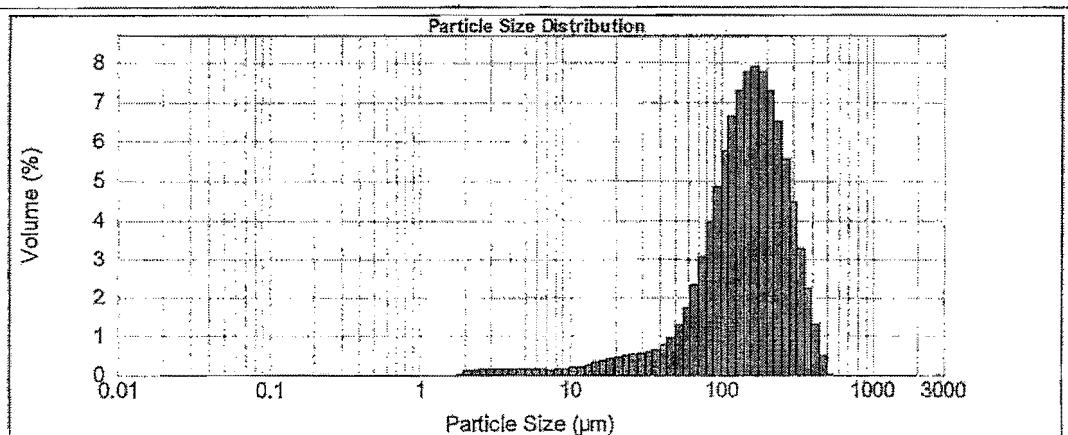
Table A.2.7: *Particle size analysis for chitosan 030912. Sample 1; Run number 1.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Chitosan (Yolanda)	**SOP Name:** Chitosan	**Measured:** 14 November 2007 09:51:42 AM	
Sample Source & type: 1st SAMPLE	**Measured by:** Micron Scientific	**Analysed:** 14 November 2007 09:51:43 AM	
Sample bulk lot ref: 30912 X	**Result Source:** Measurement		
Particle Name: Talc	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 1.589	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 13.48 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 1.841 %	**Result Emulation:** Off
Concentration: 0.1370 %Vol	**Span :** 1.576	**Uniformity:** 0.487	**Result units:** Volume
Specific Surface Area: 0.0856 m²/g	**Surface Weighted Mean D[3,2]:** 70.060 um	**Vol. Weighted Mean D[4,3]:** 165.084 um	

d(0.1): 56.460 um **d(0.5):** 151.263 um **d(0.9):** 294.852 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 %
0.020	0.00	0.142	0.00	1.002	0.00	7.096	0.13	50.238	1.27	355.656	2.24
0.022	0.00	0.159	0.00	1.125	0.00	7.962	0.13	56.368	1.73	399.052	1.29
0.025	0.00	0.178	0.00	1.262	0.00	8.934	0.15	63.245	2.34	447.744	0.50
0.028	0.00	0.200	0.00	1.416	0.00	10.024	0.18	70.963	3.08	502.377	0.02
0.032	0.00	0.224	0.00	1.589	0.00	11.247	0.21	79.621	3.94	563.877	0.00
0.036	0.00	0.252	0.00	1.783	0.00	12.619	0.26	89.337	4.88	632.456	0.00
0.040	0.00	0.283	0.00	2.000	0.03	14.159	0.31	100.237	5.77	709.627	0.00
0.045	0.00	0.317	0.00	2.244	0.10	15.887	0.37	112.466	6.82	796.214	0.00
0.050	0.00	0.356	0.00	2.518	0.12	17.825	0.42	126.191	7.28	893.387	0.00
0.056	0.00	0.399	0.00	2.825	0.14	20.000	0.47	141.599	7.74	1002.374	0.00
0.063	0.00	0.448	0.00	3.170	0.15	22.440	0.50	158.905	7.86	1124.683	0.00
0.071	0.00	0.502	0.00	3.557	0.16	25.179	0.52	178.250	7.73	1261.915	0.00
0.080	0.00	0.564	0.00	3.991	0.17	28.251	0.54	200.000	7.25	1416.892	0.00
0.089	0.00	0.632	0.00	4.477	0.17	31.698	0.57	224.404	6.49	1589.658	0.00
0.100	0.00	0.710	0.00	5.024	0.16	35.566	0.63	251.785	5.52	1782.502	0.00
0.112	0.00	0.796	0.00	5.637	0.15	39.905	0.74	282.508	4.43	2000.000	
0.126	0.00	0.893	0.00	6.325	0.14	44.774	0.95	316.979	3.30		
0.142	0.00	1.002	0.00	7.096	0.13	50.238	0.95	355.656	2.24		

Operator notes:

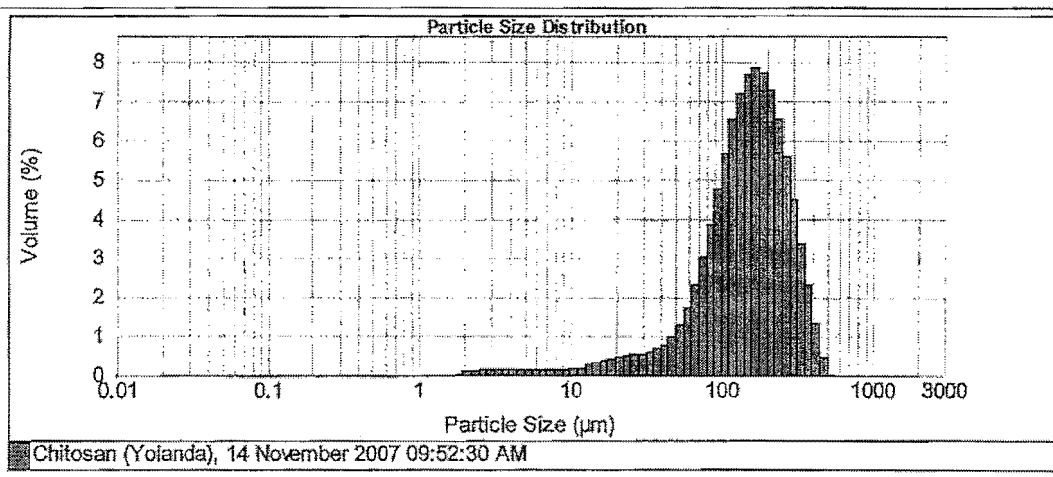
Table A.2.8: *Particle size analysis for chitosan 030912. Sample 1; Run number 2.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Chitosan (Yolanda)	**SOP Name:** Chitosan		**Measured:** 14 November 2007 09:52:30 AM
Sample Source & type: 1st SAMPLE	**Measured by:** Micron Scientific		**Analysed:** 14 November 2007 09:52:31 AM
Sample bulk lot ref: 30912 X	**Result Source:** Measurement		
Particle Name: Talc	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 1.589	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 13.40 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 2.147 %	**Result Emulation:** Off
Concentration: 0.1354 %Vol	**Span :** 1.585	**Uniformity:** 0.488	**Result units:** Volume
Specific Surface Area: 0.086 m^2/g	**Surface Weighted Mean D[3,2]:** 69.735 um	**Vol. Weighted Mean D[4,3]:** 165.677 um	

d(0.1): 55.643 um **d(0.5):** 152.001 um **d(0.9):** 296.564 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 %
0.020	0.00	0.142	0.00	1.002	0.00	7.096	0.13	50.238	1.27	355.856	2.32
0.022	0.00	0.159	0.00	1.125	0.00	7.962	0.14	56.369	1.72	399.052	1.32
0.025	0.00	0.178	0.00	1.262	0.00	8.934	0.15	63.246	2.31	447.744	0.46
0.028	0.00	0.200	0.00	1.416	0.00	10.024	0.18	70.963	3.04	502.377	0.01
0.032	0.00	0.224	0.00	1.589	0.00	11.247	0.21	79.621	3.88	563.677	0.00
0.036	0.00	0.252	0.00	1.783	0.03	12.619	0.25	89.337	4.79	632.456	0.00
0.040	0.00	0.283	0.00	2.000	0.10	14.159	0.29	100.237	5.69	709.527	0.00
0.045	0.00	0.317	0.00	2.244	0.12	15.887	0.32	112.466	6.53	796.214	0.00
0.050	0.00	0.356	0.00	2.518	0.14	17.825	0.37	126.191	7.20	893.357	0.00
0.056	0.00	0.399	0.00	2.825	0.16	20.000	0.43	141.589	7.67	1002.574	0.00
0.063	0.00	0.448	0.00	3.170	0.17	22.440	0.47	158.866	7.85	1124.883	0.00
0.071	0.00	0.502	0.00	3.557	0.17	25.179	0.51	178.250	7.72	1261.916	0.00
0.080	0.00	0.564	0.00	3.991	0.17	28.251	0.54	200.000	7.27	1415.892	0.00
0.089	0.00	0.632	0.00	4.477	0.16	31.698	0.58	224.404	6.55	1588.668	0.00
0.100	0.00	0.710	0.00	5.024	0.15	35.565	0.65	251.785	5.60	1782.502	0.00
0.112	0.00	0.795	0.00	5.637	0.14	39.905	0.76	282.508	4.53	2000.000	0.00
0.126	0.00	0.893	0.00	6.325	0.14	44.774	0.96	316.979	3.39		
0.142	0.00	1.002	0.00	7.096	0.14	50.238	0.96	355.856	2.32		

Operator notes:

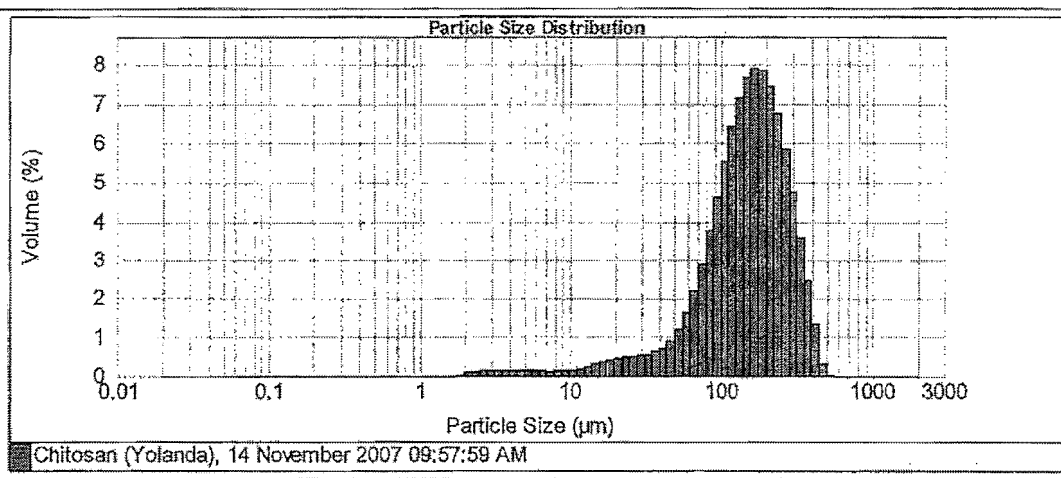
Table A.2.9: *Particle size analysis for chitosan 030912. Sample 2; Run number 1.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Chitosan (Yolanda)	**SOP Name:** Chitosan		**Measured:** 14 November 2007 09:57:59 AM
Sample Source & type: 2nd SAMPLE	**Measured by:** Micron Scientific		**Analysed:** 14 November 2007 09:58:00 AM
Sample bulk lot ref: 30912 X	**Result Source:** Measurement		
Particle Name: Talc	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 1.589	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 15.24 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 3.071 %	**Result Emulation:** Off
Concentration: 0.1585 %Vol	**Span :** 1.558	**Uniformity:** 0.48	**Result units:** Volume
Specific Surface Area: 0.0844 m²/g	**Surface Weighted Mean D[3,2]:** 71.063 um	**Vol. Weighted Mean D[4,3]:** 167.808 um	

d(0.1): 57.459 um **d(0.5):** 154.833 um **d(0.9):** 298.669 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 %
0.020	0.00	0.142	0.00	1.002	0.00	7.056	0.13	50.238	1.20	355.656	2.45
0.022	0.00	0.159	0.00	1.125	0.00	7.962	0.13	56.368	1.62	399.062	1.31
0.025	0.00	0.178	0.00	1.262	0.00	8.934	0.15	63.246	2.20	447.744	0.34
0.028	0.00	0.200	0.00	1.416	0.00	10.024	0.17	70.953	2.91	502.377	0.01
0.032	0.00	0.224	0.00	1.589	0.00	11.247	0.21	79.621	3.75	563.677	0.00
0.036	0.00	0.252	0.00	1.783	0.00	12.619	0.25	89.337	4.66	632.456	0.00
0.040	0.00	0.283	0.00	2.000	0.03	14.159	0.31	100.237	5.57	709.627	0.00
0.045	0.00	0.317	0.00	2.244	0.10	15.887	0.36	112.468	6.44	796.214	0.00
0.050	0.00	0.356	0.00	2.518	0.12	17.825	0.42	126.191	7.16	893.367	0.00
0.056	0.00	0.399	0.00	2.825	0.14	20.000	0.46	141.589	7.67	1002.374	0.00
0.063	0.00	0.448	0.00	3.170	0.15	22.440	0.50	158.866	7.91	1124.683	0.00
0.071	0.00	0.502	0.00	3.557	0.16	25.179	0.52	178.250	7.85	1261.915	0.00
0.080	0.00	0.564	0.00	3.991	0.17	28.251	0.54	200.000	7.49	1415.892	0.00
0.089	0.00	0.632	0.00	4.477	0.16	31.698	0.56	224.404	6.77	1588.856	0.00
0.100	0.00	0.710	0.00	5.024	0.16	35.566	0.61	251.785	5.94	1782.502	0.00
0.112	0.00	0.796	0.00	5.637	0.15	39.905	0.72	282.508	4.78	2000.000	
0.125	0.00	0.893	0.00	6.325	0.14	44.774	0.80	316.979	3.58		
0.142	0.00	1.002	0.00	7.096	0.13	50.238	0.80	355.656	2.45		

Operator notes:

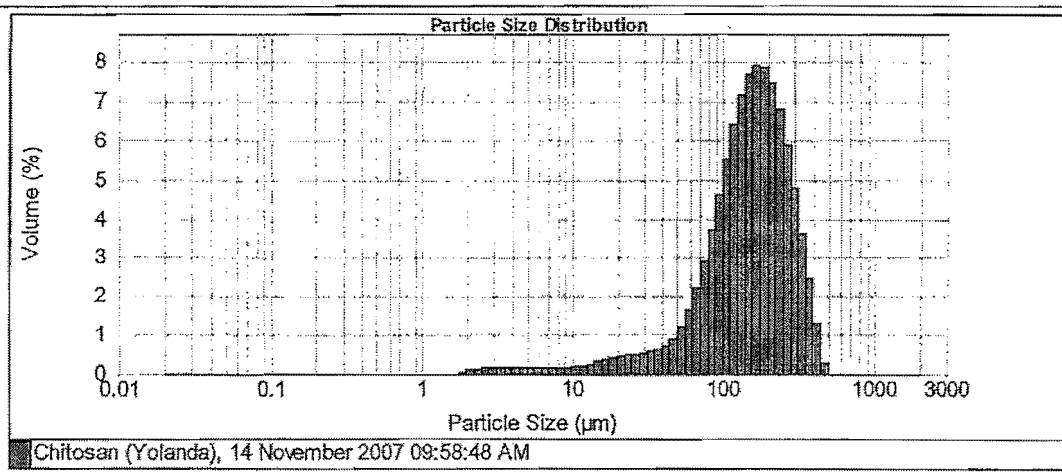
Table A.2.10: *Particle size analysis for chitosan 030912. Sample 2; Run number 2.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Chitosan (Yolanda)	**SOP Name:** Chitosan		**Measured:** 14 November 2007 09:58:48 AM
Sample Source & type: 2nd SAMPLE	**Measured by:** Micron Scientific		**Analysed:** 14 November 2007 09:58:49 AM
Sample bulk lot ref: 30912 X	**Result Source:** Measurement		
Particle Name: Talc	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 1.589	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 15.26 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 3.441 %	**Result Emulation:** Off
Concentration: 0.1579 %Vol	**Span :** 1.558	**Uniformity:** 0.479	**Result units:** Volume
Specific Surface Area: 0.0849 m²/g	**Surface Weighted Mean D[3,2]:** 70.688 um	**Vol. Weighted Mean D[4,3]:** 167.779 um	

d(0.1): 57.183 um **d(0.5):** 155.020 um **d(0.9):** 298.671 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 %
0.020	0.00	0.142	0.00	1.002	0.00	7.096	0.13	50.238	1.20	355.656	2.48
0.022	0.00	0.159	0.00	1.125	0.00	7.962	0.14	56.358	1.62	399.062	1.30
0.025	0.00	0.178	0.00	1.262	0.00	8.934	0.15	63.246	2.19	447.744	0.27
0.028	0.00	0.200	0.00	1.416	0.00	10.024	0.16	70.963	2.90	502.377	0.00
0.032	0.00	0.224	0.00	1.589	0.00	11.247	0.21	79.621	3.73	563.677	0.00
0.036	0.00	0.252	0.00	1.783	0.00	12.619	0.26	89.337	4.63	632.456	0.00
0.040	0.00	0.283	0.00	2.000	0.03	14.159	0.31	100.237	5.55	709.627	0.00
0.045	0.00	0.317	0.00	2.244	0.10	15.887	0.35	112.468	6.41	796.214	0.00
0.050	0.00	0.355	0.00	2.518	0.12	17.825	0.42	126.191	7.13	893.357	0.00
0.056	0.00	0.399	0.00	2.825	0.14	20.001	0.46	141.589	7.66	1002.374	0.00
0.063	0.00	0.448	0.00	3.170	0.16	22.440	0.50	158.863	7.90	1124.683	0.00
0.071	0.00	0.502	0.00	3.557	0.17	25.179	0.52	178.250	7.85	1261.915	0.00
0.080	0.00	0.564	0.00	3.991	0.17	28.251	0.54	200.000	7.47	1415.892	0.00
0.089	0.00	0.632	0.00	4.477	0.16	31.696	0.57	224.404	6.79	1588.555	0.00
0.100	0.00	0.710	0.00	5.024	0.15	35.566	0.62	251.785	5.87	1782.503	0.00
0.112	0.00	0.796	0.00	5.637	0.14	39.905	0.72	282.508	4.80	2000.000	0.00
0.126	0.00	0.893	0.00	6.325	0.14	44.774	0.90	316.979	3.61		
0.142	0.00	1.002	0.00	7.096	0.14	50.238	0.90	355.656	3.61		

Operator notes:

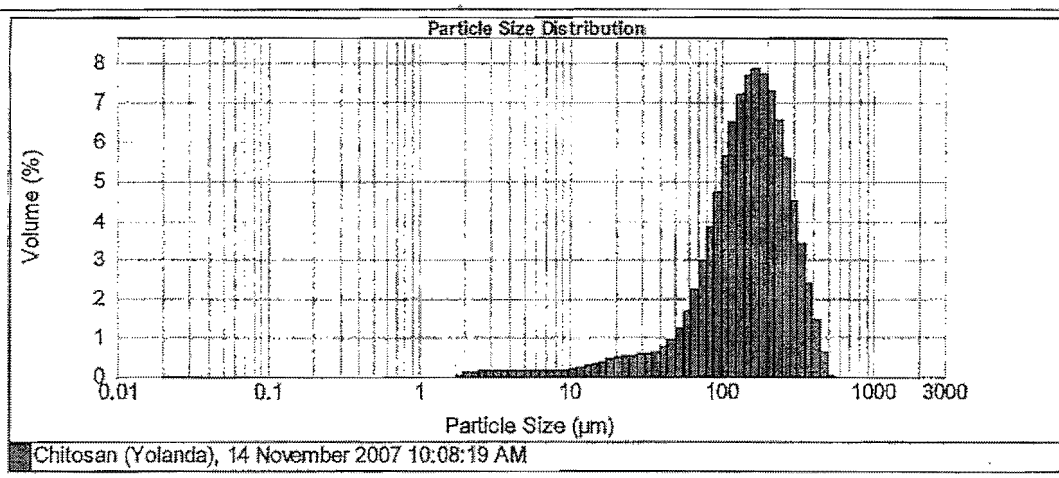
Table A.2.11: *Particle size analysis for chitosan 030912. Sample 3; Run number 1.*

MASTERSIZER 2000

Result Analysis Report

Sample Name: Chitosan (Yolanda)	**SOP Name:** Chitosan		**Measured:** 14 November 2007 10:08:19 AM
Sample Source & type: 3rd SAMPLE	**Measured by:** Micron Scientific		**Analysed:** 14 November 2007 10:08:20 AM
Sample bulk lot ref: 30912 X	**Result Source:** Measurement		
Particle Name: Talc	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 1.589	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 20.19 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 1.597 %	**Result Emulation:** Off
Concentration: 0.2110 %Vol	**Span :** 1.592	**Uniformity:** 0.491	**Result units:** Volume
Specific Surface Area: 0.0865 m²/g	**Surface Weighted Mean D[3,2]:** 69.378 um	**Vol. Weighted Mean D[4,3]:** 156.908 um	

d(0.1): 55.665 um **d(0.5):** 152.878 um **d(0.9):** 299.034 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 %
0.020	0.00	0.142	0.00	1.002	0.00	7.096	0.14	50.238	1.29	355.656	2.35
0.022	0.00	0.159	0.00	1.125	0.00	7.962	0.14	56.368	1.86	399.052	1.43
0.025	0.00	0.178	0.00	1.262	0.00	8.934	0.15	63.246	2.25	447.744	0.84
0.028	0.00	0.200	0.00	1.416	0.00	10.024	0.16	70.953	2.97	502.377	0.02
0.032	0.00	0.224	0.00	1.589	0.00	11.247	0.22	79.621	3.81	563.677	0.00
0.036	0.00	0.252	0.00	1.783	0.03	12.619	0.26	89.337	4.73	632.456	0.00
0.040	0.00	0.283	0.00	2.000	0.04	14.159	0.32	100.237	5.65	709.627	0.00
0.045	0.00	0.317	0.00	2.244	0.11	15.887	0.38	112.468	6.50	796.214	0.00
0.050	0.00	0.356	0.00	2.518	0.12	17.825	0.44	126.191	7.20	893.367	0.00
0.056	0.00	0.399	0.00	2.825	0.14	20.000	0.48	141.599	7.68	1002.374	0.00
0.063	0.00	0.448	0.00	3.170	0.16	22.440	0.52	158.866	7.87	1124.593	0.00
0.071	0.00	0.502	0.00	3.557	0.17	25.179	0.54	178.250	7.74	1261.916	0.00
0.080	0.00	0.564	0.00	3.991	0.17	28.251	0.55	200.000	7.29	1415.992	0.00
0.089	0.00	0.632	0.00	4.477	0.16	31.698	0.59	224.404	6.55	1588.656	0.00
0.100	0.00	0.710	0.00	5.024	0.16	35.566	0.64	251.785	5.59	1782.502	0.00
0.112	0.00	0.796	0.00	5.637	0.16	39.905	0.74	282.608	4.52	2000.000	0.00
0.126	0.00	0.893	0.00	6.325	0.15	44.774	0.93	316.979	3.40		
0.142	0.00	1.002	0.00	7.096	0.14	50.238	0.93	355.656	2.35		

Operator notes:

Table A.2.12: *Particle size analysis for chitosan 030912. Sample 3; Run number 2.*

MASTERSIZER 2000

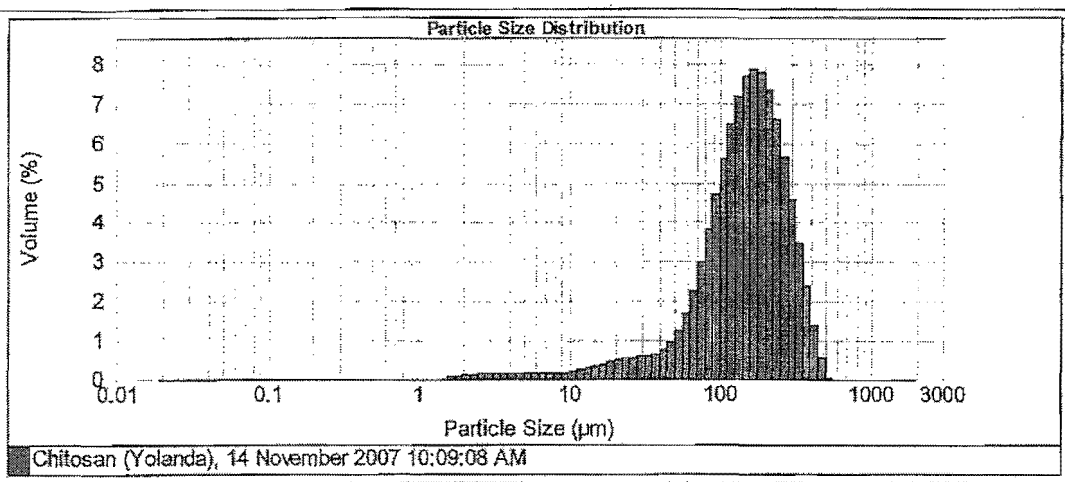
Result Analysis Report

Sample Name: Chitosan (Yolanda)	**SOP Name:** Chitosan	**Measured:** 14 November 2007 10:09:08 AM
Sample Source & type: 3rd SAMPLE	**Measured by:** Micron Scientific	**Analysed:** 14 November 2007 10:09:09 AM
Sample bulk lot ref: 30912 X	**Result Source:** Measurement	

Particle Name: Talc	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 1.589	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 20.27 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 1.595 %	**Result Emulation:** Off

Concentration: 0.2040 %Vol	**Span :** 1.588	**Uniformity:** 0.489	**Result units:** Volume
Specific Surface Area: 0.0892 m²/g	**Surface Weighted Mean D[3,2]:** 67.248 um	**Vol. Weighted Mean D[4,3]:** 166.699 um	

d(0.1): 55.152 um **d(0.5):** 153.134 um **d(0.9):** 298.326 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 %
0.020	0.00	0.142	0.00	1.002	0.00	7.096	0.14	50.238	1.23	355.656	2.35
0.022	0.00	0.159	0.00	1.125	0.00	7.952	0.14	56.368	1.65	399.052	1.98
0.025	0.00	0.178	0.00	1.262	0.00	8.934	0.16	63.246	2.23	447.744	0.56
0.028	0.00	0.200	0.00	1.416	0.00	10.024	0.18	70.963	2.95	502.377	0.02
0.032	0.00	0.224	0.00	1.589	0.04	11.247	0.22	79.621	3.78	563.677	0.00
0.036	0.00	0.252	0.00	1.783	0.08	12.619	0.26	89.337	4.69	632.456	0.00
0.040	0.00	0.283	0.00	2.000	0.10	14.159	0.32	100.237	5.61	709.627	0.00
0.045	0.00	0.317	0.00	2.244	0.12	15.887	0.38	112.456	6.47	796.214	0.00
0.050	0.00	0.356	0.00	2.518	0.14	17.825	0.43	126.191	7.17	893.357	0.00
0.056	0.00	0.399	0.00	2.825	0.16	20.000	0.48	141.589	7.67	1002.374	0.00
0.063	0.00	0.448	0.00	3.170	0.17	22.440	0.52	158.866	7.87	1124.693	0.00
0.071	0.00	0.502	0.00	3.557	0.17	25.179	0.55	178.250	7.76	1261.915	0.00
0.080	0.00	0.564	0.00	3.991	0.17	28.251	0.57	200.000	7.33	1415.892	0.00
0.089	0.00	0.632	0.00	4.477	0.16	31.698	0.59	224.404	6.60	1588.656	0.00
0.100	0.00	0.710	0.00	5.024	0.16	35.568	0.65	251.785	5.65	1782.502	0.00
0.112	0.00	0.796	0.00	5.637	0.15	39.905	0.75	282.508	4.57	2000.000	0.00
0.125	0.00	0.893	0.00	6.325	0.14	44.774	0.93	316.979	3.43		
0.142	0.00	1.002	0.00	7.096	0.14	50.238	0.93	355.656			

Operator notes:

A.3: SCANNING ELECTRON MICROSCOPY (SEM) PHOTOS

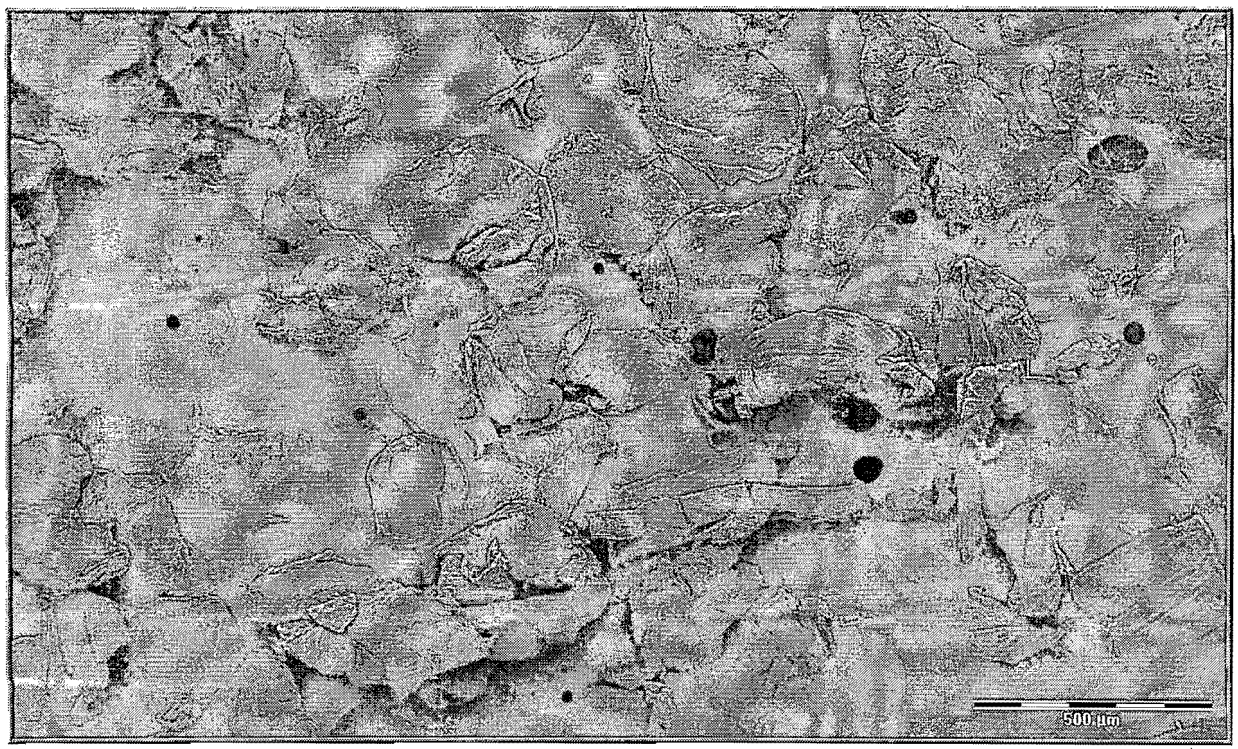


Figure A.3.1: *SEM photo of chitosan 021010 (unsieved fraction).*

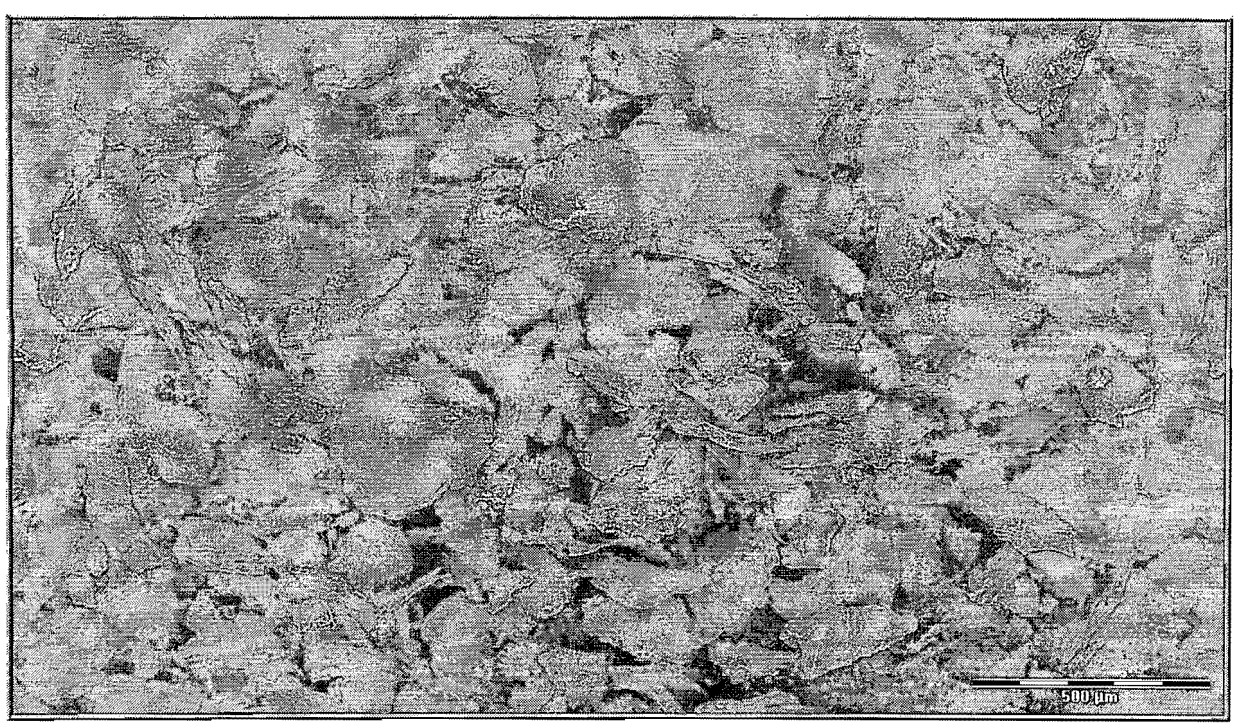


Figure A.3.2: *SEM photo of chitosan 030912 (unsieved fraction).*

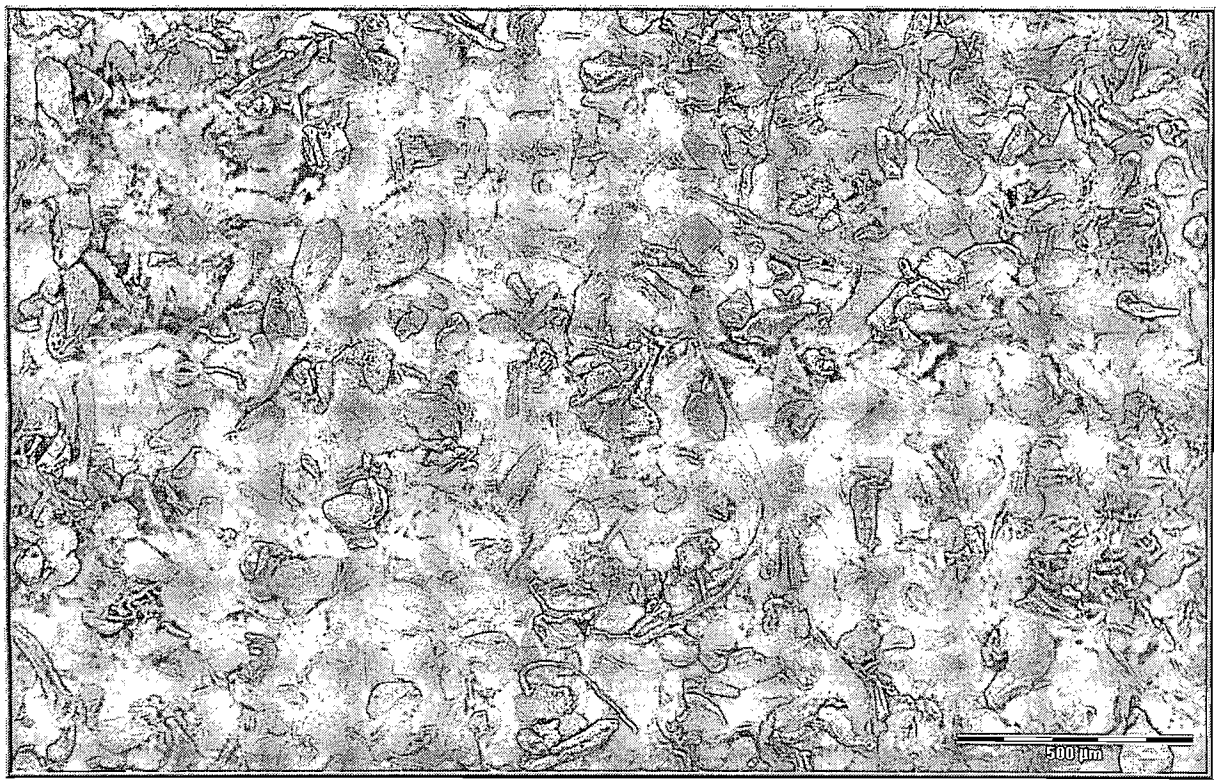


Figure A.3.3: *SEM photo of chitosan 021010; fraction <90 µm.*

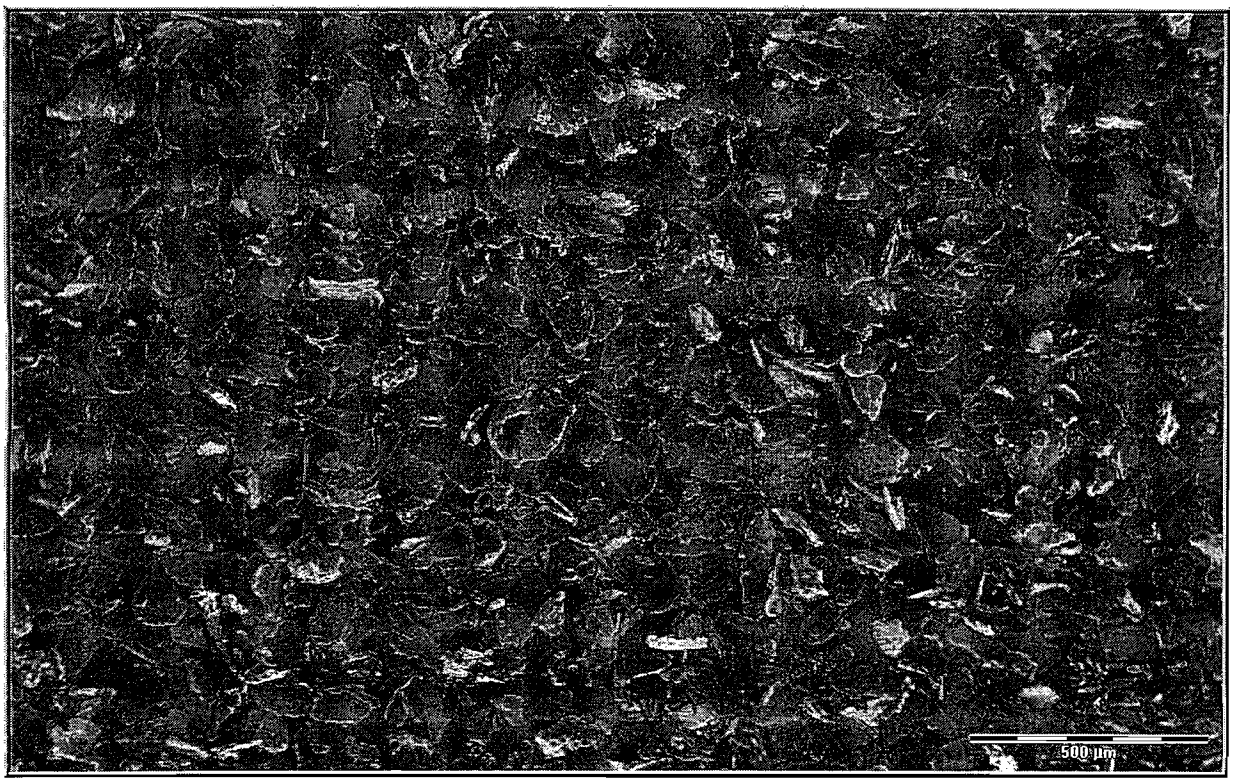


Figure A.3.4: *SEM photo of chitosan 030912; fraction <90 µm.*

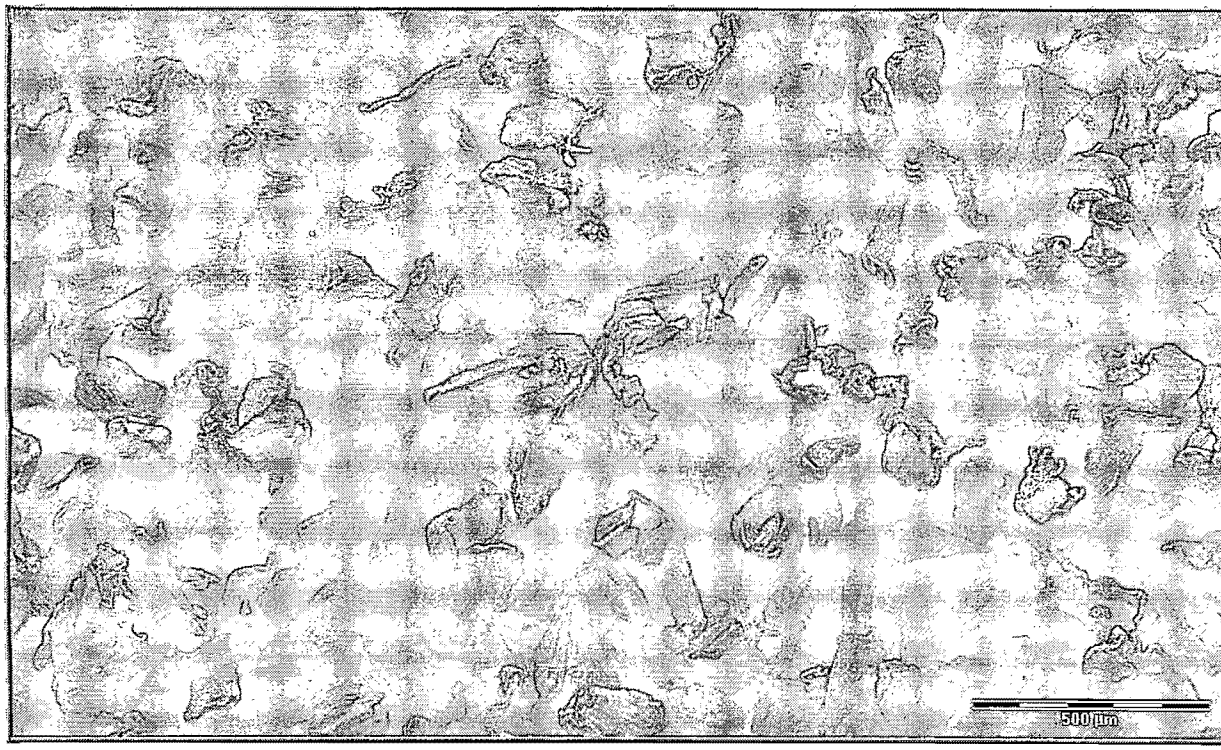


Figure A.3.5: *SEM photo of chitosan 021010; fraction 90-125 µm.*

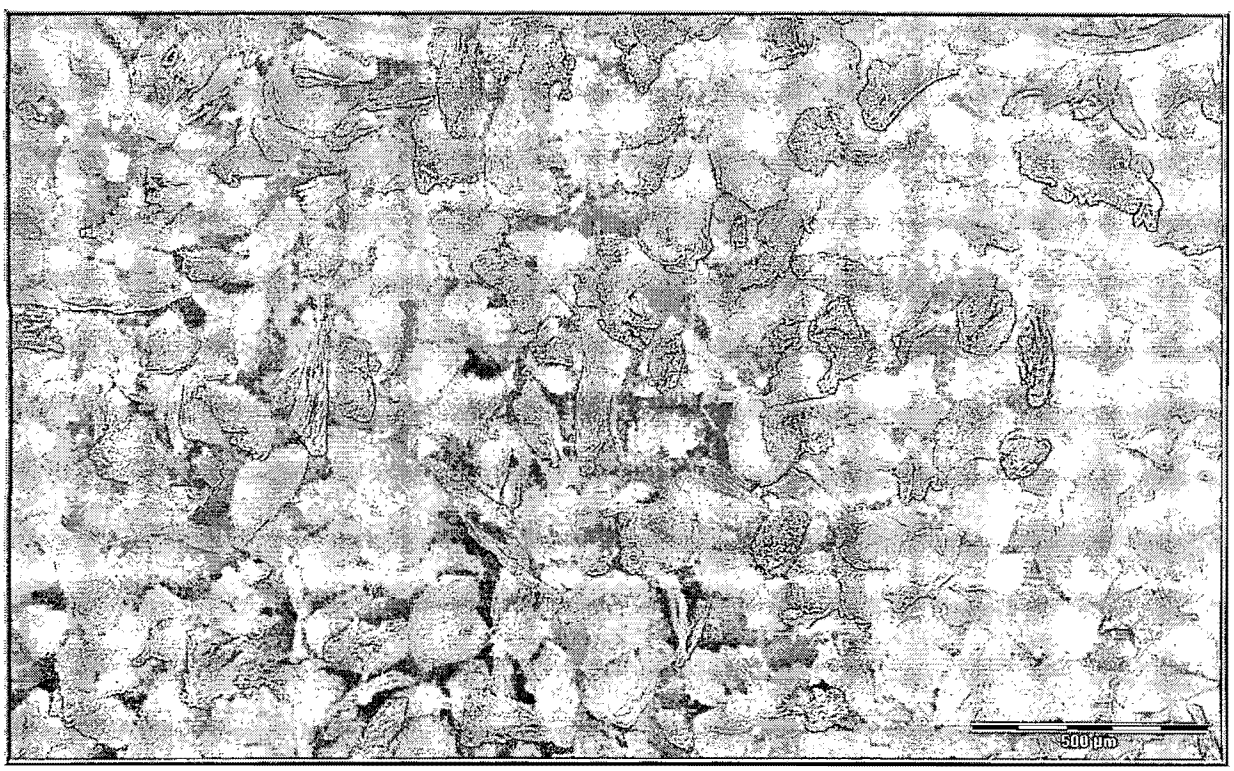


Figure A.3.6: *SEM photo of chitosan 030912; fraction 90-125 µm.*

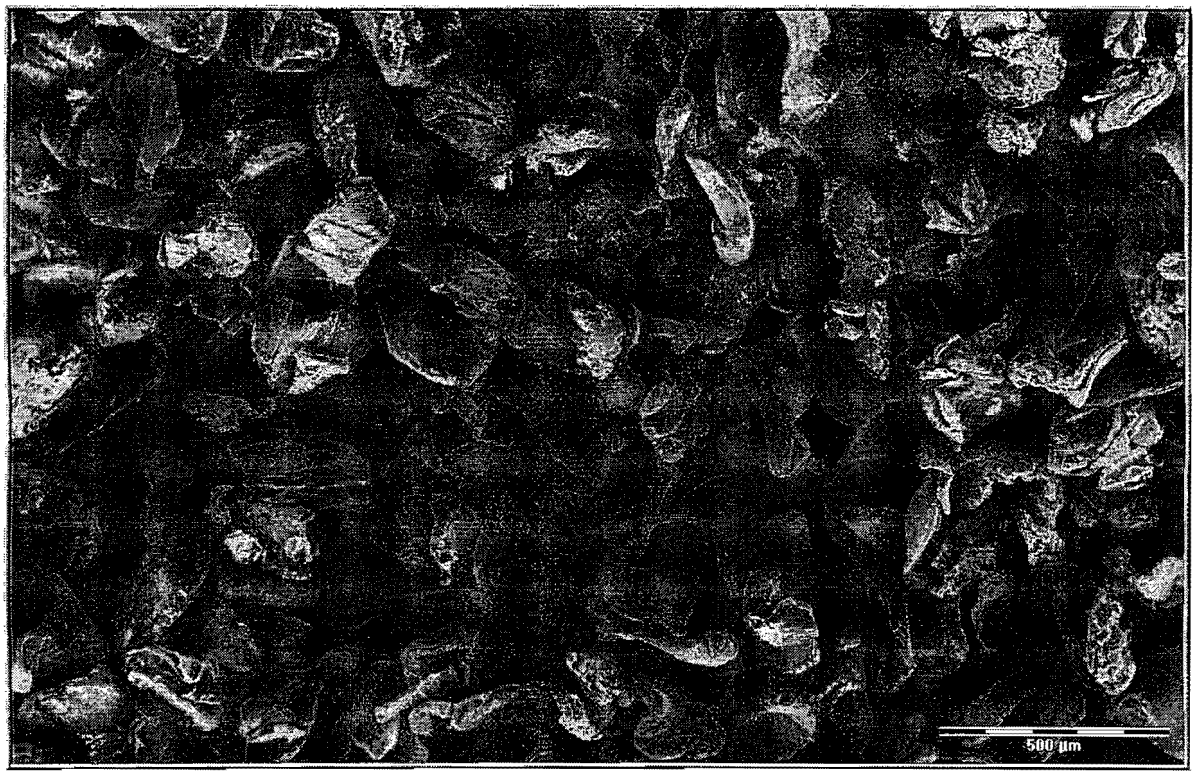


Figure A.3.7: *SEM photo of chitosan 021010; fraction >150 µm.*

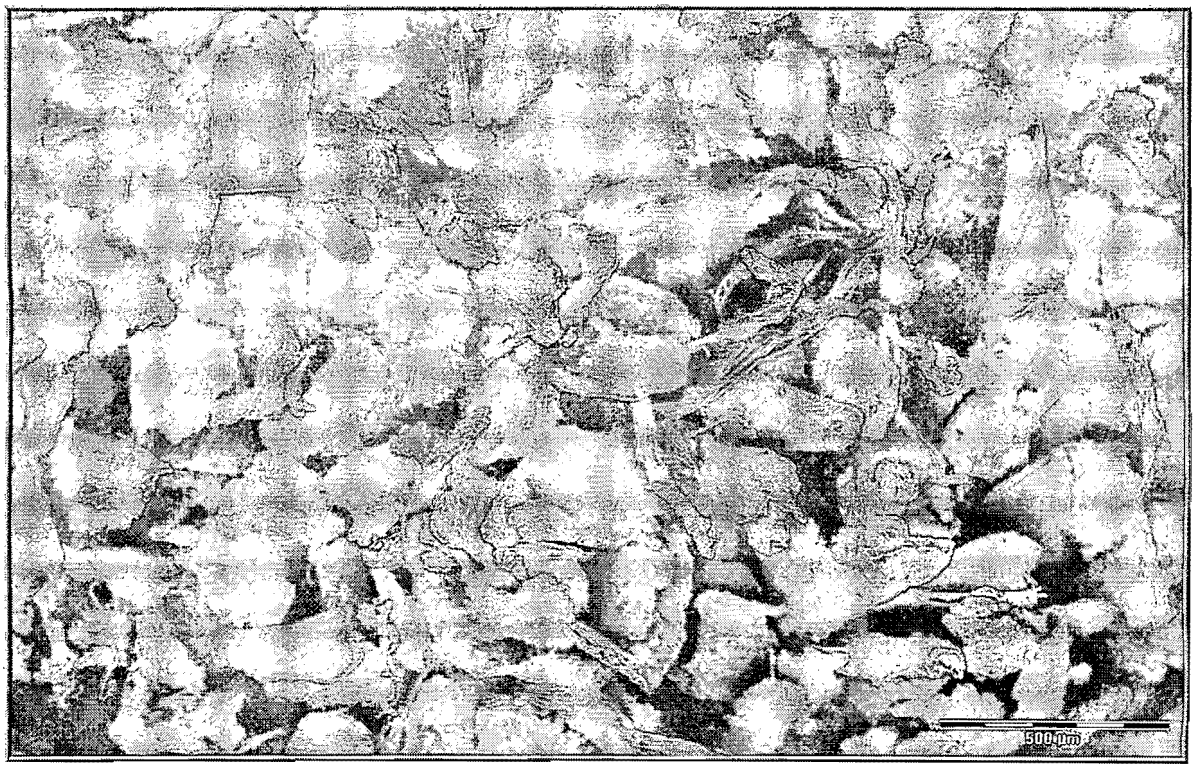


Figure A.3.8: *SEM photo of chitosan 030912; fraction >150 µm.*

A.4: INFRARED ANALYSIS (IR)

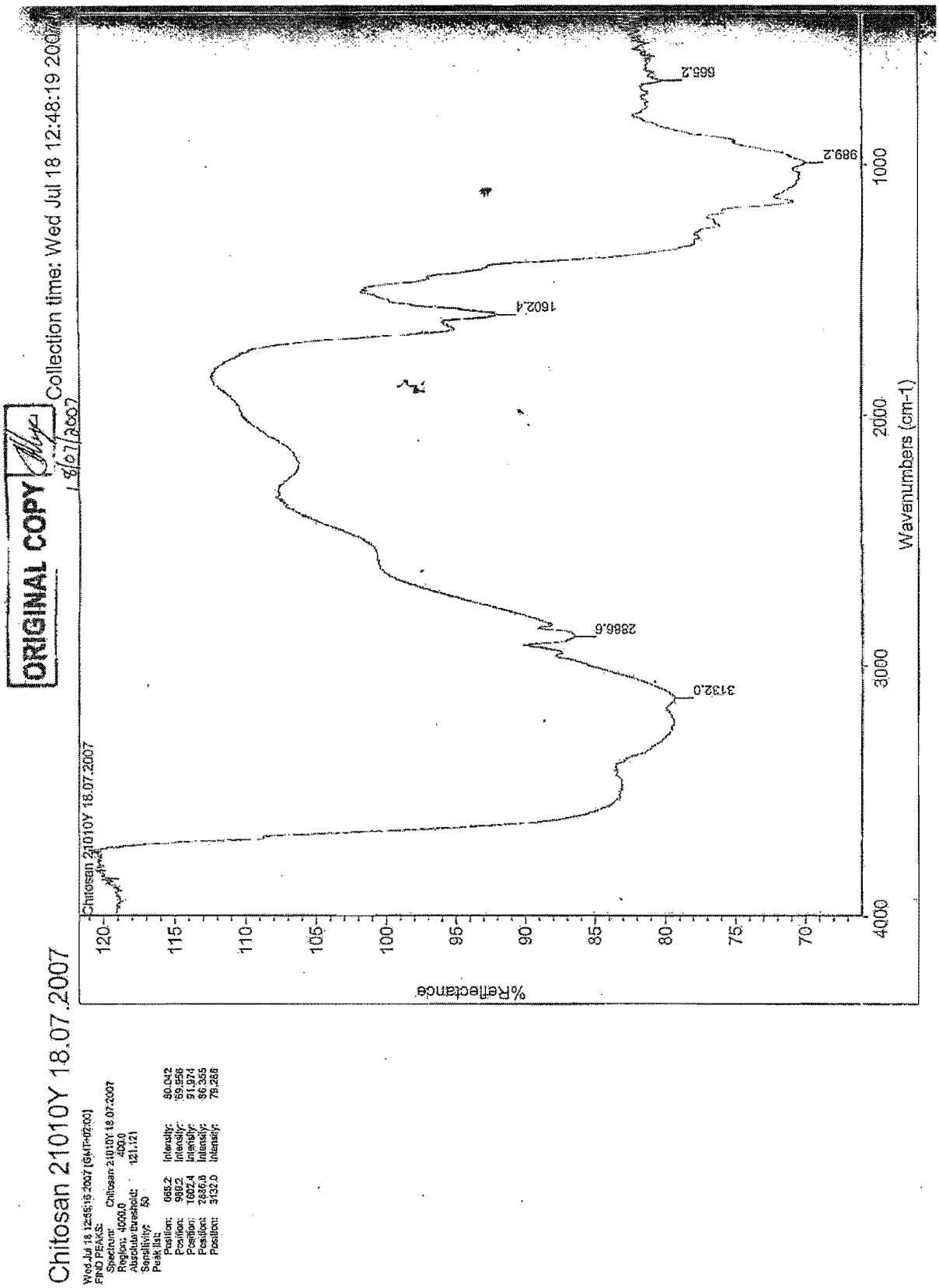


Figure A.4.1: *Infrared analysis of chitosan batch 021010.*

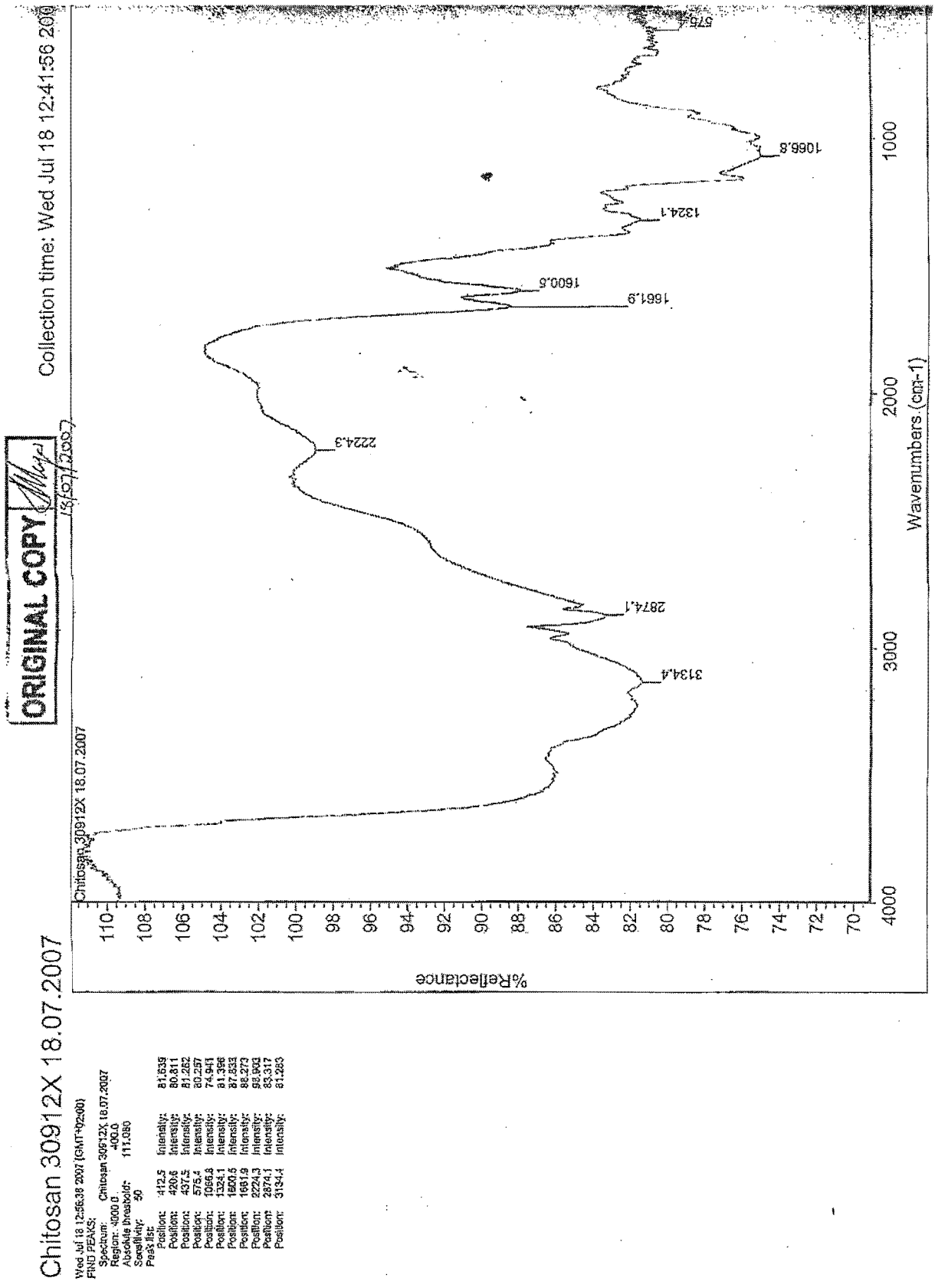


Figure A.4.2: *Infrared analysis of chitosan batch 030912.*

A.5: FLOW PROPERTIES OF EXCIPIENTS

Table A.5.1: *Angle of repose for chitosan 030912.*

Chitosan 030912				
	Height (x) (mm)	Radius (y) (mm)	x/y	Angle (°)
1	16.00	20.00	0.80	38.66
2	14.00	20.00	0.70	34.99
3	12.00	15.00	0.80	38.66
Average	**14.00**	**18.33**	**0.77**	**37.44 ±2.118**

Table A.5.2: *Angle of repose for chitosan 030912 fraction <90µm.*

Chitosan 030912 **<90 µm**				
	Height (x) (mm)	Radius (y) (mm)	x/y	Angle (°)
1	11.00	30.00	0.37	20.14
2	11.00	34.00	0.32	17.93
3	14.00	37.00	0.38	20.73
Average	**12.00**	**33.67**	**0.36**	**19.60 ±1.475**

Table A.5.3: *Angle of repose for chitosan 030912 fraction 90-125µm*

Chitosan 030912 **90-125 µm**				
	Height (x) (mm)	Radius (y) (mm)	x/y	Angle (°)
1	21.00	27.00	0.78	37.87
2	21.00	35.00	0.60	30.96
3	20.00	25.00	0.80	38.66
Average	**20.67**	**29.00**	**0.73**	**35.83 ±4.235**

Table A.5.4: *Angle of repose for chitosan 030912 fraction 125-150µm.*

Chitosan 030912 125-150 µm				
	Height (x) (mm)	Radius (y) (mm)	x/y	Angle (°)
1	26.00	32.00	0.81	39.09
2	34.00	35.00	0.97	44.17
3	10.00	11.00	0.91	42.27
Average	**23.33**	**26.00**	**0.90**	**41.85 2.565**

Table A.5.5: *Angle of repose for chitosan 030912 fraction >150µm.*

Chitosan 030912 >150 µm				
	Height (x) (mm)	Radius (y) (mm)	x/y	Angle (°)
1	23.00	25.00	0.92	42.61
2	25.00	30.00	0.83	39.81
3	24.00	26.00	0.92	42.71
Average	**16.00**	**27.00**	**0.89**	**41.71 ±1.650**

Table A.5.6: *Angle of repose for chitosan 021010.*

Chitosan 021010				
	Height (x) (mm)	Radius (y) (mm)	x/y	Angle (°)
1	25.00	25.00	1.00	45.00
2	18.00	20.00	0.90	41.99
3	22.00	35.00	0.63	32.15
Average	**21.67**	**26.67**	**0.84**	**39.71 ±6.719**

Table A.5.7: *Angle of repose for chitosan 021010 fraction <90 µm.*

Chitosan 021010 <90 µm				
	Height (x) (mm)	Radius (y) (mm)	x/y	Angle (°)
1	14.00	17.00	0.82	39.47
2	16.00	19.00	0.84	40.10
3	13.00	20.00	0.65	33.02
Average	**14.33**	**18.67**	**0.77**	**37.53 ±3.917**

Table A.5.8: *Angle of repose for chitosan 021010 fraction 90-125 µm*

Chitosan 021010 90-125 µm				
	Height (x) (mm)	Radius (y) (mm)	x/y	Angle (°)
1	11.00	17.00	0.65	32.91
2	14.00	25.00	0.56	29.25
3	12.00	19.00	0.63	32.28
Average	**12.33**	**20.33**	**0.61**	**31.48 ±1.955**

Table A.5.9: *Angle of repose for chitosan 021010 fraction 125-150 µm.*

Chitosan 021010 125-150 µm				
	Height (x) (mm)	Radius (y) (mm)	x/y	Angle (°)
1	23.00	20.00	1.15	48.99
2	16.00	16.00	1.00	45.00
3	17.00	16.00	1.06	46.74
Average	**18.67**	**17.33**	**1.07**	**46.91 ±2.001**

Table A.5.10: *Angle of repose for chitosan 021010 fraction >150 µm.*

Chitosan 021010 >150 µm				
	Height (x) (mm)	**Radius (y) (mm)**	**x/y**	**Angle (°)**
1	18.00	19.00	0.95	43.45
2	17.00	18.00	0.94	43.36
3	19.00	18.00	1.06	46.55
Average	**18.00**	**18.33**	**0.98**	**44.45 ±1.814**

Table A.5.11: *Bulk density of chitosan.*

		mass powder in *g*				
Batch	**Fraction *µm***	**1**	**2**	**3**	**Average (g)**	**Density (g/cm^3)**
030912	*	31.030	29.640	30.010	30.227	**0.302 ±0.007**
	<90	28.820	29.160	28.870	28.950	**0.290 ±0.002**
	90-125	30.490	30.470	30.460	30.473	**0.305 ±0.0002**
	125-150	32.700	33.150	33.070	32.973	**0.330 ±0.002**
	>150	27.980	27.750	27.520	27.750	**0.278 ±0.002**
021010	*	15.710	15.830	15.500	15.680	**0.157 ±0.002**
	<90	17.100	17.000	17.020	17.040	**0.170 ±0.0005**
	90-125	15.500	15.910	15.880	15.763	**0.158 ±0.002**
	125-150	16.040	16.060	15.920	16.007	**0.160 ±0.0008**
	>150	16.990	16.230	16.410	16.543	**0.165 ±0.004**

** = unsieved fraction. bulk volume 100 cm^3*

Table A.5.12: *Tapped density of chitosan.*

Batch	Fraction µm		1	2	3	Average
021010	*	*mass (g)*	15.710	15.830	15.500	15.680
		volume (cm³)	63.000	62.000	61.000	62.000
		density (g/cm³)	0.249	0.255	0.254	**0.253 ±0.003**
	<90	*mass (g)*	17.100	17.000	17.020	17.040
		volume (cm³)	61.000	61.000	60.000	60.667
		density (g/cm³)	0.280	0.279	0.284	**0.281 ±0.003**
	90-125	*mass (g)*	15.500	15.910	15.880	15.763
		volume (cm³)	64.000	62.000	63.000	63.000
		density (g/cm³)	0.242	0.257	0.252	**0.250 ±0.007**
	125-150	*mass (g)*	16.040	16.060	15.920	16.007
		volume (cm³)	69.000	70.000	68.000	69.000
		density (g/cm³)	0.232	0.229	0.234	**0.232 ±0.002**
	>150	*mass (g)*	16.990	16.230	16.410	16.543
		volume (cm³)	72.000	72.000	70.000	71.333
		density (g/cm³)	0.236	0.225	0.234	**0.232 ±0.006**
030912	*	*mass (g)*	31.030	29.640	30.010	30.227
		volume (cm³)	62.000	60.000	61.000	61.000
		density (g/cm³)	0.500	0.494	0.492	**0.496 ±0.004**
	<90	*mass (g)*	28.820	29.160	28.870	28.950
		volume (cm³)	63.000	61.000	60.000	61.333
		density (g/cm³)	0.457	0.478	0.481	**0.472 ±0.013**
	90-125	*mass (g)*	30.490	30.470	30.460	30.473
		volume (cm³)	65.000	65.000	66.000	65.333
		density (g/cm³)	0.469	0.469	0.462	**0.466 ±0.004**
	125-150	*mass (g)*	32.700	33.150	33.070	32.973
		volume (cm³)	67.000	68.000	68.000	67.667
		density (g/cm³)	0.488	0.488	0.486	**0.487 ±0.001**
	>150	*mass (g)*	27.980	27.750	27.520	27.750
		volume (cm³)	66.000	65.000	64.000	65.000
		density (g/cm³)	0.424	0.427	0.430	**0.427 ±0.003**

** = unsieved fraction*

Table A.5.13: *Bulk density of excipients.*

	Mass powder in *g*				
Excipient	**1**	**2**	**3**	**Average (g)**	**Density (g/cm^3)**
Ludipress®	58.514	57.956	58.336	58.269	0.583 ±0.003
Tablettose®	59.670	59.402	59.105	59.392	0.594 ±0.003
Avicel®PH200	37.037	36.824	36.674	36.845	0.368 ±0.002
Emcompress®	75.864	74.495	76.601	75.653	0.757 ±0.011

**Bulk volume = 100 cm^3*

Table A.5.14: *Tapped density of excipients.*

Excipient		**1**	**2**	**3**	**Average**
Ludipress®	*mass (g)*	58.514	57.956	58.336	58.269
	volume (cm^3)	82.000	81.000	81.500	81.500
	density (g/cm^3)	0.714	0.716	0.716	**0.715** ±0.001
Tablettose®	*mass (g)*	59.670	59.402	59.105	59.392
	volume (cm^3)	76.000	77.000	76.000	76.333
	density (g/cm^3)	0.785	0.771	0.778	**0.778** ±0.007
Emcompress®	*mass (g)*	54.100	54.200	54.600	54.300
	volume (cm^3)	57.900	60.800	59.600	59.433
	density (g/cm^3)	0.934	0.891	0.916	**0.914** ±0.022
Avicel®PH200	*mass (g)*	37.037	36.824	36.674	36.845
	volume (cm^3)	84.000	82.000	80.000	82.000
	density (g/cm^3)	0.441	0.449	0.458	**0.449** ±0.009

Table A.5.15: *Angle of repose of excipients.*

Excipient		Height (x) (mm)	Radius(y) (mm)	x/y	Angle (°)
Ludipress®	1	35.50	49.00	0.72	35.92
	2	35.50	55.00	0.65	32.84
	3	31.00	46.50	0.67	33.69
	4	31.00	43.00	0.72	35.79
	5	32.00	47.00	0.68	34.25
	6	32.00	44.00	0.73	36.03
	Average	32.83	47.42	0.69	**34.75** ±1.350
Tablettose®	1	39.00	50.00	0.78	37.95
	2	39.00	49.00	0.80	38.52
	3	29.00	38.00	0.76	37.35
	4	29.00	40.00	0.73	35.94
	5	38.00	49.00	0.78	37.79
	6	38.00	54.00	0.70	35.13
	Average	35.33	46.67	0.76	**37.12** ±1.303
Avicel®PH200	1	39.00	61.00	0.64	32.59
	2	39.00	62.00	0.63	32.17
	3	32.50	50.00	0.65	33.02
	4	32.50	53.00	0.61	31.52
	5	39.00	61.00	0.64	32.59
	6	39.00	60.00	0.65	33.02
	Average	36.83	57.83	0.64	**32.49** ±0.573
Emcompress®	1	37.00	47.00	0.79	38.21
	2	35.00	44.00	0.80	38.50
	3	48.00	61.00	0.79	38.20
	4	45.00	57.00	0.79	38.29
	5	35.00	52.00	0.67	33.94
	6	37.00	50.00	0.74	36.50
	Average	39.50	51.83	0.76	**37.27** ±1.787

Table A.5.16.1: *Flow rate of chitosan 021010.*

Opening size (mm)	Time (sec.)	Run 1 (g)	Run 2 (g)	Run 3 (g)	Average (g)	Powder (g) per second
11	*2*	3.732	3.649	3.417	3.599	1.800
	3	6.013	4.905	5.013	5.310	1.770
	4	7.857	6.830	7.025	7.237	1.809
	5	9.503	8.719	8.557	8.926	1.785
	6	10.995	10.350	10.076	10.474	1.746
	7	12.992	12.457	12.328	12.592	1.799
	8	14.683	14.635	13.675	14.331	1.791
	9	17.292	15.963	15.988	16.414	1.824
	10	19.341	18.036	17.645	18.341	1.834
Average						**1.795**
SD						**0.027**
%RSD						**1.50%**
12	*2*	3.805	3.317	3.199	3.440	1.720
	3	5.311	4.764	5.235	5.103	1.701
	4	7.618	6.375	7.087	7.027	1.757
	5	9.663	7.851	8.889	8.801	1.760
	6	12.502	11.991	10.748	11.747	1.958
	7	14.282	13.853	13.084	13.740	1.963
	8	15.919	17.789	15.344	16.351	2.044
	9	18.558	18.785	18.312	18.552	2.061
	10	20.085	21.280	20.574	20.646	2.065
Average						**1.892**
SD						**0.155**
%RSD						**8.20%**
13	*2*	5.061	5.582	5.221	5.288	2.644
	3	7.719	9.114	7.933	8.255	2.752
	4	10.318	11.390	11.127	10.945	2.736
	5	13.290	15.443	14.102	14.278	2.856
	6	15.627	17.516	17.493	16.879	2.813
	7	17.323	20.737	20.757	19.606	2.801
	8	19.618	23.704	23.329	22.217	2.777
	9	21.885	27.096	27.373	25.451	2.828
	10	25.511	29.856	30.309	28.559	2.856
Average						**2.785**
SD						**0.067**
%RSD						**2.42%**

Table A.5.16.2: *Flow rate of chitosan 030912.*

Opening size (mm)	Time (sec.)	Run 1 (g)	Run 2 (g)	Run 3 (g)	Run 4 (g)	Average (g)	Powder (g) per second
13	2	13.358	5.337	6.170	3.657	7.131	3.565
	3	18.195	12.106	11.555	11.823	13.420	4.473
	4	18.572	15.056	19.935	19.541	18.276	4.569
	5	-	21.097	28.578	-	24.838	4.968
Average							**4.394**
SD							**0.592**
%RSD							**13.48%**
14	2	9.191	7.634	6.274		7.700	3.850
	3	23.202	18.086	12.902		18.063	6.021
	4	38.054	28.803	27.706		31.521	7.880
	5	43.454	35.393	35.515		38.121	7.624
	6	53.061	45.368	42.391		46.940	7.823
	7	61.184	58.819	48.769		56.257	8.037
	8	66.770	79.703	53.465		66.646	8.331
	9	72.884	90.263	62.356		75.168	8.352
Average							**7.240**
SD							**1.556**
%RSD							**21.49%**
15	2	14.805	10.142	15.008		13.318	6.659
	3	25.875	18.882	23.840		22.866	7.622
	4	33.619	23.438	39.848		32.302	8.075
	5	41.286	37.901	44.917		41.368	8.274
	6	47.963	47.103	50.104		48.390	8.065
	7	52.890	52.170	57.368		54.143	7.735
	8	58.879	59.891	71.766		63.512	7.939
	9	64.373	69.799	86.597		73.590	8.177
	10	79.482	78.088	87.264		81.611	8.161
Average							**7.856**
SD							**0.496**
%RSD							**6.32%**

Table A.5.16.3: *Flow rate of Emcompress®.*

Opening size (mm)	Time (sec.)	Run 1 (g)	Run 2 (g)	Run 3 (g)	Average (g)	Powder (g) per second
2	2	0.113	0.254	0.191	0.186	0.093
	3	0.198	0.386	0.316	0.300	0.100
	4	0.306	0.535	0.441	0.427	0.107
	5	0.387	0.685	0.581	0.551	0.110
	6	0.480	0.819	0.702	0.667	0.111
	7	0.573	0.954	0.833	0.787	0.112
	8	0.676	1.086	0.951	0.904	0.113
	9	0.768	1.233	1.071	1.024	0.114
	10	0.872	1.382	1.190	1.148	0.115
Average						**0.108**
SD						**0.007**
%RSD						**6.75%**
3	2	1.169	1.175	1.299	1.214	0.607
	3	1.733	1.747	1.874	1.785	0.595
	4	2.301	2.377	2.442	2.373	0.593
	5	2.868	2.946	3.142	2.985	0.597
	6	3.494	3.520	3.723	3.579	0.597
	7	4.115	4.164	4.302	4.194	0.599
	8	4.682	4.744	4.873	4.766	0.596
	9	5.243	5.327	5.448	5.339	0.593
	10	5.864	5.975	6.154	5.998	0.600
Average						**0.597**
SD						**0.004**
%RSD						**0.72%**
4	2	1.257	0.990	1.298	1.182	0.591
	3	2.070	1.714	2.011	1.932	0.644
	4	2.737	2.440	2.817	2.665	0.666
	5	3.422	3.249	3.537	3.403	0.681
	6	4.191	4.055	4.348	4.198	0.700
	7	4.965	4.778	5.084	4.942	0.706
	8	5.656	5.497	5.810	5.654	0.707
	9	6.351	6.227	6.530	6.369	0.708
	10	7.130	6.952	7.336	7.139	0.714
Average						**0.680**
SD						**0.041**
%RSD						**5.97%**

ANNEXURE B

CHARACTERIZATION OF THE COMPRESSIBILITY OF CHITOSAN POWDER

B.1: COMPRESSIBILITY OF CHITOSAN RAW MATERIAL BATCH 030912.

Table B.1.1: *Compressibility properties of chitosan 030912; 100 mg tablets stroke length 17.*

Tablet	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	103.30	2.34	7.98	8.60
2	102.30	2.34	7.97	6.50
3	100.40	2.32	7.97	7.80
4	100.90	2.30	7.95	8.60
5	103.10	2.32	7.99	10.60
6	102.40	2.33	8.01	9.40
7	101.00	2.35	8.00	7.40
8	102.70	2.32	8.00	8.20
9	103.90	2.32	7.96	7.80
10	103.00	2.33	7.97	8.20
11	101.90			
12	102.20			
13	99.40			
14	100.00			
15	103.00			
16	102.60			
17	97.70			
18	100.10			
19	100.20			
20	100.60			
Average	101.54	2.33	7.98	8.31
SD	1.5922	0.0142	0.0194	1.1180
%RSD	1.57%	0.61%	0.24%	13.45%

* n/a = no results were found.

Table B.1.2: *Compressibility properties of chitosan 030912; 100 mg tablets stroke length 18.*

Tablet	Weight (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)
1	102.40	1.92	7.98	31.90
2	102.40	1.90	7.99	26.20
3	100.70	1.90	7.99	24.10
4	104.30	1.91	8.00	28.20
5	103.40	1.89	8.01	27.80
6	100.70	1.90	7.99	32.30
7	99.60	1.92	8.00	34.70
8	101.90	1.90	8.01	24.90
9	102.40	1.92	8.01	30.60
10	102.10	1.91	8.00	27.40
11	101.40			
12	103.20			
13	103.50			
14	104.30			
15	100.80			
16	101.80			
17	98.50			
18	101.90			
19	102.50			
20	101.40			
Average	101.96	1.91	8.00	28.81
SD	1.4609	0.0106	0.0103	3.4527
%RSD	1.43%	0.56%	0.13%	11.98%

* n/a = no results were found.

Table B.1.3: *Compressibility properties of chitosan 030912; 100 mg tablets stroke length 19.*

Tablet	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	102.60	1.61	7.94	89.90
2	99.70	1.65	7.94	94.00
3	101.30	1.61	7.94	93.20
4	105.30	1.58	7.94	77.60
5	101.90	1.62	7.95	90.70
6	102.00	1.63	7.94	76.40
7	101.20	1.63	7.93	103.00
8	101.60	1.63	7.94	93.20
9	103.80	1.61	7.94	79.70
10	100.70	1.63	7.93	96.80
11	99.10			
12	103.30			
13	103.70			
14	103.00			
15	102.80			
16	100.90			
17	99.70			
18	103.60			
19	103.90			
20	101.80			
Average	102.10	1.62	7.94	89.45
SD	1.6211	0.0189	0.0057	8.7813
%RSD	1.59%	1.16%	0.07%	9.82%

* n/a = no results were found.

Table B.1.4: *Compressibility properties of chitosan 030912; 100 mg tablets stroke length 20.*

Tablet	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	102.00	1.56	8.04	105.40
2	103.10	1.52	8.04	103.80
3	101.80	1.53	8.04	100.10
4	99.90	1.54	8.04	106.60
5	103.30	1.55	8.05	105.00
6	105.30	1.52	8.05	103.00
7	102.50	1.55	8.03	107.50
8	101.70	1.57	8.05	103.80
9	104.40	1.50	8.01	98.50
10	98.70	1.53	8.02	103.80
11	102.20			
12	101.40			
13	103.20			
14	102.30			
15	101.20			
16	102.90			
17	102.10			
18	101.60			
19	103.80			
20	102.20			
Average	102.28	1.54	8.04	103.75
SD	1.4598	0.0211	0.0134	2.7472
%RSD	1.43%	1.37%	0.17%	2.65%

* n/a = no results were found.

Table B.1.5: *Compressibility properties of chitosan 030912; 150 mg tablets stroke length 24.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	154.10	3.43	7.98	12.30
2	154.00	3.41	7.96	11.40
3	154.20	3.43	7.97	10.20
4	152.90	3.43	7.99	13.10
5	149.50	3.44	7.98	12.30
6	151.70	3.39	7.97	15.50
7	151.00	3.44	7.98	12.70
8	151.20	3.43	7.98	11.40
9	153.50	3.41	7.99	15.10
10	151.10	3.45	7.99	14.70
11	150.10			
12	152.50			
13	147.70			
14	153.90			
15	149.40			
16	152.20			
17	153.40			
18	150.60			
19	151.60			
20	151.10			
Average	151.79	3.43	7.98	12.87
SD	1.8039	0.0178	0.0099	1.7455
% RSD	1.19%	0.52%	0.12%	13.56%

* n/a = no results were found.

Table B.1.6: *Compressibility properties of chitosan 030912; 150 mg tablets stroke length 25.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	148.80	2.91	7.97	37.60
2	150.70	2.87	7.95	34.70
3	153.60	2.89	7.94	34.70
4	148.60	2.87	7.93	28.60
5	152.80	2.88	7.94	30.20
6	149.70	2.87	7.93	40.00
7	151.50	2.89	7.94	37.20
8	151.60	2.88	7.94	33.90
9	154.80	2.89	7.98	38.80
10	150.80	2.88	7.94	31.90
11	154.70			
12	154.20			
13	152.20			
14	154.90			
15	152.60			
16	145.90			
17	149.70			
18	146.40			
19	152.10			
20	151.50			
Average	151.36	2.88	7.95	34.76
SD	2.5997	0.0125	0.0165	3.7337
% RSD	1.72%	0.43%	0.21%	10.74%

* n/a = no results were found.

Table B.1.7: *Compressibility properties of chitosan 030912; 150 mg tablets stroke length 26.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	152.90	2.48	7.91	98.90
2	149.70	2.49	7.91	99.30
3	155.70	2.46	7.91	85.80
4	149.80	2.46	7.91	81.30
5	151.20	2.48	7.91	85.00
6	152.30	2.47	7.91	89.50
7	146.30	2.51	7.93	96.00
8	151.60	2.46	7.91	79.70
9	154.80	2.48	7.90	102.60
10	145.90	2.47	7.91	96.80
11	150.60			
12	148.80			
13	154.90			
14	150.80			
15	150.80			
16	155.30			
17	151.40			
18	155.20			
19	152.50			
20	152.10			
Average	151.63	2.48	7.91	91.49
SD	2.7679	0.0158	0.0074	8.2271
% RSD	1.83%	0.64%	0.09%	8.99%

* n/a = no results were found.

Table B.1.8: *Compressibility properties of chitosan 030912; 150 mg tablets stroke length 27.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	151.60	2.38	7.90	176.10
2	159.00	2.27	7.89	162.20
3	152.10	2.29	7.93	159.40
4	151.90	2.26	7.92	155.30
5	151.00	2.27	7.89	164.70
6	153.30	2.18	7.89	136.50
7	154.70	2.32	7.90	167.90
8	156.80	2.25	7.90	165.50
9	152.90	2.31	7.89	169.20
10	147.10	2.36	7.90	165.90
11	150.30			
12	151.70			
13	148.80			
14	154.50			
15	149.40			
16	150.30			
17	155.10			
18	152.50			
19	156.00			
20	157.10			
Average	152.81	2.29	7.90	162.27
SD	3.0353	0.0574	0.0137	10.6532
% RSD	1.99%	2.51%	0.17%	6.57%

* n/a = no results were found.

Table B.1.9: *Compressibility properties of chitosan 030912; 200 mg tablets stroke length 30.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	198.90	4.44	8.00	14.70
2	192.70	4.49	8.02	17.20
3	194.90	4.58	7.97	7.80
4	193.30	4.47	8.03	15.90
5	197.90	4.49	8.00	16.30
6	200.40	4.45	8.03	19.60
7	200.60	4.42	8.01	18.40
8	197.20	4.43	8.02	18.00
9	195.80	4.46	8.03	15.90
10	194.50	4.44	7.99	17.20
11	196.70			
12	193.70			
13	197.90			
14	198.60			
15	193.00			
16	196.30			
17	189.50			
18	197.90			
19	196.80			
20	199.50			
Average	196.31	4.47	8.01	16.10
SD	2.8818	0.0462	0.0200	3.2411
% RSD	1.47%	1.03%	0.25%	20.13%

* n/a = no results were found.

Table B.1.10: *Compressibility properties of chitosan 030912; 200 mg tablets stroke length 31.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	197.30	3.97	7.99	23.70
2	196.90	3.89	7.96	35.10
3	198.20	3.89	7.97	38.80
4	195.50	3.95	7.97	23.70
5	198.40	3.89	7.96	33.90
6	199.00	3.92	7.96	30.20
7	201.30	3.94	7.95	25.30
8	197.90	3.92	7.97	31.10
9	193.90	3.97	7.98	22.50
10	200.30	3.91	7.96	35.50
11	196.00			
12	191.80			
13	199.20			
14	197.00			
15	199.80			
16	192.20			
17	192.40			
18	196.10			
19	193.70			
20	195.60			
Average	196.63	3.93	7.97	29.98
SD	2.7656	0.0314	0.0116	5.8488
% RSD	1.41%	0.80%	0.15%	19.51%

* n/a = no results were found.

Table B.1.11: *Compressibility properties of chitosan 030912; 200 mg tablets stroke length 32.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	198.00	3.47	7.96	75.20
2	200.80	3.48	7.95	81.30
3	196.50	3.48	7.96	79.30
4	196.40	3.48	7.96	79.30
5	197.80	3.50	7.97	75.20
6	199.90	3.49	7.96	85.40
7	197.50	3.48	7.96	95.20
8	191.50	3.50	7.97	79.30
9	194.30	3.51	7.97	75.60
10	198.20	3.49	7.96	81.70
11	194.70			
12	191.50			
13	198.90			
14	195.30			
15	195.00			
16	194.10			
17	202.50			
18	197.80			
19	196.60			
20	198.10			
Average	196.77	3.49	7.96	80.75
SD	2.8096	0.0123	0.0063	6.0191
% RSD	1.43%	0.35%	0.08%	7.45%

* n/a = no results were found.

Table B.1.12: *Compressibility properties of chitosan 030912; 200 mg tablets stroke length 33.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	196.60	3.12	7.92	125.00
2	204.60	3.14	7.95	123.80
3	195.80	3.14	7.94	122.60
4	199.30	3.15	7.92	148.30
5	189.60	3.16	7.93	150.00
6	203.70	3.16	7.95	147.90
7	197.30	3.13	7.92	133.20
8	197.80	3.15	7.93	137.70
9	199.00	3.15	7.93	143.80
10	199.20	3.14	7.94	135.30
11	200.30			
12	198.70			
13	201.10			
14	199.30			
15	193.80			
16	195.20			
17	203.80			
18	192.50			
19	202.40			
20	199.50			
Average	198.48	3.14	7.93	136.76
SD	3.8499	0.0126	0.0116	10.5651
% RSD	1.94%	0.40%	0.15%	7.73%

* n/a = no results were found.

Table B.1.13: *Compressibility properties of chitosan 030912; 200 mg tablets stroke length 34.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	193.40	3.00	7.94	198.60
2	198.50	2.97	7.95	188.80
3	195.90	2.97	7.95	179.80
4	193.50	3.05	7.96	208.40
5	195.30	2.98	7.91	190.00
6	200.10	3.01	7.95	206.80
7	200.10	3.02	7.95	208.00
8	193.40	3.02	7.93	213.70
9	194.40	3.03	7.94	204.70
10	196.20	3.02	7.94	221.90
11	201.30			
12	196.00			
13	197.20			
14	198.10			
15	193.60			
16	194.80			
17	197.60			
18	193.40			
19	195.50			
20	195.60			
Average	196.20	3.01	7.94	202.07
SD	2.4371	0.0267	0.0140	12.7488
% RSD	1.24%	0.89%	0.18%	6.31%

* n/a = no results were found.

Table B.1.14: *Percentage friability of chitosan 030912; 100 mg tablets.*

	Weight (mg)		
Stroke length	**Before rotation**	**After rotation**	**% Friability**
17	1007.9	892.4	11.46%
18	1025.2	1006.7	1.80%
19	1014.7	1009.0	0.56%
20	1018.7	1016.3	0.24%

Table B.1.15: *Percentage friability of chitosan 030912; 150 mg tablets.*

	Weight (mg)		
Stroke length	**Before rotation**	**After rotation**	**% Friability**
24	1515.1	1323.2	12.67%
25	1500.3	1458.7	2.77%
26	1521.9	1508.5	0.88%
27	1526.4	1522.9	0.23%

Table B.1.16: *Percentage friability of chitosan 030912; 200 mg tablets.*

	Weight (mg)		
Stroke length	**Before rotation**	**After rotation**	**% Friability**
30	1960.9	1606.4	18.08%
31	1970.1	1891.9	3.97%
32	1976.7	1951.2	1.29%
33	1977.5	1968.2	0.47%
34	1949.1	1945.5	0.18%

B.2: COMPRESSIBILITY OF CHITOSAN RAW MATERIAL; DOUBLE FILL CYCLE (BATCH 021010 AND 030912).

Table B.2.1: *Compressibility properties of chitosan 030912; stroke length 30, compaction 0%.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	198.90	4.44	8.00	14.70
2	192.70	4.49	8.02	17.20
3	194.90	4.58	7.97	7.80
4	193.30	4.47	8.03	15.90
5	197.90	4.49	8.00	16.30
6	200.40	4.45	8.03	19.60
7	200.60	4.42	8.01	18.40
8	197.20	4.43	8.02	18.00
9	195.80	4.46	8.03	15.90
10	194.50	4.44	7.99	17.20
11	196.70			
12	193.70			
13	197.90			
14	198.60			
15	193.00			
16	196.30			
17	189.50			
18	197.90			
19	196.80			
20	199.50			
Average	196.31	4.47	8.01	16.10
SD	2.8818	0.0462	0.0200	3.2411
% RSD	1.47%	1.03%	0.25%	20.13%

Table B.2.2: *Compressibility properties of chitosan 030912; stroke length 30, compaction 10%.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	210.50	4.66	8.06	24.90
2	207.00	4.68	8.07	17.20
3	212..4	4.74	8.07	15.50
4	211.90	4.67	8.07	22.50
5	212.30	4.68	8.09	26.60
6	208.20	4.62	8.06	29.00
7	214.90	4.64	8.06	21.20
8	210.00	4.67	8.08	20.80
9	211.00	4.66	8.07	26.60
10	214.50	4.64	8.06	22.90
11	206.40			
12	210.00			
13	210.90			
14	206.30			
15	213.90			
16	212.20			
17	208.60			
18	206.60			
19	206.90			
20	211.00			
Average	210.16	4.67	8.07	22.72
SD	2.7667	0.0324	0.0099	4.2554
% RSD	1.32%	0.69%	0.12%	18.73%

Table B.2.3: *Compressibility properties of chitosan 030912; stroke length 30, compaction 20%.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	217.20	4.58	8.06	37.60
2	222.00	4.58	8.06	38.00
3	215.50	4.60	8.05	31.90
4	222.40	4.61	8.07	34.70
5	226.80	4.59	8.07	34.70
6	228.90	4.57	8.05	41.30
7	227.70	4.58	8.06	36.80
8	221.50	4.61	8.07	30.20
9	222.70	4.55	8.06	35.10
10	225.20	4.60	8.07	38.80
11	222.30			
12	222.80			
13	225.10			
14	222.80			
15	228.10			
16	226.20			
17	225.10			
18	224.50			
19	229.00			
20	223.60			
Average	223.97	4.59	8.06	35.91
SD	3.5184	0.0189	0.0079	3.2946
% RSD	1.57%	0.41%	0.10%	9.17%

Table B.2.4: *Compressibility properties of chitosan 030912; stroke length 30, compaction 30%.*

	Weight (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)
1	228.50	4.54	8.04	83.90
2	236.80	4.54	8.04	47.00
3	235.20	4.56	8.04	54.30
4	234.00	4.55	8.06	59.70
5	230.80	4.56	8.04	48.60
6	235.80	4.53	8.05	64.20
7	225.50	4.53	8.04	51.90
8	233.40	4.53	8.05	58.40
9	235.00	4.55	8.05	60.10
10	233.10	4.50	8.06	62.10
11	238.20			
12	226.60			
13	234.50			
14	235.40			
15	231.90			
16	234.80			
17	230.20			
18	233.90			
19	236.30			
20	234.50			
Average	233.22	4.54	8.05	59.02
SD	3.3632	0.0179	0.0082	10.4529
% RSD	1.44%	0.39%	0.10%	17.71%

Table B.2.5: *Compressibility properties of chitosan 030912; stroke length 30, compaction 40%.*

	Weight (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)
1	246.60	4.50	8.03	83.80
2	242.90	4.51	8.03	70.70
3	249.50	4.53	8.04	74.00
4	245.40	4.51	8.04	93.60
5	244.40	4.51	8.04	73.10
6	248.00	4.53	8.04	75.60
7	248.10	4.51	8.06	72.70
8	246.30	4.51	8.03	78.50
9	251.00	4.53	8.04	72.70
10	244.90	4.51	8.04	85.80
11	247.60			
12	243.80			
13	240.90			
14	248.20			
15	246.50			
16	243.60			
17	248.90			
18	248.90			
19	244.00			
20	244.40			
Average	246.20	4.52	8.04	78.05
SD	2.5826	0.0108	0.0088	7.4035
% RSD	1.05%	0.24%	0.11%	9.49%

* n/a = no results were found.

Table B.2.6: *Compressibility properties of chitosan 030912; stroke length 30, compaction 50%.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	253.30	4.50	8.02	138.90
2	256.10	4.48	8.02	141.00
3	262.00	4.49	8.03	116.00
4	260.40	4.49	8.03	125.40
5	250.70	4.49	8.02	134.00
6	261.30	4.50	8.02	133.20
7	262.70	4.49	8.03	116.90
8	254.10	4.49	8.02	131.60
9	259.90	4.49	8.02	122.60
10	264.20	4.50	8.03	115.60
11	264.00			
12	254.30			
13	260.30			
14	261.60			
15	264.80			
16	256.20			
17	261.50			
18	256.10			
19	260.50			
20	259.30			
Average	259.17	4.49	8.02	127.52
SD	4.0070	0.0063	0.0052	9.5359
% RSD	1.55%	0.14%	0.06%	7.48%

* n/a = no results were found.

Table B.2.7: *Compressibility properties of chitosan 030912; stroke length 30, compaction 60%.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	273.90	4.50	8.02	154.50
2	260.90	4.51	8.01	168.80
3	268.30	4.50	8.02	165.50
4	257.30	4.53	8.03	176.50
5	273.40	4.51	8.01	185.90
6	275.80	4.53	8.02	152.40
7	272.40	4.50	8.02	174.90
8	270.80	4.52	8.02	185.10
9	273.20	4.50	8.01	171.60
10	273.40	4.50	8.01	163.00
11	269.70			
12	274.70			
13	272.60			
14	271.30			
15	270.80			
16	268.00			
17	266.00			
18	270.90			
19	267.90			
20	269.00			
Average	270.02	4.51	8.02	169.82
SD	4.5485	0.0125	0.0067	11.4018
% RSD	1.68%	0.28%	0.08%	6.71%

* n/a = no results were found.

Table B.2.8: *Compressibility properties of chitosan 030912; stroke length 30, compaction 70%.*

	Weight (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)
1	289.60	4.63	8.00	261.50
2	284.70	4.57	8.00	226.40
3	288.00	4.54	8.01	194.90
4	290.80	4.56	8.01	233.70
5	291.70	4.58	8.00	269.30
6	287.80	4.59	8.01	272.10
7	285.30	4.60	7.99	254.20
8	285.80	4.56	8.00	216.20
9	289.20	4.58	8.01	235.40
10	284.80	4.60	8.01	251.30
11	290.30			
12	285.20			
13	288.30			
14	285.40			
15	287.70			
16	286.90			
17	292.50			
18	290.70			
19	286.80			
20	289.60			
Average	288.06	4.58	8.00	241.50
SD	2.4235	0.0256	0.0070	24.7302
% RSD	0.84%	0.56%	0.09%	10.24%

* n/a = no results were found.

Table B.2.9: *Compressibility properties of chitosan 030912; stroke length 30, compaction 80%.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	312.90	4.68	8.01	276.60
2	304.40	4.65	8.01	264.40
3	297.00	4.79	8.01	293.00
4	303.90	4.76	8.00	303.20
5	299.30	4.77	8.02	306.90
6	297.30	4.71	8.00	284.80
7	300.20	4.76	8.01	313.40
8	304.80	4.70	7.99	297.50
9	296.00	4.80	8.02	301.10
10	299.90	4.71	8.01	272.50
11	295.30			
12	298.90			
13	302.00			
14	296.10			
15	296.90			
16	303.70			
17	302.90			
18	305.10			
19	306.50			
20	303.10			
Average	301.31	4.73	8.01	291.34
SD	4.4404	0.0499	0.0093	16.1456
% RSD	1.47%	1.05%	0.12%	5.54%

* n/a = no results were found.

Table B.2.10: *Compressibility properties of chitosan 021010; stroke length 33, compaction 30%.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	118.00	3.57	8.01	9.00
2	117.10	3.58	8.02	13.10
3	110.00	3.52	8.04	13.50
4	124.00	3.45	8.03	18.80
5	115.90	3.52	8.00	11.00
6	116.60	3.57	8.02	9.00
7	119.20	3.53	7.97	8.60
8	117.70	3.53	8.00	10.60
9	117.50	3.57	7.99	8.20
10	122.10	3.54	8.03	9.40
11	113.10			
12	120.30			
13	116.10			
14	118.10			
15	121.10			
16	118.20			
17	118.20			
18	125.20			
19	113.30			
20	120.50			
Average	118.11	3.54	8.01	11.12
SD	3.6152	0.0385	0.0213	3.2605
% RSD	3.06%	1.09%	0.27%	29.32%

Table B.2.11: *Compressibility properties of chitosan 021010; stroke length 33, compaction 40%.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	121.20	3.52	8.01	15.10
2	124.80	3.47	8.05	20.40
3	123.40	3.55	8.01	11.00
4	122.70	3.51	8.02	11.40
5	124.30	3.50	8.01	11.00
6	121.60	3.48	8.03	12.30
7	122.40	3.49	8.03	16.30
8	127.90	3.49	8.04	13.50
9	124.20	3.61	8.03	11.80
10	119.30	3.46	8.04	12.70
11	116.40			
12	130.80			
13	118.50			
14	123.30			
15	126.00			
16	98.80			
17	124.40			
18	115.70			
19	123.30			
20	124.10			
Average	121.66	3.51	8.03	13.55
SD	6.4467	0.0442	0.0142	2.9789
% RSD	5.30%	1.26%	0.18%	21.98%

Table B.2.12: *Compressibility properties of chitosan 021010; stroke length 33, compaction 50%.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	134.70	3.53	8.02	18.00
2	125.80	3.53	8.03	11.00
3	131.50	3.65	8.00	8.20
4	136.60	3.47	8.07	21.20
5	129.10	3.59	8.01	11.80
6	124.70	3.45	8.05	18.00
7	134.70	3.57	8.02	11.00
8	124.70	3.48	8.04	14.70
9	130.70	3.38	8.04	32.30
10	130.70	3.50	8.04	12.70
11	139.00			
12	135.50			
13	135.10			
14	129.20			
15	127.90			
16	132.80			
17	131.10			
18	133.70			
19	119.70			
20	123.80			
Average	130.55	3.52	8.03	15.89
SD	4.9690	0.0769	0.0204	7.0053
% RSD	3.81%	2.19%	0.25%	44.09%

Table B.2.13: *Compressibility properties of chitosan 021010; stroke length 33, compaction 60%.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	154.20	3.49	8.04	19.20
2	135.30	3.25	8.03	57.60
3	137.80	3.27	8.03	53.90
4	126.60	3.32	8.04	33.90
5	139.30	3.28	8.03	56.00
6	136.20	3.32	8.04	42.50
7	132.30	3.52	8.06	19.60
8	151.00	3.34	8.04	32.70
9	127.70	3.50	8.06	15.50
10	135.30	3.47	8.05	26.20
11	134.90			
12	141.00			
13	133.10			
14	136.90			
15	128.80			
16	136.30			
17	143.40			
18	133.60			
19	143.60			
20	132.40			
Average	136.99	3.38	8.04	35.71
SD	7.0395	0.1064	0.0114	16.0249
% RSD	5.14%	3.15%	0.14%	44.88%

Table B.2.14: *Compressibility properties of chitosan 021010; stroke length 33, compaction 70%.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	158.30	3.22	8.02	85.40
2	135.10	3.23	8.02	64.60
3	145.70	3.21	8.01	59.20
4	160.10	3.19	8.02	72.30
5	151.10	3.19	8.03	76.40
6	152.80	3.20	8.02	74.80
7	146.30	3.24	8.03	58.00
8	151.30	3.20	8.03	77.20
9	167.90	3.22	8.02	69.90
10	154.00	3.21	8.02	65.40
11	151.30			
12	152.10			
13	141.00			
14	146.50			
15	144.50			
16	166.00			
17	160.60			
18	153.70			
19	150.90			
20	159.90			
Average	152.46	3.21	8.02	70.32
SD	8.1505	0.0166	0.0063	8.6168
% SD	5.35%	0.52%	0.08%	12.25%

* n/a = no results were found.

Table B.2.15: *Compressibility properties of chitosan 021010; stroke length 33, compaction 80%.*

	Weight	Thickness	Diameter	Crushing strength
	(mg)	(mm)	(mm)	(N)
1	144.80	3.21	7.99	159.80
2	177.60	3.18	8.00	111.60
3	174.20	3.19	8.01	125.00
4	163.80	3.17	8.00	110.70
5	168.80	3.19	8.00	126.30
6	181.40	3.19	8.01	83.80
7	177.40	3.18	8.01	96.00
8	172.60	3.20	8.00	145.10
9	186.60	3.20	8.00	159.80
10	163.40	3.25	8.05	44.90
11	173.50			
12	170.10			
13	173.00			
14	172.80			
15	175.30			
16	170.10			
17	167.50			
18	169.40			
19	153.60			
20	171.90			
Average	170.39	3.20	8.01	116.30
SD	9.1601	0.0222	0.0164	35.6049
% RSD	5.38%	0.69%	0.20%	30.61%

* n/a = no results were found.

Table B.2.16: *Percentage friability of chitosan batch 030912 and 021010*

		Weight (mg)		
Batch	Percentage compression	Before rotation	After rotation	% Friability
030912	0	1.9609	1.6064	18.08
	10	2.0126	1.7356	13.76
	20	2.2280	2.1024	5.64
	30	2.3329	2.2557	3.31
	40	2.4429	2.3894	2.19
	50	2.5535	2.5144	1.53
	60	2.7067	2.6812	0.94
	70	2.8893	2.8707	0.64
	80	3.0163	2.9999	0.54
021010	30	1.1767	1.0554	10.31
	40	1.2115	1.0517	13.19
	50	1.2955	1.2424	4.10
	60	1.4221	1.3995	1.59
	70	1.5381	1.5285	0.62
	80	1.6536	1.6462	0.45