YUNIBESITI YA BOKONE-BOPHIRIMA
NORTH WEST UNIVERSITY
NOORDWES UNIVERSITEIT

ASSESSMENT OF THE TABLETING PROPERTIES OF CHITOSAN THROUGH WET GRANULATION AND DIRECT COMPRESSION FORMULATIONS

MARIQUE ELIZABETH AUCAMP (B.PHARM.)

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Supervisor: Dr. A.F. Marais

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AIM AND OBJECTIVES OF THE INVESTIGATION

AIM

The aim of the study was to determine the function and effect of chitosan raw material in tablet formulations prepared by method of direct compression and wet granulation. Furthermore, to optimise chitosan raw material to improve its tabletability and to attempt the design of a multipurpose excipient (MPE) that will meet industrial standards.

BACKGROUND

Chitosan is the principal derivative of chitin. The primary industrial sources of chitin are the shell wastes of shrimp, lobster and crab. Chitosan is obtained through alkaline deacetylation of chitin. The advantageous biological properties i.e. nontoxicity, biocompatibility and biodegradability of chitosan makes it a useful polymer for application in the pharmaceutical and biomedical fields. Recently a chitosan salt (e.g. chitosan glutamate) is studied for its ability to enhance gastro-intestinal peptide drug delivery by mechanism of opening of the epithelial tight junctions, therefore, allowing paracellular peptide drug transport. Furthermore, a major contribution of chitosan is its ability to act as a fat absorber in dietary products. Although chitosan is present in various tablet preparations, little if any is known about its tabletability and function in tablet formulations.

Tablets are still considered as the dosage form of choice due to low manufacturing cost, good stability and excellent patient compliance. Since chitosan is a naturally abundant and relatively inexpensive polymer the application thereof in tablet formulations will prove to be advantageous from an economical point of view.

OBJECTIVES

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

1. Characterisation of chitosan raw material in terms of flow and compressibility properties to identify certain shortcomings of the powder.
2. Study and improve the compressibility of chitosan by addition of diluents. Determine the optimum concentration as well as type of diluent.
3. Investigate the compressibility of chitosan by addition of single dry binders. Determine the optimum concentration and type of binder if any effect is seen.
4. Investigate the effect of binder combinations on the compressibility of the polymer as well as the possible potentiation of binding of chitosan particles during compression.
5. Improve the flowability and compressibility of chitosan through the implementation of wet granulation and determine its applicability as processing variable.
6. Select appropriate drug carrier systems based on previous optimisations and add a tracer drug to these formulations.
7. Investigate the effects of formulation variables on drug dissolution profiles.
8. Investigate the effect of ambient conditions on the stability of chitosan raw material and chitosan tablets.

ABSTRACT

THE ASSESSMENT OF THE TABLETING PROPERTIES OF CHITOSAN THROUGH WET GRANULATION AND DIRECT COMPRESSION

Chitosan is a natural polysaccharide that is obtained by the partial deacetylation of chitin, the second most abundant natural polymer. Chitosan is currently extensively utilised in various pharmaceutical and non-pharmaceutical preparations. It has found wide applicability in conventional pharmaceutical devices as a potential formulation excipient. As a pharmaceutical excipient, its main contribution seems to be as an absorption enhancer of large molecule drugs from the gastro-intestinal tract (through "tight junctions") and as a fat absorber in dietary products. Although it is present in various tablet preparations, little if any is known about the tabletability of this versatile polymer.

Characterisation of chitosan raw material revealed poor flowability, a large particle size distribution and poor compressibility. These properties provided the challenges circumvented in this study. The direct compression of chitosan indicated that the flowability and compressibility of the polymer were insufficient to produce acceptable tablets comprising of pure chitosan raw material. Therefore, chitosan was combined with Avicel® PH200 and Prosolv® SMCC™ 90 respectively. The properties of tablets comprising of chitosan and these directly compressible fillers were compared in terms of filler concentration and mixing time. It was found that Avicel® PH200 proved to be most effective at a concentration of 30% (w/w). Furthermore, a mixing time of 10 minutes produced optimal results for all the chitosan / filler combinations.

The inclusion of single dry binders was investigated to assess the suitability of dry binders as enhancers of the binding properties of chitosan raw material. Kollidon® VA-64 (co-polyvidone) and Methocel® K100M (hydroxypropylmethylcellulose) were combined respectively with chitosan raw material in concentrations of 4, 5, 7, 10, 15 or 20% w/w. It was evident that chitosan exhibited a significantly higher sensitivity for Kollidon® VA-64 than for Methocel® K100M. A log-linear relation between the Kollidon® VA-64 concentration and crushing strength was identified. This could be considered a significant attribute of the chitosan / Kollidon® VA-64 combination, since this correlation could be utilised to predict the crushing strength of tablets comprising of chitosan and Kollidon® VA-64 at any given concentration of the binder. In comparison with the combinations containing the directly compressible fillers the

formulation comprising of 20% w/w Kollidon® VA-64 produced superior crushing strength and friability. Conversely, the chitosan / Methocel® K100M mixtures revealed erratic and relatively unacceptable results in terms of crushing strength and friability. However, the presence of Methocel® K100M in the formulations seemed advantageous to tablet disintegration. Therefore, the combination of both binders in different concentration ratios were investigated to determine whether a combination of the dry binders would result in potentiation of the binding effect during compression and furthermore if the presence of Methocel® K100M would enhance the disintegration of the tablets. Concentration ratios of 1:1; 3:1 and 1:3 (Kollidon® VA-64 : Methocel® K100M) were utilised during these experiments. The formulations comprising of single dry binders produced superior results compared to the formulations containing the dry binder combinations. Furthermore, it was evident that the binder combinations did not result in the potentiation of the binding effect nor did it prove advantageous in terms of tablet disintegration.

Since the characterisation of chitosan raw material proved that this polymer exhibited poor flowability, the subsequent wet granulation of chitosan was investigated utilising low and high speed granulation. Kollidon® VA-64 (co-polyvidone) and Methocel® K100M (hydroxypropylmethylcellulose) were the two binders utilised in concentrations of 3% and 5% w/w respectively during granulation. Wet granulation of the polymer did improve the flowabillity, however, the inherent characteristics of chitosan still affected the tabletability of the material. Therefore, the inclusion of extragranular binder was necessitated to improve the binding of chitosan granules during compression. Kollidon® VA-64 and Methocel® K100M were utilised as external binders in concentrations of 3, 5, 7 and 10% w/w. Generally, the granulation processes overall improved the tabletability of the polymer since it was possible to compress larger quantities of chitosan with the aid of selected binders. Kollidon® VA-64 posed to be better suited as a granulation binder for chitosan, compared to Methocel® K100M.

Dissolution studies provided a method to determine the effect(s) of chitosan as well as the included binders on drug release. Furosemide was included in selected formulations as a tracer drug. The gel-forming ability of chitosan in acidic pH evidently decreased the release rate of the incorporated drug. Dissolution profiles of all the formulations containing chitosan granules and extragranular binder indicated sustained release of furosemide (24 hour period). Since Methocel® K100M also possesses the ability to form a gel layer on contact with water or biological fluid, the

production of matrix tablets was a possibility. However, it was clear that a total concentration of 15% w/w Methocel® K100M was insufficient to achieve matrix-like dissolution profiles. The combination of chitosan and Methocel® K100M proved to be advantageous in the formulation of sustained release dosage forms.

Short-term stability testing of chitosan raw material proved that the exposure of chitosan to elevated temperatures had a detrimental effect on the tabletability of the polymer. Furthermore, it was evident that lower moisture content (sorbed water) detrimentally affected the compressibility of chitosan raw material. Long-term stability testing indicated that ambient conditions could have pronounced effects on the physical properties of the raw material, chitosan tablets as well as the granules. Furthermore, the tablets comprising of Methocel® K100M revealed the most significant deterioration in terms of crushing strength and friability. In contradiction, the tablets containing Avicel® PH200 revealed the most acceptable results, confirming that direct compression produced the optimal system in terms of product stability. However, the combination of chitosan with binders allows the exclusion of Avicel® PH200. However, the formulations containing binders (granulate) revealed poor stability. It could be concluded that the storage of chitosan raw material, tablets or granules should be ensured at temperatures lower that 25 °C and relative humidity not exceeding 60%.

The optimisation of chitosan raw material for utilisation in tablet formulations as well as its applicability as pharmaceutical excipient was pertinently illustrated.

UITTREKSEL

DIE BEPALING VAN DIE TABLETERINGSEIENSKAPPE VAN KITOSAAN DEUR MIDDEL VAN NATGRANULERING EN DIREKTE SAMEPERSING

Kitosaan is 'n natuurlike polisakkaried wat verkry word deur die gedeeltelike deasetiliering van chitien, die naas volopste natuurlike polimeer. Kitosaan word tans op groot skaal gebruik in verskeie farmaseutiese en nie-farmaseutiese preparate. Dit beskik oor 'n wye reeks toepassings in konvensionele farmaseutiese uitvindings as 'n potensiële formuleringshulpstof. Die belangrikste bydrae van kitosaan as 'n hulpstof is om die absorpsie te bevorder van groot geneesmiddelmolekules vanuit die spysverteringskanaal asook om op te tree as 'n vetabsorbant in verskeie verslankingsprodukte. Alhoewel, dit teenwoordig is in verskeie tabletpreparate, is min bekend oor die tabletteringseienskappe van hierdie veelsydige polimeer.

Karakterisering van kitosaan grondstof het getoon dat hierdie poeier oor swak vloei-eienskappe, 'n groot deeltjiegrootteverspreiding en swak saampersbaarheid beskik. Hierdie eienskappe het die uitdagings gestel vir die voltooiing van hierdie studie. Die direkte samepersing van kitosaan het getoon dat die vloei-eienskappe en saampersbaarheid van die polimeer onvoldoende was om aanvaarbare tablette te lewer wat net uit kitosaan grondstof bestaan. Kitosaan is geformuleer met Avicel® PH200 en Prosolv® SMCC™ 90 respektiewelik. Die eienskappe van tablette wat saamgestel is uit kitosaan en die onderskeie direksaampersbare vulstowwe is vergelyk in terme van die konsentrasie van die vulstowwe asook die mengtyd. Dit is gevind dat Avicel® PH200 die effektiefste vulstof was met 'n konsentrasie van 30% m/m. Verder het 'n mengtyd van 10 minute optimale resultate gelewer vir alle kitosaan / vulstof kombinasies.

Die insluiting van afsonderlike droë bindmiddels is ondersoek om die geskiktheid van bindmiddels as hulpmiddels vir die bindingseienskappe van kitosaan grondstof te bepaal. Kollidon® VA-64 en Methocel® K100M is respektiewelik gekombineer met kitosaan in konsentrasies van 4, 5, 7, 10, 15 of 20 %m/m. Dit is gevind dat kitosaan betekenisvol meer sensitief was vir Kollidon® VA-64 as vir Methocel® K100M. 'n Logaritmiese verwantskap is geïdentifiseer tussen die Kollidon® VA-64 konsentrasie en die breekstrekte. Laasgenoemde kan beskou word as 'n beduidende eienskap van die kitosaan / Kollidon® VA-64 kombinasie, siende dat die korrelasie aangewend kan word om die breeksterkte van tablette te voorspel wat saamgestel is uit kitosaan

en Kollidon® VA-64 met enige gegewe konsentrasie van die bindmiddel. In vergelyking met die vulstofbevattende formules, het die formulering bestaande uit 20% m/m Kollidon® VA-64 optimale breeksterkte en afsplyting gelewer. In teenstelling daarmee is wisselvallige en relatiewe onaanvaarbare breeksterkte en afsplyting getoon vir kitosaan / Methocel® K100M kombinasies. Nogtans was die teenwoordigheid van Methocel® K100M voordelig ten opsigte van tabletdisintegrasie. Gevolglik is die kombinasie van beide bindmiddels in verskeie konsentrasieverhoudings ondersoek om vas te stel of dit die bindingseffek gedurende samepersing potensieër asook of die teenwoordigheid van Methocel® K100M die disintegrasie van die tablette bevorder. Konsentrasieverhoudings van 1: 1, 3:1 en 1:3 (Kollidon® VA-64 : Methocel® K100M) is aangewend gedurende hierdie eksperimente. Die formulerings saamgestel uit afsonderlike droë bindmiddels het die beste resultate gelewer in vergelyking met die formulerings bestaande uit die bindmiddelkombinasies. Verder is dit waargeneem dat die bindmiddelkombinasies nie die bindingseffek gepotensieër het nie en dat daar ook nie 'n verbetering in tabletdisintegrasie was nie.

Aangesien die karakterisering van kitosaan grondstof bewys het dat die polimeer oor swak vloei-eienskappe beskik is die natgranulering van kitosaan ondersoek. Tydens hierdie fase is lae spoed sowel as hoë spoed granulering geïmplimenteer. Kollidon® VA-64 en Methocel® K100M is ingesluit in konsentrasies van 3% en 5% m/m respektiewelik. Natgranulering van die polimeer het die vloei-eienskappe verbeter, nogtans is die inherente, nadelige eienskappe van kitosaan nie ten volle onderdruk nie. As gevolg hiervan is die insluiting van 'n ekstragranulêre bindmiddel genoodsaak om die bindingseienskappe van kitosaan granules te bevorder. Kollidon® VA-64 en Methocel® K100M is ingesluit as ekstragranulêre bindmiddels in konsentrasies van 3, 5, 7 en 10% m/m. Die granuleringsproses het die tabletteringseienskappe van die polimeer verbeter aangesien dit moontlik gemaak is om groter hoeveelhede kitosaan saam te pers met behulp van geselekteerde bindmiddels. In vergelyking met Methocel® K100M was dit duidelik dat Kollidon® VA-64 'n meer geskikte granuleringsbindmiddel was.

Dissolusiestudies was effektief as analisemetode vir die bepaling van die effek van kitosaan asook van die ingeslote bindmidels op geneesmiddelvrystelling. Furosemied is ingesluit in geselekteerde formulerings as 'n spoorgeneesmiddel. Die jelvormingseienskap van kitosaan in 'n suur oplossing het die vrystellingstempo van die geneesmiddel duidelik verlaag. Dissolusieprofiele van al die mengsels wat

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kitosaan granulaat sowel as ekstragranulêre bindmiddel bevat het, het vertraagde vrystelling van furosemied getoon (24 uur periode). Methocel® K100M beskik ook oor die vermoë om 'n jellaag te vorm wanneer dit in kontak kom met water of biologiese vloeistowwe. Gevolglik is die moontlikheid geïdentifiseer om matrikstablette te vorm. Nogtans was dit duidelik dat 'n totale konsentrasie van 15% m/m Methocel® K100M onvoldoende was om matrikstablette te produseer. Die kombinasie van kitosaan en Methocel® K100M was egter voordelig in die formulering van verlengde vrystellingsdoseervorme.

Met behulp van korttermyn stabiliteitsevaluering van kitosaan grondstof is daar bewys dat blootstelling van kitosaan aan verhoogde temperature 'n negatiewe effek op die tabletteringseienskappe van die polimeer het. Verder is dit getoon dat 'n laer voginhoud (geadsorbeerde vog) 'n negatiewe effek op die saampersbaarheid van kitosaan grondstof het. Langtermyn stabiliteitsevaluering het aangedui dat sekere strestoestande noemenswaardige effekte op die fisiese tableteienskappe gehad het. Die Methocel® K100M tablette het die mees uitgesproke afname getoon ten opsigte van breeksterkte en verbrokkeling. Die Avicel® PH200 tablette het egter die beste resultate gelewer, wat daarop dui dat direkte samepersing die optimale metode gelewer het in terme van produkstabiliteit. Die kombinasie van kitosan met bindmiddels laat egter die uitsluiting van Avicel® PH200 toe, maar het gelei tot die swakste stabiliteit. Die gevolgtrekking was dus dat kitosaan grondstof en kitosaan tablette bewaar moet word by temperature onder 25 °C en relatiewe humiditeit van nie meer as 60% nie.

Die optimalisering van kitosaan grondstof en die aanwending daarvan in tabletformulering asook die toepaslikheid daarvan as 'n farmaseutiese hulpstof is doeltreffend geïllustreer tydens die studie.

CHAPTER 1

THE APPLICATION OF CHITOSAN IN THE FORMULATION OF COMPRESSIBLE TABLETS

1.1 INTRODUCTION

The last three decades saw pharmaceutical industry invest vast amounts of time and money in the study of tablet compaction (Rudnic & Kottke, 1996:333). Tablets are seen as the most popular dosage form, considering that it constitutes 70% of all pharmaceutical preparations. Tablets present the following advantages as a dosage form:

- It allows accurate and easy administration.
- Easy transportation from the manufacturer to the patient.
- Patient compliance is also less complicated compared to other dosage forms.
- Manufacturing simplicity, therefore resulting in greater cost efficiency.
- Tablets are more stable and uniform regarding weight and appearance.

(Rubinstein, 2000:305).

1.2. Basic considerations in the formulation of compressed tablets

Virtually all solid dosage forms are manufactured from powders and an understanding of the unique properties of powder systems is necessary for their rational application in the formulation and manufacturing of tablets (Davies, 2004:381). The majority of formulations are not composed solely of the drug, but also consists of various excipients. Accurate and reproducible dosage form production necessitates that these raw materials adhere to certain criteria (Rudnic & Kottke, 1996:335).

Flowability, compressibility and compactibility are three important physicotechnical properties of a powder. These properties characterise the tabletability of individual components or mixtures and are also greatly influenced by properties i.e. particle shape and size, density, moisture content, crystalline structure, purity and

compatibility (Rubinstein, 2000:306, Rudnic & Kottke, 1996:335-340, Leuenberger, 1986:12).

1.2.1. Powder flowability

For efficient and successful tableting, the flow properties of powders are critical. Good flow of a powder or granulation is a prerequisite to assure adequate filling of the compression dies to produce tablets of consistent weight. If a powder possesses poor flow it will result in variable die filling which will, in turn, produce tablets of variable weight and strength. The use of regular-shaped, smooth particles with a narrow size distribution enhances flowability. If such conditions are not met, the application of methods i.e. granulation, spheronisation or the incorporation of a glidant into the formulation are usually implemented to improve the flow properties of a powder (Rubinstein, 2000:306, Rudnic & Kottke, 1996:335 and Wadke *et al.*, 1989:54).

1.2.2. Powder compressibility

Leuenberger and Rohera (1986:12) described compressibility as the ability of a powder bed to decrease in volume when pressure is applied, resulting the powder bed to form an intact, stable compact (Rubinstein, 2000:306). Compressibility is an important characteristic that describes the extent to which the density of a powder is increased when subjected to a given pressure (Heckel, 1961:671). Compressibility may be markedly influenced by the particle shape and size of a powder. Therefore, it may be required to modify these attributes to optimise density, resulting in an enhancement of compressibility. Therefore an indication of the compressibility characteristics of a powder form a significant section of the preformulation evaluation (Shangraw, 1989:214-215, Wadke *et al.*, 1989:56).

1.2.3. Powder compactibility

The ability of a powder to be compressed into a tablet of specified strength is known as the compactibility (Leuenberger, 1986:12). The primary objective of tablet formulation design is the production of easily compactible, strong, pharmaceutically acceptable tablets. Therefore, it is paramount to have a sound comprehension of the effects of certain parameters on powder compaction behaviour. The parameters that predominate the compaction behaviour of pharmaceutical materials are bonding mechanisms and effective bonding surface area (Davies, 2004:409, Michrafy *et al.*, 2002:257, Nyström *et al.*, 1993:2143).

1.2.4. Consolidation and bonding mechanisms of pharmaceutical solids

The onset of the tableting process consists of the filling of the die with powder or granules at zero pressure. Initiation of the compression cycle results in particle rearrangement in the bulk powder bed. Initial rearrangements reduce the contact distances without particle deformation. This process is greatly influenced by surface characteristics, frictional properties and particle size. Mounting of the pressure results in elastic and plastic deformation of the particles, resulting in an additional reduction of the inter- and intraparticulate distances. Furthermore, an overall increase in the density of the powder bed is observed. At this stage interparticular bonding occurs and a coherent mass is formed.

The mechanism of consolidation is not solely dependant on the properties of the powder but also particle shape and size, the applied pressure and the rate of compaction (Leuenberger & Rohera, 1986:13-14).

The abovementioned facts reveal that consolidation occurs due to forces acting at the areas of true interparticle contact. There are three dominating bonding mechanisms that influence the compression of dry powders, namely: (1) solid bridges, (2) intermolecular forces and (3) mechanical interlocking (Nyström *et al.*, 1993:2158).

1.2.4.1. Solid bridges

This mechanism of bonding can be described as contact between joining surfaces in a compact at an atomic level. Solid bridges develop through interparticulate diffusion of molecules caused by partial melting at points of contact where high pressures exist. Recrystallisation of dissolved substances, chemical reactions, melting and hardening of binders may also facilitate the formation of solid bridges (Nyström *et al.*, 1993:2159, Augsburger *et al.*, 1999:10).

1.2.4.2. Intermolecular forces

High compression pressures force the powder particles into closer proximity, inducing extensive areas of true contact between the particles. Consequently, the forces at the surfaces of the particles interact to bond the powder particles. These forces are termed intermolecular forces and include Van der Waals forces, electrostatic forces as well as hydrogen bonding. Intermolecular forces are surface forces and are, therefore, significantly influenced by particle size. Accordingly, the

magnitude of these forces is increased by a reduction of the interparticulate distance (Leuenberger & Rohera, 1986:15).

Van der Waals forces are considered to be the dominant bonding force between solid surfaces and exist in vacuum, gas and liquid environments over a distance of 100 - 1000 Å (Nyström *et al.*, 1993:2158). The magnitude of the Van der Waals forces is highly dependent on the microscopic surface structure of the bonding particles. The microscopic structure is a major determinant of interparticle distance. Therefore, surface roughness in addition to specific energy of adhesion determines the magnitude of Van der Waals forces of small, bonding particles. Furthermore, it has a relative short interaction range, the overall magnitude of the Van der Waals forces on a particle can be highly sensitive to the microscopic surface structure (Feng *et al.*, 2003:65-67).

Hydrogen bonding acts as an electrostatic force and occurs inter- and intramolecularly. Electrostatic forces on powder particles result from an electric charge on the particles or from the external application of an electric field. If the molecules of a powder particle have permanent dipoles (polar molecules) the necessary charges for hydrogen bonding are complete (Feng *et al.*, 2003:66). If the molecule is not polar, the electric field will induce a temporary dipole resulting in hydrogen bonding. During the process of powder mixing electrostatic forces may effect cohesion and formation of agglomerates. Hydrogen bonding will be observed if the negative pole of a strong dipole approaches the positive charge end of another dipole which consists of a hydrogen atom. The resultant force is a particularly strong interaction. However, these temporary electrostatic forces become neutralised because of electrostatic discharging and, therefore, do not significantly contribute to the final strength of a compact (Summers, 2000:620, Wray, 1992:645).

1.2.4.3. Mechanical interlocking

This mechanism is the only mechanism that does not involve atomic forces and can be described as the hooking and twisting behaviour of a packed material under pressure. The degree to which interlocking will be evidenced significantly depends on the particle shape and surface characteristics of the particles. Particles that are needle-shaped, fibrous and irregular tend to hook and twist together more easily than smooth particles during compression. Therefore, mechanical interlocking facilitates intermolecular attraction by locking particles in close proximity to each other

(Adolfsson *et al.*, 1997:244). Mechanical interlocking is considered to have a minor effect on the bonding of particles during powder compression (Nyström *et al.*, 1993:2160, Leuenberger & Rohera, 1986:14, Wray, 1992:646).

1.3 Processes involved in tablet manufacturing

1.3.1 Powder mixing

The successful mixing of powders is a very important step in the manufacturing of tablets and can be regarded as one of the most difficult unit operations, since absolute homogeneity is almost unattainable. However, it is possible to achieve a maximum degree of randomisation. In this case the probability of finding a particle of a given component is the same at all positions. The cohesiveness and resistance to movement of the individual particles may lead to problems during the mixing process. The occurrence of different particle shapes and sizes as well as different densities of the various components of the mixture may also have an influence on the successful mixing (Rudnic & Kottke, 1996:359 and Davies, 2004:388-389).

1.3.2 The powder compaction process

The compression of powdered or granular material into a cohesive mass is a complex and irreversible process (Leuenberger, 1986:12). The following processes are involved in the compaction of a powder: (1) particle rearrangement, (2) elastic deformation of particles, (3) plastic deformation of particles, (4) fragmentation of particles, and (5) formation of interparticulate bonds (Nyström *et al.*, 1993:2146).

At the onset of the compaction process, the only forces that exist between the particles are those that are related to the packing characteristics of the particles i.e. the density of the particles and the total mass of the powder. The characteristics of the individual particles (particle shape, size and surface area) have a considerable influence on these forces (Wray, 1992:628).

As the upper punch descends into the die cavity it exerts pressure on the powder bed in the die cavity while approaching the tip of the lower punch the pressure on the powder will increase (Wray, 1992:629-630). During this step the particles rearrange themselves to achieve a closer packing. As the upper punch continues to advance on the powder bed, the rearrangement of the particles becomes more stunted and deformation of particles at points of contact begins (Rudnic & Kottke, 1996:361). At first the particle will undergo elastic deformation. Elastic deformation describes the

reversible deformation of particles as a result of the application of pressure. Consequently, alienation of pressure results in relaxation of particles to assume their original form (Wray, 1992:629-630).

The application of pressure that exceeds the elastic limit of a material produces plastic deformation. This process is irreversible; subsequently the alienation of pressure does not facilitate relaxation of particles to their original state. As an alternative to plastic deformation, brittle fracture may be observed. This irreversible, destructive deformation may be described as deformation which results in the fracture or fragmentation of the material. This arises if the material is stressed to such an extent that it is not able to withstand either through elastic or plastic deformation. This results in fragmentation of the material. Plastic deformation is considered to be a major contributing factor to the mechanical strength of a tablet whereas brittle fracture produces poor quality compacts that crumble when ejected from the die (Rudnic & Kottke, 1996:361, Davies 2004:391).

During compaction the main factor that influences the formation of a tablet is the compaction load. The primary function of the compaction load is to increase the true area of contact between the particles, and therefore, increasing the strength of the bonds formed between the particles. Factors that should be considered regarding the compaction load are the magnitude of the load, the rate as well as the duration (dwell time) of the load being applied (Wray, 1992:634).

The compaction of a powder may also be greatly influenced by some physical characteristics of the powder. These physical characteristics include crystallinity, particle size, particle shape and surface properties (Wray, 1992:636). A powder mass undergoing compaction in a die exerts pressure on the die wall at right angles to the direction of pressures. Upon completion of compression the upper punch withdraws from the die and the formed compact must be forced from the die. For the ejection of the tablet the friction between the die wall and the tablet must be overcome and the tablet must be able to withstand the expansion or elastic recovery which it will undergo following the ejection. After the removal of the force from the upper punch the relaxation of the compact is facilitated. Initially, only upward expansion is seen and is restrained by the die wall and the lower punch. As the compact is forced upward in the die, stress is generated and this stress radiates inward from the edges of the surface of contact between the die and the compact. Subsequently, the compact emerges from the die and exposes the upper edge

surface and the relaxation of the compact may progress in the radial directions outward as the tablet moves higher and higher in the die until it is completely ejected from the die (Wray 1992:653-654, Armstrong 2000:655).

1.3.3 Direct compression

Direct compression of a mixture can be considered as an easy, less labour intensive and more economical process than granulation. Considerable time and money were spent to develop direct compression formulations and especially diluents that can be used as directly compressible excipients (Carstensen, 2001:408). A multitude of direct compression vehicles are currently available and many others are currently being developed. The improvement of these excipients (diluents) leads to enhancement of performance in direct compressible formulations. Some frequently used diluents employed in direct compression are microcrystalline cellulose, silicified microcrystalline cellulose, lactose and calcium phosphate (Nada & Graf, 1998:347).

The process of direct compression provides a lot of advantages. There are few stages involved in the process, resulting in a reduction of handling cost. In addition, less machinery and equipment are needed in the formulation of direct compressible tablets. The stability of most drugs is not affected negatively since the addition of heat and water is not involved (Armstrong, 2000:654, Bolhuis & Lerk, 1973:469). However, this process is not completely flawless and has some disadvantages. The attainment of adequate content uniformity can be difficult, especially with low drug loads. Differences in particle size and bulk density between the diluent and active ingredient may occur and can easily lead to stratification during handling. The direct compression process can also be dusty and the punch wear is considerably higher compared to granulation formulations (Armstrong, 2000:654-655, Carstensen, 2001:410).

Diluents that are intended to be used in direct compression formulations have to adhere to certain prerequisites. Firstly, it should have good flow properties, ensuring uniform flow into the die. It should have a high bulk density - if the solid is light and fluffy, a relative low quantity of powder would fill the die and after compression the resultant tablet will be correspondingly thin. The particle size should minimise the segregation of the powder blend prior to compression. The substance should have a high dilution for drug substances. It should have a good pressure-strength profile so that acceptable tablets are obtained at relatively low pressures. The diluent should

be physiologically inert, not interfere with bioavailability and be compatible with the drug substance. The diluent should not be expensive as to nullify the economic advantages of the direct compression process (Armstrong 2000:654).

1.3.4 Granulation

Granulation is the most popular technique in the pre-treatment stage of a powder in order to improve the compaction characteristics of a specific powder. Granulation may be considered as a particle size enlargement process. Small particles adhere to each other facilitated by certain mechanisms to form larger and physically stronger granules than the original particles (Davies, 2004:422, Augsburger *et al.*,1999:7-8). 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 advantages of granulation are the following:

- Improved flow properties
- Densification
- Improved compression characteristics
- Better distribution of colourants / dye substances and soluble drugs if added in binder solution.
- Reduction in dusting.
- Prevention of segregation of powder mixtures.
- Increase in hydrophilicity of surfaces.

The disadvantages of the process of granulation are less in comparison with the advantages and are as follow:

- Multiple steps add complexity and make validation and control difficult.
- Time, space and equipment required are costly.
- Stability problems for moisture-sensitive and thermolabile drugs.
- Loss of material during various stages of processing.

(Augsburger *et al.*, 1999:7-8).

The three main categories of granulation are: wet granulation, dry granulation and other processes i.e. slugging.

1.3.4.1 Wet granulation

Wet granulation is an agglomeration process of individual powder particles by utilising a granulation liquid. The granulation liquid (solvent) must be non-toxic as well as volatile to accelerated removal by drying. The solvent may be used alone or in conjunction with other solvents to enhance the adhesion of the particles. It is not always practical to use water as a solvent, since it may cause the hydrolysis of susceptible products. Furthermore, water is not as volatile and, therefore, requires a longer drying time, leading to extended exposure of the drug to heat. These factors may have a negative influence on the stability of a drug. Organic solvents, i.e. ethanol and isopropanol are used when water-sensitive drugs are processed (Summers 2000:618).

The mechanisms of bonding during wet granulation depend on capillary and interfacial forces between the particles. If sufficient liquid is present a very thin, immobile layer will be formed around the particles. This adsorbed surface liquid effectively reduces surface imperfections as well as interparticulate distance and, therefore, increases surface contact between the particles. Additional liquid would result in the mobilisation of the liquid film layer. The four states of liquid distribution between particles are: pendular, funicular, capillary and droplet or suspension state. At low moisture levels, particles are held together by discreet lens-shaped rings at the points of contact. The surface tension forces of the liquid-air interface and the hydrostatic suction pressure in the liquid bridge cause adhesion. This state is known as the pendular state (Figure 1.1).

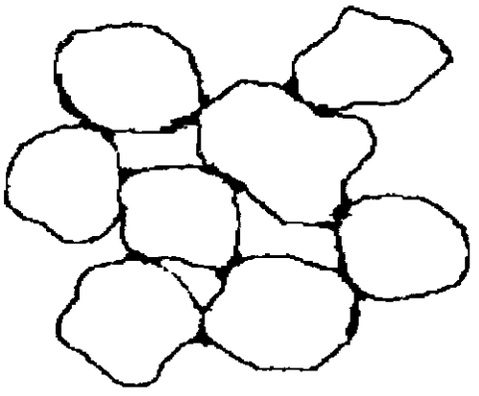


Figure 1.1: *The pendular state.*

As the moisture content increases, the lens-shaped rings combine to form a continuous network of liquid interspersed with air. This is called the funicular state (Figure 1.2). The funicular state is an intermediate state between the pendular and the capillary states.

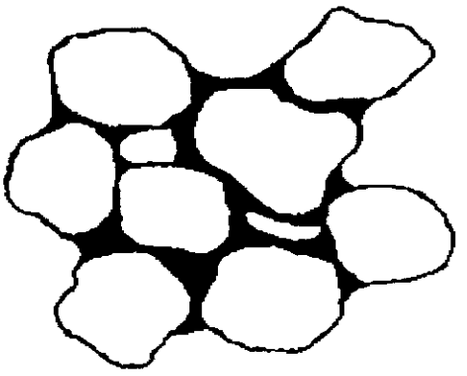


Figure 1.2: *The funicular state.*

Additional water (moisture) leads to the capillary state, characterised by completely filled pore spaces and concave menisci at the surface (Figure 1.3). However, the capillary state may also be reached just by decreasing the pore volume occupied by air and not by adding additional liquid. This can be attained by the kneading or mixing process during wet granulation.

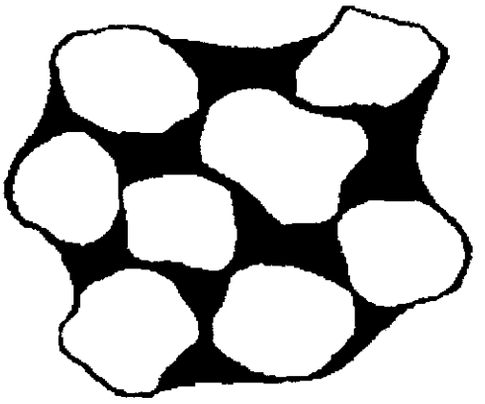


Figure 1.3: *The capillary state.*

The droplet state (Figure 1.4) is reached when the liquid completely surrounds the granule, resulting in an external liquid phase and an internal solid phase. The strength of the droplet depends upon the surface tension of the binding liquid.

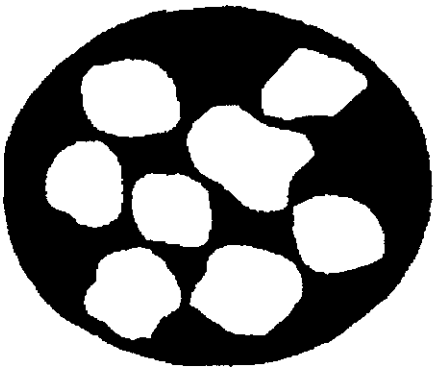


Figure 1.4: *The droplet state.*

From the four states of liquid distribution the conclusion may be drawn that the mechanism of agglomeration during wet granulation is a gradual change, from a triphasic stage (air-liquid-solid), where most granules are in the pendular and funicular states, to a biphasic stage (liquid-solid), where the granules are in the capillary and droplet states (Summers, 2000:619-620, Augsburger *et al.*, 1999:12-13).

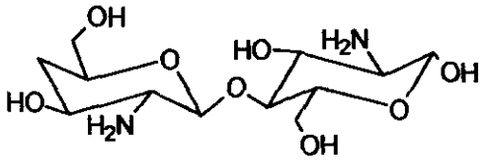
1.3.4.2 Dry granulation

During this method of granulation the particles are aggregated using high pressure. This is performed either by compressing a large tablet (slugging) or by squeezing the powder between two rollers to form a sheet (roller compaction). Either the tablet or the sheet is then milled to produce granules. The granulated material is sieved to achieve the desired size fraction. The dry granulation method is commonly used for drugs that do not comply with the wet granulation i.e. moisture sensitive materials (Summers 2000:618).

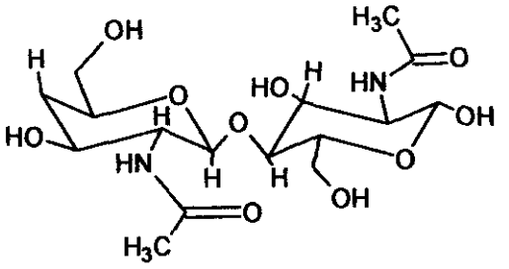
1.4. Chitosan as a pharmaceutical excipient

1.4.1. Background and characterisation of chitosan

Chitin is the second most abundant polysaccharide that exists in nature and is the major constituent of the exoskeleton of crustaceous water animals (Li *et al.*, 1997:3, Felt *et al.*, 1998:979). Chitin is an aliphatic homopolymer of which the sugar backbone consists of β -1,4 -linked glucosamine with a high degree of N-acetylation units with a three dimensional α-helical configuration stabilised by intramolecular hydrogen bonding (Figure 1.5). Chitosan is the principal derivative of chitin and is obtained through the partial alkaline deacetylation of chitin. A series of chitosan polymers exist and it differs in molecular weight (50 kDa to 200 kDa), viscosity and degree of acetylation (Felt *et al.*, 1998:979, Singla *et al.*, 2001:1047).



(1)



(2)

Figure 1.5: *The chemical structure of (1) chitin and (2) chitosan (Singla et al., 2001:1048).*

1.4.2. The physicochemical properties of chitosan

Chitosan is a collective term used to describe a series of polymers formed through the deacetylation of chitin. An important chemical characteristic of chitosan is its degree of deacetylation, since this determines the amount of free amino groups. The free amino groups are available for chemical reaction and salt formation with acids (Li *et al.*, 1997:5-6).

Its linear unbranched structure as well as the high molecular weight makes chitosan an excellent viscosity enhancer in acidic environments. Additionally, the degree of deacetylation affects the viscosity of a chitosan solution. The viscosity of chitosan solutions increases in an extent directly proportional to the degree of deacetylation. Furthermore, the viscosity is significantly influenced by temperature as well as the chitosan concentration. An increase in concentration and a decrease in temperature will also lead to an increase in viscosity of a chitosan solution. Additionally, the degree of deacetylation of chitosan influences the solubility. Chitosan with a low degree of deacetylation (40%), has been found to be soluble in media up to a pH value of 9.00. Chitosan with a degree of deacetylation of about 85% is only soluble up to a pH of 6.50. Several methods have been developed to determine of the degree of deacetylation including: infrared spectroscopy, titration, gas chromatography and dye adsorption.

The high density of amino groups in chitosan leads to a high charge density (in acidic environments) conferring strong adhesion to negatively charged substances, i.e. proteins, solids, dyes and polymers. This is an important property that renders chitosan an ideal substance for the chelation of metal ions (Singla *et al.*, 2001:1048-1049, Li *et al.*, 1997:9). Additional properties of chitosan include its insolubility in water, alkaline solvents and organic solvents and its solubility in common organic acids i.e. acetic and formic acid. Some inorganic acids may also be used to dissolve chitosan i.e. nitric acid, hydrochloric acid and perchloric acid. However chitosans with a 50% degree of deacetylation are water-soluble and are very useful in applications thereof in cosmetic, medicinal and food products where the presence of certain acids are undesirable (Li *et al.*, 1997:8).

1.4.3. The manufacturing process of chitosan

Crab and shrimp shells are the primary source of chitin, but insects and fungi also contain chitin. Chitosan is produced on a large scale in different parts of the world. Japan, North America, Poland, Norway, Russia and India are the main producers of this polymer. Seven steps are followed to manufacture chitosan. The basis of this process is the removal of proteins and minerals through the treatment of chitin with alkali and acid, respectively. The chitin-containing shells are washed and ground, preceding the treatment process that is depicted (Figure 1.6).

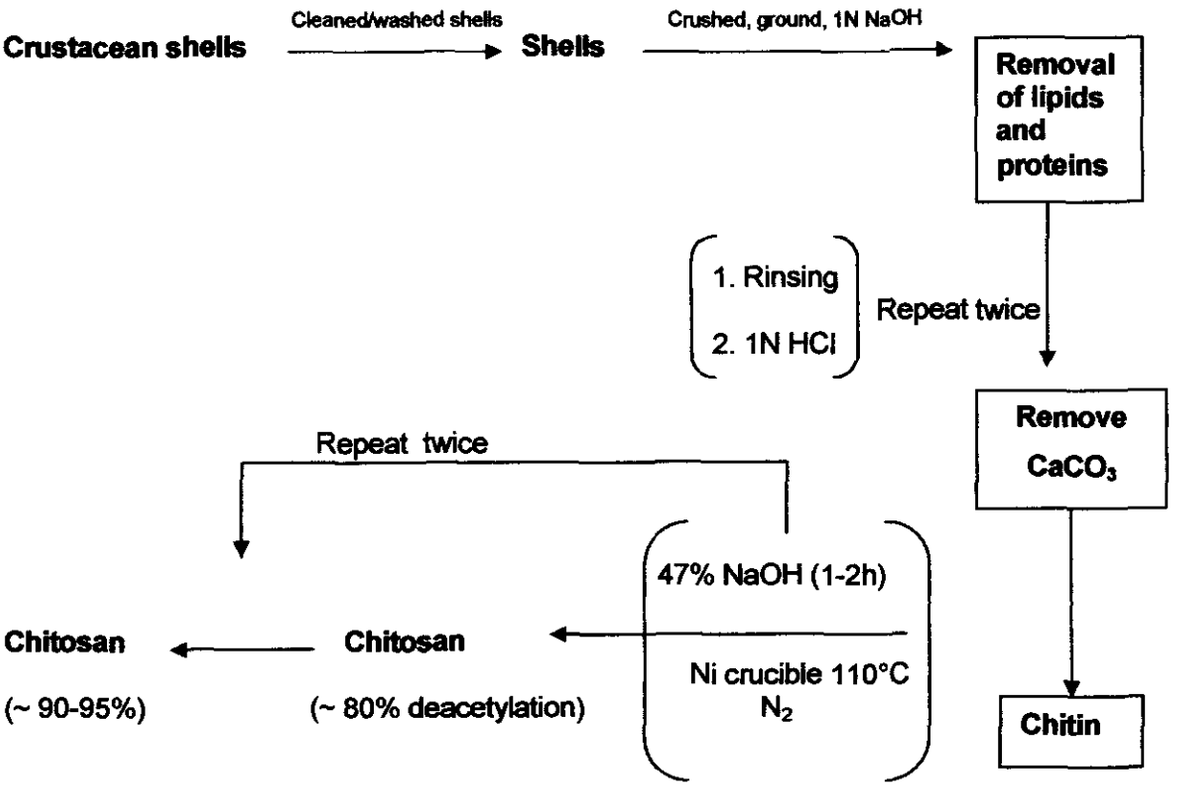


Figure 1.6: *The manufacturing process of chitosan (Singla et al., 2001:1048).*

1.4.4. General applications of chitosan

Waste water frequently contains traces of metal ions like copper, iron, lead, mercury and uranium. These metal ions may be hazardous to humans when consumed. Since chitosan is non-toxic to humans and it has very good chelating properties, one of the earliest and most important applications of chitosan is water purification. Chitosan is a powerful chelating agent and presents the best adsorbing ability of all

polymers that have been studied for this application (Li *et al.*, 1997:11, Hirano 1997:45).

Various potential applications of chitosan in agricultural processing are found since it is a natural and biodegradable polymer that does not cause pollution. The coating of seeds with chitosan has many beneficial effects. The coating inhibits fungal pathogens in the vicinity of the seeds and may shorten the germation period of seeds. Chitosan also aids in the enhancement of soil properties and is used in the manufacturing of soil fertilizers (Li *et al.*, 1997:16).

Chitosan contributes significantly to the food processing industry. The chelating and coagulating properties of chitosan are utilised in the removal of dies, solids and acid substances from juices and foods. The antimicrobial properties of chitosan assist in the extension of the preservation time of food. The coating of fruit and vegetables with chitosan prevents the release of CO_2 and ethylene that delay in their ripening and microbial infections (Li *et al.*, 1997:16, Hirano 1997:39).

1.4.5. The pharmaceutical applications of chitosan

1.4.5.1 Oral drug delivery

Deterrents of the oral route preclude the successful administration of tablets. The first-pass effect, poor oral bioaviablability and gastric mucosal irritation are major deterrents. Furthermore, controlled drug release poses another challenge to successful tablet administration (Felt *et al.*, 1998:980). Taking in account all these factors, the application of chitosan as a tablet excipient may be considered as a solution. Chitosan may be added to pharmaceutical formulations to achieve a sustained release effect and to improve the dissolution of poorly soluble drugs. This attribute can be ascribed to the fact that the chitosan base does not swell rapidly enough to be the rate-determining step during the dissolution process (Dodane *et al.*, 1998:249, Felt *et al.*, 1998:981).

Various methods have been developed to deliver sustained-release systems with chitosan. Films formed from chitosan can be used to coat granules, pellets or tablets. The use of chitosan in the spray-drying process is another method to achieve sustained release of a drug (Dodane *et al.*, 1998:249).

Chitosan has been evaluated as a directly compressible vehicle for tablets, however due to insufficient flow properties and inadequate compressibility, its utility is limited. However, chitosan may also function as a binder, lubricant or disintegrant in tablet formulations, but still the most important property of chitosan, namely the degree of deacetylation greatly influences the use of chitosan as a tablet excipient as well as its effect on tablet properties (Singla *et al.*, 2001:1050, Dodane *et al.*, 1998:249 & Felt *et al.*, 1998:981). The formation of granules or beads using chitosan are typical methods to establish controlled drug release. The drug is incorporated into the granules or beads and the mechanism of drug release depends on the disintegration of the matrix in the granules or the diffusion of the drug from the beads (Singla *et al.*, 2001:1050 and Felt *et al.*, 1998:983).

1.4.5.2 Parenteral drug delivery

Chitosan microspheres are successfully used for drug delivery via the parenteral route. Drugs i.e. furosemide, indomethacin, methotrexate and theophylline may be entrapped in the chitosan microspheres. These microspheres has the ability to localize to the target site and since chitosan is biodegradable and non-toxic to living tissues it is a safe and effective method to deliver a drug to a specific site. Additionally, microspheres control the release rate of the drug and protect the drug from denaturation and degradation. This is especially useful in the administration of chemotherapy drugs (Felt *et al.*, 1998:982, Dodane *et al.*, 1998:250).

1.4.5.3 Ocular drug delivery

Topically applied ophthalmic drugs usually depict poor bioavailability and frequent administration of the drug is required to assure successful treatment. Therefore, chitosan dosage forms could ensure increased drug absorption and prolonged contact time of the drug to the corneal area. The use of a chitosan-based colloidal suspension can be useful to facilitate in the prolonged release of a drug in the corneal area, since this suspension shows pseudoplastic and viscoelastic properties (Felt *et al.*, 1998:987-989, Dodane *et al.*, 1998:250).

1.4.5.4 Nasal drug delivery

The nasal route of administration provides an effective alternative for drugs with a poor oral bioavailability, since the nasal cavity has a large epithelial surface area due to the large amount of microvilli. However, a disadvantage of the nasal cavity as a drug delivery site is the rapid mucociliary clearance. This is where the application of

chitosan in nasal delivery systems is of importance. Chitosan exhibits good mucoadhesive properties and controls the release rate of the drug in the nasal cavity (Felt *et al.*, 1998:987).

1.4.5.5 Other delivery systems containing chitosan

The film-forming characteristics of chitosan may be exploited in the formulation of membrane delivery systems. These chitosan membranes may be incorporated into transdermal devices to transport both hydrophobic and hydrophilic drugs to their sites of action. Since chitosan is a natural biodegradable, non-toxic polymer, it is also useful in the development of implants. The development of new carrier systems for gene delivery is another area of pharmaceutical technology where chitosan may be applied. DNA-chitosan complexes may be formed and the addition of appropriate ligands results in efficient gene delivery via receptor-mediated endocytosis. Therefore, it can be accepted that chitosan exhibits comparable efficacy in gene delivery without the associated toxicity of other synthetic vectors (Singla *et al.*, 2001:1056, Felt *et al.*, 1998:989, Dodane *et al.*, 1998:251).

1.4.6. Concluding remarks

Chitin has few applications in the pharmaceutical industry compared to chitosan. Chitosan provides a multitude of possibilities to its unique properties. It has been shown that chitosan is a versatile, cost-effective and therefore, useful excipient. Therefore, the main areas of application of chitosan in the pharmaceutical industry are as matrix material and bioadhesive materials.

1.5. Pharmaceutical excipients used in combination with chitosan

As mentioned, chitosan is useful in tablet formulations. Nevertheless, certain characteristics of chitosan may be a drawback that may limit the application thereof in tablet compression. Therefore, chitosan formulations may require the inclusion of some tablet excipients to either improve the tabletability or the characteristics of the final tablets. The selection of excipients is based on their functions and the challenges posed by the filler. Furthermore, the selection of excipients is compounded by the vast array of available excipients. The following sections focus on the types and functions of selected excipients.

1.5.1 Basic tablet excipient principles

Pharmaceutical excipients may be defined as inert substances that are included in formulations to improve the manufacturing process, the stability, bioavailability as well as patient compliance. It should, additionally, enhance the safety and effectiveness of the product. An excipient should also be physically and chemically stable when it comes in contact with air, heat or moisture. To avoid adverse reactions of the excipients it has to be compatible with the other tablet components as well as the packaging components. Some excipients may possess multi-functionality as a disintegrant, lubricant, diluent or binder. However, this attribute depends on the concentration at which it is employed (Jivraj *et al.,* 2000:58 and Moreton, 1995:12).

1.5.2 Diluents

Diluents are bulking agents; they are added to produce tablets of an appropriate size since most drugs are administered in very low dosages. Diluents are often used in large quantities and should be cost-effective and comply with the prerequisites of direct compression. Organic and inorganic materials are utilised as diluents. Carbohydrates are the primary organic material since it possesses properties i.e. low toxicity, acceptable taste, compatibility with other components, and good solubility characteristics (Rudnic & Kottke, 1999:344). Table 1 summarises the commonly formulated diluents and some of their characteristics.

Table 1.1: *Tablet diluents and some characteristics (Armstrong, 2000:310).*

Lactose	Dissolves easily in water and adsorbs little moisture that enhances stability Produces acceptable tablets since it is easily compressible Possesses however poor flow properties and is quite expensive
Dicalcium phosphate	Insoluble in water, adsorbs very little moisture and is therefore used with hygroscopic drugs Produces hard, white granules of excellent quality
Starches	Are multifunctional since it may be used as a binder as well Contain ±14% moisture and may lead to stability problems
Microcrystalline cellulose	Very popular diluent, since it possesses disintegrating as well as lubricative properties and is therefore usually used in direct compression formulations
Dextrose	Is not a very acceptable diluent in comparison with the other diluents since it produces soft granules and adsorbs a substantial amount of moisture
Sucrose	Its main use is in the formulation of lozenges Very hygroscopic
Mannitol	Possesses the ability to dissolve very quickly, is therefore used in tablets that have to dissolve quickly Possesses negative heat of solution, resulting in a cooling sensation when chewed, therefore it is used in chewable tablets since it has a pleasant taste and leave a cooling sensation when chewed.

Since microcrystalline cellulose and silicified microcrystalline cellulose were selected as diluents during this study a complete discussion of these materials will follow. Vast amounts of time and money have been spent by the pharmaceutical industry to investigate the application of cellulose and cellulose derivatives in solid dosage forms. In September 1962 the microcrystalline form of cellulose, namely Avicel®, was produced. Microcrystalline cellulose is derived from a special grade of alpha purified wood cellulose. Acid hydrolysis of wood cellulose forms matchlike microcrystals followed by spray-drying of the slurry to produce microcrystalline cellulose (Fox *et al.*, 1963:161).

Microcrystalline cellulose is an inert material that may be compressed into very hard tablets using normal tableting equipment, since it is a free-flowing material with an extremely high surface area. The fact that microcrystalline cellulose has excellent compactability is one of the main reasons why it is used as a diluent in directly compressible formulations. Considering all these attributes it is clear to see why microcrystalline cellulose is a widely used tablet excipient (Fox *et al.*, 1963:161).

Recently silicified microcrystalline cellulose has been developed. It is a co-processed product which is manufactured of 98% microcrystalline cellulose that is silicified with 2% colloidal silicon dioxide. These two components are spray-dried together to produce agglomerated crystals (Jivraj *et al.*, 2000:62). Studies conducted by Tobyn *et al.* (1998), proved that the silicification process does not induce marked changes in the shape and texture of the microcrystalline particles in comparison with microcrystalline cellulose. Furthermore, compared to microcrystalline cellulose there exist little difference between these two materials regarding density and porosity measurements. Hereby, it could be concluded that it is not the change in the chemical attributes of silicified microcrystalline cellulose, but some other intrinsic factor that contribute to the improved functionality of this material (Tobyn *et al.*, 1998:187). This diluent exhibits good binding characteristics in direct compression and wet granulated formulations and is therefore a good alternative to utilise in tablet formulation (Edge *et al.*, 2000:67).

1.5.3 Binding agents

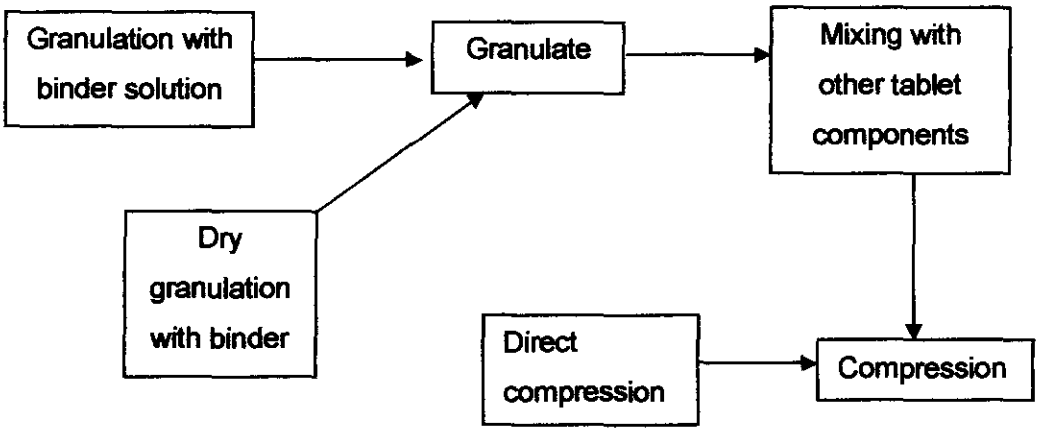
Binders are materials that act as adhesives to adhere the individual particles or crystals together. Binders are commonly used in wet granulation but may also be applied effectively in direct compression formulations. In wet granulation, binders aid in the size enlargement of particles and the formation of granules, resulting in the improvement of the flowability of the powders (Khankari 2001:60).

Most binders tend to have polymeric characteristics and are derivatives of cellulose or starch. The following binders are most commonly applied in granulation: cellulose derivates, polyvinylpirrolidone, starch mucilage, glucose syrups and gelatine solutions.

1.5.3.1. Polyvinylpirrolidone

Polyvinylpirrolidone constitutes a part of the synthetic polymers utilised as binding agents. Since it is a versatile material, it is one of the most commonly used binders. Polyvinylpirrolidone (PVP) is classified into different grades according to its molecular weight. Since it is readily soluble in water and alcohol it is usually applied as a solution. Aqueous solutions of PVP are frequently utilised in the granulation of water-insoluble materials whereas PVP dissolved in alcohol are used to granulate water-soluble materials (Khankari 2001:64).

The molecular weight, particle size and density of the binder influence the dissolution rate of the tablets. Furthermore, the degree of distribution of the binder has a significant influence on the characteristics of the formed compact (Drummond, 1995:80). Polyvinylpirrolidone occurs in soluble and insoluble grades. The soluble grades are obtained by free-radical polymerization of vinylpirrolidone in water. The most common soluble grades are Kollidon® 25, Kollidon® 30 and Kollidon® 90F. An advantage of the soluble grades is their universal solubility that ranges from hydrophilic solvent i.e. water to more hydrophobic solvents i.e. ethanol. The viscosity of solutions of Kollidon® is directly proportional to the molecular weight of the polymer and is independent of the pH value of the solution. PVP is a hygroscopic substance, possessing enhanced in the presence of moisture. The soluble Kollidon® grades also exhibit film forming properties that may be utilised for the film coating of tablets (Bühler, 1993:71).



Scheme 1.1: *General methods in the application of Kollidon®.*

A good correlation exists between the percentage binding agent present in the formulation and the achieved strength of the granules. A low concentration binding agent may result in soft granules that may be unsuitable for tableting. Whereas a high concentration binder may result in large, hard granules that also has a negative effect on tabletability (Rubinstein, 2000:310). Frequently applied concentrations of Kollidon® as a binder in tablets and granules are the following: Kollidon® 25 2-5%, Kollidon® 30 2-5%, Kollidon® 90 1-3%.

Kollidon® VA 64 (copolyvidone) differs from the soluble Kollidon® grades regarding the number 64 in the trade name. The number is not a K-value but the mass ratio of the two monomers, vinylpirrolidone and vinyl acetate. As for the soluble Kollidon® grades, Kollidon® VA 64 is useful as a binder in tablets and granules. Kollidon® VA 64 has the advantage of being less hygroscopic compared to the soluble grades. It also absorbs approximately three times less water than Kollidon® 25, 30 and 90F. Additionally, Kollidon® VA 64 may be utilised in the formulation of sustained release preparations. In comparison with tablets containing the soluble grades of Kollidon® the tablets containing Kollidon® VA 64 dissolve more slowly resulting in a decrease of the dissolution rate (Bühler, 1993:227). Another property of Kollidon® VA 64 that the soluble grades do not possess is plasticity. This characteristic decreases capping during compaction. Additionally, the tablets are less brittle than the water-soluble counterparts (Bühler, 1993:214).

1.5.3.2. Cellulose derivatives

The cellulose derivatives used as binders include methylcellulose, hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose and ethylcellulose.

Methylcellulose is a substituted long-chain cellulose where approximately 27 – 32% of the hydroxyl groups are converted to the methyl ether. Methylcellulose is also available in different variety of grades depending on the various degrees of substitution and molecular weight. A drawback of methylcellulose is that it is practically insoluble in hot water, ethanol, chloroform and ether. However, it swells in cold water to form a clear opalescent and viscous solution. Methylcellulose may be formulated as a binder in solution or simply as a dry binder. However, application of methylcellulose as a binder solution produces granules of significant compressibility, a fact not evident for its dry binder incorporation (Khankari, 2001:64).

Sodium carboxymethylcellulose (Na–CMC) is a sodium salt derivative of the carboxymethyl ethers of cellulose. In comparison to methylcellulose it is readily soluble in water at any temperature and produces clear solutions. This attribute makes it an ideal binding agent for water insoluble drugs. The granules produced from Na-CMC are softer but easy compressible. Hydroxypropylmethylcellulose (HPMC) is characterised as a propyleneglycol ether of methylcellulose. HPMC exists in a variety of viscosity grades. These grades are determined by the molecular weight of the polymer (Khankari 2001:64). HPMC is the excipient of choice in the formulation of hydrophilic tablet matrices, obtaining controlled drug release. An important characteristic is the different ratios of methoxy and hydroxypropyl groups. This attribute may affect the compaction behaviour and the dissolution profiles of the compacts. A higher percentage of the more hydrophobic methoxy groups may result in a decrease in hydrogen bonding between the particles, resulting in a reduction of the compact strength. The methoxy content determines the hydration rate and hydration is inversely proportional to the methoxy content. In turn, the hydration rate will determine the rate of swelling in a directly proportional relation. Consequently, drug release is inhibited in a controllable fashion (Gustaffson *et al.*, 1999:183).

1.5.4 Other excipients

The aim of the study is to investigate the behaviour of chitosan as an excipient. Therefore, other excipients will only be mentioned and will not be described in detail. Other excipients used in tablet formulation are disintegrants, glidants and lubricants. Disintegrating agents are added to tablets to facilitate the destruction of the tablets submerged in an aqueous environment. Disintegrants are utilised to rapidly disintegrate the tablet to increase the surface area and to accelerate the drug release process. Common disintegrants are starch, cross-linked polyvinylpirrolidone and cellulose materials (Rubinstein, 2000:312). Glidants are added to tablet formulations in order to improve the flow properties of the powder mixture, by reduction of the interparticulate friction i.e. colloidal silica. Magnesium stearate is the most popular lubricant that is applied in tablet formulations. Lubricants are added to powder mixtures to prevent the adherence of the tablets to the tooling of the tablet press. Lubricants facilitate the ejection of the tablet from the die (Rubinstein 2000:311).

1.5.5 Concluding remarks

Chitosan has been investigated as a potential excipient in the pharmaceutical industry, to be used in direct tablet compression, as a tablet disintegrant, for the production of controlled release solid dosage forms and the improvement of drug dissolution, respectively. Compared to other excipients chitosan exhibits superior characteristics and flexibility in its use (Lisbeth 1998:1326). Substantial progress has been made in the application of chitosan in various pharmaceutical fields. However, the application of chitosan as a direct compression filler requires additional investigation prior to its acceptance as a tableting excipient. Therefore the aim of this study is the characterisation of chitosan regarding compressibility. Consequently, the drawbacks of the material will be identified and circumvented. The appropriate incorporation of excipients should render the material multifunctional as well as economically satisfactory. Furthermore, the optimisation of chitosan would ensure compatibility with the processes of both direct compression and wet granulation.

CHAPTER 2

EXPERIMENTAL METHODS, APPARRATUS AND MATERIALS

2.1 INTRODUCTION

This chapter discusses the experimental methods and apparatus that were used to conduct this study. Additionally, the selection of materials and their purpose are discussed.

2.2 MATERIALS

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

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

MATERIALS	LOT NUMBER	MANUFACTURER
Chitosan	021010	Warren Chemicals Ltd, Durban, South Africa
Avicel® PH200	M926C	FMC Corporation, Little Island, Cork, Ireland
Prosolv® SMCC™ 90	P951027	Penwest, Surrey, England
Kollidon® VA-64	62-8826	BASF, Aktiengesellschaft, Ludwigshaven, Germany
Methocel® K100M	QI25012	Colorcon, Kent, England
Furosemide	3017HJ11	D.B. Fine Chemicals, Johannesburg, South Africa

2.3 CHARACTERISATION

2.3.1. Particle size and particle size distribution

A sound knowledge of the particle size and size distribution of a material is essential to predict the behaviour of the material during mixing and compression. The method of laser diffraction by means of a Malvern® Mastersizer X (Malvern Instruments Ltd., Worcestershire, UK) was applied to measure the particle size of chitosan. A MSX1 sample unit suspension and a 300 mm lens were used during this procedure. Samples were prepared by suspension of 1.5 g chitosan in 15 cm^3 ethanol. The sample was transferred to the sample unit and cycled through the apparatus by addition of 300 cm^3 of dispersion liquid. The analysis was repeated four times to calculate the particle size and particle size distribution of chitosan.

2.3.2 Determination of density

The density of a powder can simply be defined as the mass of a known amount of powder per unit volume of powder. Several parameters are utilised to describe the density of a powder, namely true density, bulk density, tapped density and porosity.

2.3.2.1 Bulk density

The bulk density of a powder is defined as a given mass of the powder that occupies a volume. This volume includes both the particulate volume and the pore volume. Thus, bulk density can be defined according to the following relationship:

$$\rho_B = \frac{w}{v} \qquad (2.1)$$

where ρ_B = bulk density ($g.cm^{-3}$), w = weight (g) and v = volume (cm^3)

The bulk density of chitosan was determined by pouring a given mass (100 g) chitosan powder into a graduated cylinder. The volume that the powder occupied was noted and the bulk density was calculated according to equation 2.1. This procedure was repeated in triplicate and the mean value was calculated.

2.3.2.2 Tapped density

The tapped density can also be defined by means of equation 2.1, the only difference being the volume occupied by the powder. Tapped density was achieved by placing a given mass (100 g) chitosan powder into a graduated cylinder. The cylinder was placed on a vibrating apparatus (Fritsch® analysette) that was set to an amplitude of 5. Subsequently, the cylinder was tapped and the volume was noted at time intervals of 5 minutes. This was repeated until the powder in the cylinder reached a constant volume after approximately 15 minutes. The tapped density was calculated using equation 2.1. The tapped volume does not include pore volume, since the air trapped between the particles has been displaced during the tapping process.

2.3.2.3 True density

The true volume of a powder is always less than the bulk volume of a powder since true density excludes intraparticulate pores or voids. A powder possesses only a single characteristic true density.

The true density of chitosan was determined by transferring an accurately weighed sample in a container of known volume. Subsequently, the sample was analysed using a Quantachrome® stereopycnometer (model SPY–4, Quantachrome Corp., Boyton Beach). The sample was analysed in triplicate and the mean value was calculated.

2.3.2.4 Porosity

The porosity 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. Porosity was calculated by means of the following equation:

$$\text{Porosity} = 1 - \left(\frac{\rho_B}{\rho_T}\right) \qquad (2.2)$$

where ρ_B = bulk density (g.cm^{-3}) and ρ_T = tapped density (g.cm^{-3})

The triplicate measurements of bulk and tapped density were used to calculate three porosity values. These values were used to calculate the mean value of porosity.

2.3.3 Determination of the flow properties

It is paramount to determine the flow properties of powders, since it aids in the prediction of die filling efficiency. This in turn ensures reproducible tableting. During these experiments it is essential to quantify this behaviour to aid in the selection of certain processes necessary to improve the flow properties of the powder. The Carr's index, Hausner ratio and angle of repose were used to quantify the flowability of chitosan raw material.

2.3.3.1 Carr's index

Carr's index quantified the flowability utilising the previously calculated poured bulk density and the tapped density (2.2 and 2.3). Equation 2.3 expresses the calculation of Carr's index.

$$\text{Carr's Index} = \frac{\rho_T - \rho_{PB}}{\rho_T} \times 100 \qquad (2.3)$$

where ρ_T = tapped density and ρ_{PB} = poured bulk density

The quantification of the Carr's index was used to indicate powder flow as indicated in table 2.1.

Table 2.2: *Indication of powder flow by means of the Carr's index (Wells et al., 2000:247).*

Carr's index (%)	Flowability
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
> 40	Extremely poor

2.3.3.2 Hausner ratio

An additional method that was applied to quantify the flow characteristics of chitosan was by means of the Hausner ratio.

$$\text{Hausner ratio} = \frac{\rho_T}{\rho_{PB}} \qquad (2.4)$$

where ρ_T = tapped density and ρ_{PB} = poured bulk density

The mean tapped and poured bulk density values were substituted into equation 2.4 to determine the Hausner ratio.

2.3.3.3 Angle of repose

The angle of repose is a well-known technique to determine flow characteristics of a powder. The experimental procedure was conducted as follow: A weighed amount of powder (100 g) was poured into the hopper and then the shutter was released, resulting in the effluence of the powder onto a vertical glass plate. The powder formed a cone of which the angle in correspondence with the vertical surface was measured. For the calculation of the angle of repose of chitosan powder a stainless steel hopper fitted with a shutter at the efflux opening was used. The diameter of the opening was determined at approximately 27.5 mm. The time it took for all the powder to flow from the hopper to the glass plate was measured and the flow rate of the chitosan powder determined.

2.3.4 The thermogravimetric analysis (TGA)

TGA thermograms were recorded with a Shimadzu® TGA-50 instrument (Shimadzu, Japan). Approximately 3 mg of chitosan powder as well as a platinum sample holder were used during the analysis. Nitrogen gas was used at a flow rate of 45 cm^3 per minute and a heating rate of 10 °C per minute was applied.

2.3.5 The Karl Fischer analysis

The moisture content was determined with a Metler® DL18 Karl Fischer titrator. The Karl Fischer solution was calibrated against a predetermined mass of water. Methanol was neutralised with the Karl Fischer solution prior to use in the analysis.

About 250 mg chitosan powder was accurately weighed and added to the methanol, in a titration beaker. The mixture was continuously using a magnetic stirrer and titrated with the Karl Fischer solution. The experiment was performed in duplicate and the percentage water content (w/w) was calculated.

2.3.6 Differential scanning calorimetry (DSC) analysis

Differential scanning calorimetry is a method to determine the melting point of a material. The DSC apparatus measures the amount of energy required to keep the sample at the same temperature as the reference, in effect measuring the enthalpy of transition (Wells *et al.*, 2000:236). DSC thermograms of chitosan powder were recorded with a Shimadzu® DSC-50 instrument (Shimadzu, Japan). Approximately 2 mg chitosan powder was analysed in a nitrogen gas atmosphere with a flow tempo of 45 cm^3 per minute. The heating rate was inducted with an increase in temperature at increments of 10 °C per minute.

2.4 THE PREPARATION AND EVALUATION OF CHITOSAN TABLETS

Direct compression and wet granulation were implemented during the formulation of chitosan tablets. Preliminary experiments ascertained that it was not possible to directly compress tablets containing pure chitosan raw material. The produced tablets exhibited poor mass uniformity and insufficient crushing strength. Therefore, it was evident that the addition of other tablet excipients (diluents and binders) was essential for the direct compression of chitosan powder.

2.4.1 Formulation of directly compressible chitosan tablets

Two microcrystalline cellulose-based diluents, Avicel® PH 200 and Prosolv® SMCC™ 90, were used to produce directly compressible formulations. These two diluents were combined with chitosan in different ratios, determining the minimum amount of diluent necessary to produce acceptable tablets. The effect of the addition of a binder or binder combination on the delivery of directly compressed tablets was also investigated.

2.4.1.1 Determination of the optimum chitosan/filler combination

Since it was not possible to directly compress chitosan without the addition of other excipients, a study was conducted to determine the minimum amount of directly compressible filler necessary for the inclusion in tablet formulations. The rationale for including a directly compressible filler was the possible improvement it would have on the flow and binding properties of the formulation.

Microcrystalline cellulose served as filler in these experiments. The excellent suitability of the filler to direct compression could augment the compactibility of formulations not compatible with direct compression (Edge *et al.*, 2000:67). Therefore, the application of two commercial grades of microcrystalline cellulose, Avicel® PH 200 and Prosolv® SMCC™ 90, in combination with chitosan was investigated. Avicel® PH 200 consists of pure microcrystalline cellulose (average particle size approximately 200 µm), whilst Prosolv® SMCC™ 90 contains microcrystalline cellulose (average particle size 90 µm) and 2% w/w silicon dioxide that is coated on the cellulose particle surface. Table 2.2 summarises the chitosan/filler combinations that were evaluated during these experiments.

Table 2.3: *The chitosan/filler combinations that were evaluated.*

Filler	Chitosan:Filler (%w/w)		
Avicel® PH200	60:40	70:30	80:20
Prosolv® SMCC™ 90	60:40	70:30	80:20

2.4.1.2 Preparation and compression of chitosan/filler mixtures

The chitosan/filler mixtures (Table 2.3) were prepared by the following procedure: The amount of each component was accurately weighed in 300 cm^3 glass containers with a total mixture weight of 100 g. Each container was sealed with Parafilm® before the lid was secured. Mixing was effected in a Turbula® mixer (model T2C W.A. Bachofen, Basel, Switzerland) at 69 rpm for periods of 5, 10 and 20 minutes.

The mixtures were compressed on a Cadmach® eccentric press using 10 mm flat-faced tooling. The applied compression load was kept at a constant setting of 50. The tablets were stored in sealed containers in a cool, dark environment for a period of 24 hours prior to analyses.

2.4.1.3 Preparation and compression of chitosan/dry binder mixtures

Since the poor compressibility of chitosan made it impossible to compress tablets containing pure chitosan raw material, the inclusion of dry binders were investigated. The motivation for the addition of binders was to achieve sufficient binding of chitosan particles during compression. Kollidon® VA-64 (vinyl acetate / polyvinylpirrolidone copolymer) and Methocel® K100M (hydroxypropylmethylcellulose) were evaluated as binders, either individually or in combination. Table 2.4 shows the composition of the tablets containing the binder(s). The formulations comprising of chitosan and added dry binders were prepared and compressed according to the protocol described (section 2.4.1.2).

Table 2.4: *Composition of chitosan tablets containing various dry binders.*

Component	Binder type	Binder ratio	Total binder concentration in chitosan mixture (% w/w)
Binder	**Single dry binder**		
	Kollidon® VA-64	Not applicable	4, 5, 7, 10, 12, 15, or 20
	Methocel® K100M	Not applicable	4, 5, 7, 10, 12, 15 or 20
	Dry binder combinations		
	Kollidon® VA-64 / Methocel® K100M	1:1	2
			6
			10
		1:3	4
			12
			20
		3:1	4
			12
			20
Chitosan	Qs 100%		

2.4.2 Formulation of chitosan tablets utilising wet granulation

During the direct compression phase of chitosan it was revealed that relative high concentrations of other excipients (diluents and binders) had to be included in order to produce acceptable tablets. Therefore, the objective of the wet granulation phase was the enhancement of the flow and compression characteristics of chitosan powder by means of the inclusion of excipients (binders) in low concentrations.

2.4.2.1 Preparation of chitosan granules

The two binders of choice for the wet granulation of chitosan powder were the same as for the direct compression phase namely, Kollidon® VA-64 and Methocel® K100M. Table 2.5 gives a description of the excipients, the type and the quantities that were used during the granulation of chitosan.

From a series of preliminary experiments it became clear that the mixing speed had a significant influence on the characteristics of the granules. Therefore, two granulation methods were implemented i.e. a low speed method (pestle and mortar) and a high speed method (automated planetary mixer).

Table 2.5: *Excipients and quantities used during the wet granulation of chitosan.*

Excipient	Type	Concentration (%w/w)	Granulation fluid	Volume granulation fluid (cm^3)
Binder	Kollidon® VA-64	3	Ethanol	400
		5		500
	Methocel® K100M	3	Distilled water	400
		5		500
Chitosan	Qs to 100%			

2.4.2.1.1 High speed granulation

The high speed granulation utilising Kollidon® VA-64 was preformed by means of the following method. The total amount of ethanol (Table 2.4) was transferred to the aluminium mixing bowl. The ethanol was agitated at the lowest speed setting (45 rpm) whilst small amounts of Kollidon® VA-64 were added. After complete addition of

binder to ethanol the mixer was switched to the maximum mixing speed (160 rpm) and the binder solution was mixed for 5 minutes. Subsequently chitosan was added to the binder solution and mixing continued for an additional 5 minutes. The paste was granulated by means of a granulator using a 16 size mesh sieve, dried in an oven at 60°C ± 5 °C for a period of 1 hour and regranulated through a 12 mesh size sieve. The granules were stored in a Parafilm®-sealed glass container and protected from light and moisture for future use.

The high speed granulation utilising Methocel® K100M as intragranular binder can be described as follows. Two thirds of the distilled water (Table 2.4) was heated on a hot plate until boiling point was reached. The heated water was transferred to the aluminium mixing bowl. The mixer was switched to the lowest speed (45 rpm) and the binder (Table 2.4) was added in small portions. After all the binder was dissolved the mixer was set to the maximum mixing speed (160 rpm) and the solution was mixed for 5 minutes. Chitosan was added and mixed at the highest speed setting for a further 5 minutes after all the chitosan was added so that a viscous slurry was obtained. The slurry was transferred to a stainless steel plate and dried at 80 °C ± 5 °C for 1 hour. The dried mass was granulated by means of a granulator using a 16 mesh size sieve. The granules were then dried for another hour followed by regranulation through a 12 mesh size sieve. The granules were stored in a glass container sealed with Parafilm® to protect it from light and moisture until compression.

2.4.2.1.2 Low speed granulation

The low speed granulation method was performed by means of the same method as described for the high speed granulation, the only difference being the mixing process. Manual mixing of the ingredients (Table 2.4) was performed utilising a pestle and mortar for a sufficient period of time.

2.4.2.2 Compression of the granules

Both the Kollidon® VA-64 and Methocel® K100M granulates, obtained through the low speed and high speed granulation methods, were compressed using a Cadmach® eccentric press and 9 mm flat-faced tooling. The applied compression load was kept constant at 50 during compression. The tablets were stored in sealed containers and protected from light and moisture for a period of 24 hours prior to the physical analyses of the tablets (section 2.5).

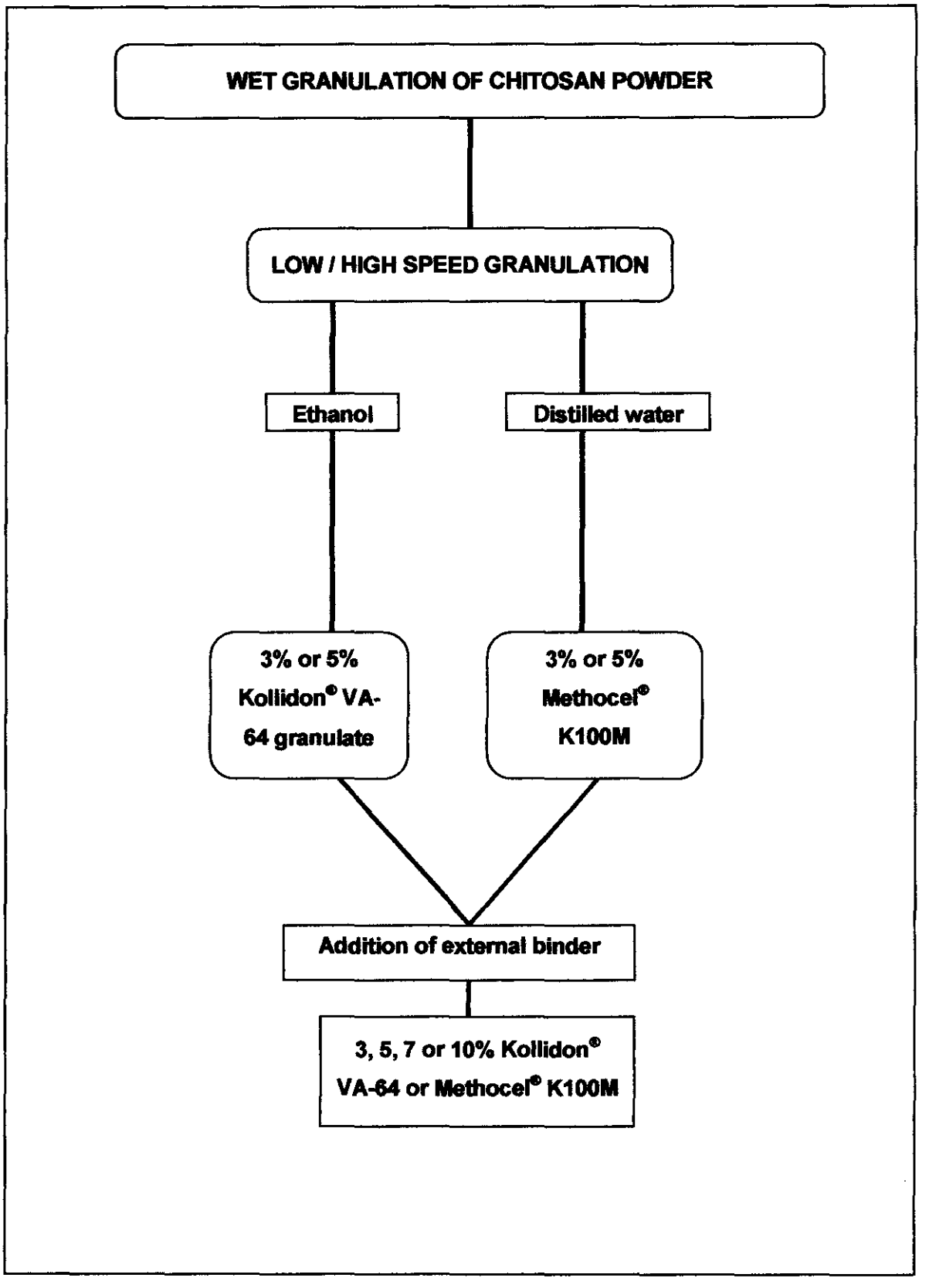
2.4.2.3 Incorporation of extragranular binder

The compression of the obtained granules yielded tablets that exhibited poor crushing strength and poor weight uniformity. Therefore, the intragranular binder was not sufficient to achieve satisfactory bonding of the granules during compression. Consequently, the incorporation of external binders was investigated as an alternative method of improving binding properties of the granules.

Various concentrations of external binders were added to the different granulates that were prepared as described in sections 2.4.2.1.1 and 2.4.1.1.2. Table 2.6 contains an outline of the binders and quantities that were used during these experiments. All the components were accurately weighed to deliver an amount of 40 g of each mixture, followed by mixing in a Turbula® mixer for 10 minutes. Subsequently, the formulations were compressed utilising a Cadmach® eccentric press equipped with 9 mm, flat-faced punches. The tablets were stored in sealed containers protected from light and moisture for a period of 24 hours prior to the physical analyses of the tablets.

Table 2.6: *Quantities external binder added to granulate to facilitate compression.*

Granulate	**External binder**	
	Concentration (%w/w)	**Weight (g)**
Kollidon® VA-64 or Methocel® K100M (3 or 5% w/w)	3	1.2
	5	2.0
	7	2.8
	10	4.0
Chitosan	Qs to 100%	



Scheme 2.1: *Summary of the wet granulation of chitosan raw material.*

2.5 Physical analyses of the tablets

The following analyses were performed on both the directly compressible and wet granulation formulations.

2.5.1 Weight variation

Twenty tablets were randomly selected from each batch, lightly dusted and weighed. A Precisa® analytical balance (model 240A, OERLIKON AG, Zurich) was used during this analysis.

2.5.2 Analysis of the crushing strength, thickness and diameter

Ten tablets were randomly selected from each batch and a Pharma Test® (model PTB-311) tablet test unit was used to determine the crushing strength, thickness and diameter of the tablets.

2.5.3 Friability

Ten tablets were randomly selected and lightly dusted. These tablets were weighed, the weight was noted. These tablets were transferred to a Roche® friabilator. The friabilator was rotated at 25 rpm for 4 minutes. On completion of the test the tablets were removed from the friabilator, lightly dusted and reweighed on the analytical balance. The weight of the ten tablets was noted. The percentage friability was calculated by means of equation 2.5.

$$\%F = 100 \times \frac{W_B - W_A}{W_B} \qquad (2.5)$$

where W_B = the total weight of the tablets before the onset of rotation and W_A = the total weight of the tablets on completion of rotation.

2.5.4 Disintegration

The disintegration test was performed on six tablets of each batch. A three station Erweka® disintegration apparatus (model ZT 500, Heusenstamm, Germany) was utilised. Three beakers containing the disintegrating medium (distilled water) were inserted into the water bath at a controlled temperature of ± 37.5 °C. A tablet was placed into each of the six tubes. The tubes were submerged into the disintegrating medium and the process was initiated. The disintegration time of each of the six

tablets was noted. The official disintegration limit of 15 minutes was applied during this analysis.

2.5.5 Dissolution testing

2.5.5.1 Apparatus and experimental conditions

Dissolution studies were performed using a six-station Erweka® dissolution apparatus (model DT6R) equipped with a thermostat and a synchronous motor (Erweka®, Heusenstamm, Germany) with adjustable speed settings. The dissolution medium was 0.1 M HCl with a pH of approximately 1.00 and was maintained at a temperature of 37 °C ± 0.5 °C. Rotational speed was maintained at 50 rpm. Baskets were attached to the shaft (USP basket method) to facilitate submersion of the tablet into the medium. The dissolution apparatus was shielded from light to avoid the photolytic degradation of furosemide.

2.5.5.2 Dissolution method for furosemide

Dissolution vessels were filled with 900 cm^3 of the dissolution medium and heated to 37 °C ± 0.5 °C. The shafts with the fitted baskets (USP method) were pushed down into the dissolution medium, approximately 5 cm^3 from the bottom of the vessels. The dissolution vessels were covered with lids. Rotation was initiated at 50 rpm followed by the sampling process.

The starting time of the dissolution process was indicated as t = 0 and samples were withdrawn at t = 1, 2, 4, 5, 6, 10, 20, 30, 45, 60, 120, 240, 360, 720 and 1440 minutes. Sampling was made through a 0.3 µm Milipore® prefilter. The prefilter tubing was placed at equal heights (in each dissolution vessel). Five cm^3 samples were withdrawn by means of an analytical grade pipette and the samples were transferred to 10 cm^3 polytops. The withdrawn volume was replaced with fresh, preheated dissolution medium. Subsequently the samples were analysed for furosemide. Analysis was performed by cycling of the samples through a 1 cm^3 flow-through quartz cell by a super sipper, connected to a Helios α Unicam®-spectrophotometer (Unicam Ltd, Cambridge, UK). The UV-absorbance of each sample was measured in duplicate at 277 nm with 0.1 M HCl as a blank. Corrections were made for the amount of drug that was lost during sampling in the calculation of the dissolution data.

2.5.5.3 Dissolution method for chitosan

A glycine hydrochloride buffer solution was prepared by dissolving glycine (1.87 g) and sodium chloride (1.46 g) in 250 cm^3 distilled water. Aliquots of the solution were diluted to 100 cm^3 with 0.1 M HCl, to yield a solution with pH of 3.2. Furthermore a Cibacron dye solution was prepared to yield a final concentration of 1.5 $mg.cm^{-3}$. Five cm^3 of the Cibacron dye was dissolved in 95 cm^3 of a 0.2 M phosphate buffer (pH 7.4). Sampling was performed according to the method for furosemide (section 2.5.5.2). Samples were transferred to disposable cuvettes and 3 cm^3 of the Cibacron dye solution was added to each cuvette. The samples were analysed for chitosan by determining the UV absorbance at 575 nm.

2.5.5.4 Dissolution of a furosemide suspension

The dissolution rate of furosemide from the various tablet formulations were compared to that from the suspension in order to assess the effect of the other excipient on the dissolution profile of the drug. An excess furosemide was added to 50 cm^3 of 0.1 M HCl (dissolution medium) containing 0.184% sodium lauryl sulphate. Fifty cm^3 dissolution medium was removed from the dissolution vessel prior to the dissolution test. The suspension was introduced into the dissolution medium (time = t_0). Samples were withdrawn as described in section 2.5.5.2.

2.5.5.5 Dissolution of a chitosan suspension

The dissolution rate of chitosan from the tablet formulations was also compared with the dissolution rate from a suspension. The dissolution method of a chitosan suspension was conducted in the same manner as the dissolution from a furosemide suspension (section 2.5.5.4), the only difference being the utilisation of chitosan raw material to form a suspension.

2.5.5.6 Furosemide standard curve

Standard curves were constructed prior to each set of dissolution tests. Standard solutions in a concentration range of 0.5 -10 $\mu g.cm^{-3}$ were used. The stock solution was prepared by dissolving of 25 mg furosemide in 50 cm^3 of absolute ethanol and 0.1 M HCl to 250 cm^3. The UV-absorbance of each standard solution was measured at 277 nm against 0.1 M HCl as blank. These absorbance values were plotted against the corresponding concentration and linear regression analysis of the data produced the best-fitted straight line through these coordinates. All standard curves

complied with the principles of Beer's law in the concentration range that was utilised and excellent correlation coefficients were obtained ($r^2 \geq 0.9999$). Additional parameters that were derived by regression, the slope (*m*) and y-intercept (*c*), were used to calculate the chitosan concentration of the samples.

2.5.5.7 Chitosan standard curve

The chitosan stock solution was prepared by dissolving 30 mg oven dried chitosan in 100 cm^3 distiled water containing 2% v/v acetic acid. Volumes ranging from 25-300 µl of the stock solution were added to disposable cuvettes. Subsequently the glycine hydrochloride buffer (pH 3.2) was added to reach a final volume of 300 µl. Exactly 3 cm^3 Cibacron dye were added to the cuvettes. The UV absorbance of each standard solution was measured at 575 nm. These absorbance values were plotted against the corresponding concentration and linear regression analysis of the data produced the best-fitted straight line through these coordinates. All standard curves complied with the principles of Beer's law in the concentration range that was utilised and excellent correlation coefficients were obtained ($r^2 \geq 0.9999$). Additional parameters that were derived by regression, the slope (*m*) and y-intercept (*c*), were used to calculate the chitosan concentration of the samples.

2.5.5.8 Computation of dissolution data

The concentration of furosemide dissolved (µg.cm^{-3}) at each sampling time was calculated using equation 2.6 and the amount of drug lost during sampling was corrected by using equation 2.7.

$$x = \frac{y^* - c}{m} \qquad (2.6)$$

Where y^* = the corrected absorbance value (from equation 2.6); x = the drug concentration (µg.cm^{-3}) and m and c are the slope and y-intercept respectively.

$$y_n^* = y_n + \frac{V_s}{V_m} \times \sum^{n-1} \cdot y^* \qquad (2.7)$$

Where y_n^* = corrected absorbance value of the n^{th} sample, y_n = measured absorbance of the n^{th} sample, V_s = sampling volume, V_m = dissolution medium volume and Σ^{n-1}. y^* = sum of all the corrected absorbance measurements prior to the n^{th} sample.

Dissolution profiles are presented as the concentration of furosemide that dissolved ($\mu g.cm^{-3}$) as a function of time (minutes).

2.5.5.9 Dissolution parameters, DR_i and AUC

The initial slope of the dissolution curve between t_0 and t_6 was proposed to be a fair approximation of the initial dissolution rate (DR_i) ($\mu g.cm^{-3}.min^{-1}$) of furosemide from the various tablet formulations. The significance of this parameter is discussed later. The area under the dissolution curve (*AUC*) was calculated from t_0 up to completion of the dissolution test at 1440 minutes (t_{1440}) and would give an indication of the extent of dissolution of the active ingredient during this period. The calculation of the *AUC* ($\mu g.min.cm^{-3}$) was carried out by application of the trapezoidal rule and the value was determined for the time interval $t_0 - t_{1440}$. The trapezoidal rule is described by equation 2.8.

$$AUC = 0.5\sum_{t=0}^{n}(t_n - t_{n-1})(c_n + c_{n-1}) \qquad (2.8)$$

Where, $(t_n - t_{n-1})$ = the time difference between two consecutive sampling intervals and c_n and c_{n-1} = corresponding concentrations of the tracer at t_n and t_{n-1}.

2.6 Stability of chitosan raw material, granules and tablets

Stability testing involved tests on the chemical, physical or microbiological characteristics of a drug, excipient or pharmaceutical formulation under stress conditions. Physical stability testing was performed on chitosan raw material and tablets by exposure to elevated temperatures and relative humidities (values denoted as % RH).

2.6.1 Preparation of samples for stability testing

Tablets comprising of 3% and 5% w/w Kollidon® VA-64 or Methocel® K100M granulate and 10% w/w external binder (Kollidon® VA-64 or Methocel® K100M) were compressed. The tablets were transferred to glass containers and sealed with Parafilm®. Tablets consisting of 30% w/w Avicel® PH 200 and 70% w/w chitosan raw material were also compressed and stored in Parafilm® sealed containers. Glass containers were filled with 200 g chitosan raw material and sealed. All the containers were stored in stability chambers at 25 °C / 60% RH and 40 °C / 75% RH.

2.6.2 Sampling and physical analyses of samples

Monthly sampling of approximately 30 g of the raw material and granules, as well as 30 tablets was performed. Tablets were compressed utilising the samples. Analyses of the tablets followed after a 24 hour time lapse (section 2.5). Analyses of reference tablets were also performed during this sampling.

2.6.3 Studies of the exposure of chitosan raw material to elevated temperatures

During these experiments chitosan raw material was exposed to 30 °C, 40 °C, 50 °C and 60 °C. Five stainless steel trays were filled with approximately 300 g chitosan powder. The powder was dried at the specified temperatures ± 0.5 °C. After 1, 2, 4 and 8 hours samples of 75 g were collected. These samples were tableted (section 2.4.3). These tablets were stored in sealed containers for a period of 24 hours prior to the physical analyses (section 2.5). Furthermore, approximately 3 g samples were collected at the same time intervals from each tray and analysed by DSC (section 2.3.6), Karl Fischer (section 2.3.5) and TGA (section 2.3.4) to determine moisture content of the samples.

2.7 Calculations

All the calculations were computed with Microsoft® Excel™ XP for Windows™ (Microsoft®, Seattle, Washington, USA).

CHAPTER 3

THE CHARACTERISATION OF CHITOSAN AND THE APPLICATION THEREOF IN DIRECT COMPRESSIBLE FORMULATIONS

3.1. INTRODUCTION

In chapter 1 the importance of the characteristics of a powder was discussed with emphasis on the flowability and compressibility of a powder. These characteristics are of primary importance to the formulator to predict certain limitations regarding the powder. Additionally, it provides selection criteria of which processes should be implemented in order to improve the properties of a powder. This chapter provides characterisation information of chitosan raw material and furthermore, deals with the application of chitosan in direct compressible formulations.

3.2. Characterisation of chitosan powder

The following characteristics of chitosan powder were evaluated according to the methods described (section 2.3) namely, particle size and distribution, density, porosity and flow properties. The results are summarized in table 3.1 and Annexure A.1 provides the collected data for these experiments.

Table 3.1: *Characteristics of chitosan raw material (% RSD indicated in parenthesis).*

Characteristic	Mean value
Particle size (µm)	215.6
Bulk density ($g.cm^{-3}$)	0.19 (1.6)
Tapped density ($g.cm^{-3}$)	0.27 (0.2)
True density ($g.cm^{-3}$)	1.44 (1.3)
Porosity (%)	0.30 (3.7)
Angle of repose (°)	37.9 (7.5)
Carr's Index (%)	28.7 (3.7)
Hausner ratio	1.40 (1.5)

According to the literature, free-flowing powders exhibit an angle of repose <25° (Staniforth, 2000:610), a Carr's index of 5-15% and a Hausner ratio of ~1.2 (Wells and Aulton, 2000:247). The results of the flow indices (table 3.1) namely angle of repose (39.7°), Carr's index (28.76%) and the Hausner ratio (1.404) indicated that chitosan powder used in this study is a cohesive powder that exhibits poor flowability.

Figure 3.1: *Scanning electronmicroscopy (SEM) micrograph of chitosan raw material.*

Particles that exhibit optimal flow are spherical with smooth surfaces and minimal particle interaction. The SEM-micrograph of chitosan powder (Figure 3.1) indicates non-spherical, irregularly shaped particles with a rough surface structure, all which explain the poor flow properties of the powder.

According to Staniforth (2000:604) particles with a particle size exceeding 250 µm are relatively free-flowing. The particle size analysis (Annexure A1) indicated that chitosan powder has a mean particle size of 215.6 µm. The analysis also indicated a large distribution of particle size with 16.2% of the particles exhibiting a particle size <100 µm, 44.3% >100 µm and 39.5% >200 µm. Thus, it could be concluded that

chitosan powder exhibits poor flowability and it is expected that variable die filling will occur resulting in tablets that vary in weight and crushing strength.

3.2.1 Conclusion

According to the presented data it is evident that chitosan exhibits poor flow. The results clearly suggest that variable die filling will occur, which will result in pronounced weight variation of compressed tablets. Therefore, it can be concluded that certain interventions are necessary in order to improve the tabletability of chitosan raw material.

3.3 The direct compression of chitosan in combination with fillers

During a preliminary experiment it was attempted to directly compress tablets containing only chitosan raw material. Subsequently, tableting failed (even at high compression loads) and the compacted powder crumbled as soon as it was ejected from the die. This was attributed to the poor compressibility of chitosan powder. Another observation made during this experiment was the variation in the die filling; this was due to the poor flowability and particle size distribution of the powder (section 3.2).

Consequently, the next objective was to combine chitosan powder with a suitable directly compressible filler and to determine the minimum amount of the filler necessary to produce acceptable directly compressible chitosan tablets. For this purpose Avicel® PH200 and Prosolv® SMCC™ 90 were employed as fillers.

3.3.1 Direct compression of chitosan in combination with Avicel®PH200 and Prosolv® SMCC™ 90

Mixtures containing varying ratios of chitosan and the filler was prepared and compressed (section 2.4.1.2). The tablets were analysed in terms of average tablet weight, weight variation, crushing strength and friability, according to the methods described in section 2.5. The results are summarised in table 3.2.

Table 3.2: *Results obtained from the physical analyses of tablets containing mixtures of varying concentrations of fillers in combination with chitosan.*

	Mixing time (min)	Avicel® PH200			Prosolv® SMCC™ 90		
		60/40	70/30	80/20	60/40	70/30	80/20
Average tablet weight (mg)	5	422.5	390.2	407.4	395.4	403.3	402.2
Weight variation (%)		3.9	2.1	6.3	5.0	3.8	2.5
Crushing strength (N)		103.4	47.2	37.9	32.9	106.8	87.2
% RSD		3.4	7.3	16.4	9.9	7.1	7.1
Friability (%)		0.06	0.02	8.64	1.56	0.35	12.7
Average tablet weight (mg)	10	441.4	497.2	408.2	408.7	468.9	405.9
Weight variation (%)		2.8	0.4	3.8	3.8	2.1	0.6
Crushing strength (N)		129.0	194.7	47.2	47.3	107.1	105.2
% RSD		1.9	1.8	7.3	7.6	2.4	1.2
Friability (%)		0.02	0.02	0.20	0.02	0.09	0.11
Average tablet weight (mg)	20	427.1	413.6	394.3	402.4	405.3	405.1
Weight variation (%)		4.0	2.3	4.8	2.5	0.4	0.3
Crushing strength (N)		113.8	49.4	34.1	37.7	30.9	35.7
%RSD		12.7	9.5	11.4	5.5	62.6	8.1
Friability (%)		0.05	0.38	8.82	0.05	0.43	0.10

The properties of chitosan powder could be correlated to the results and the interpretation thereof. As was described in section 1.2.1, uniform flowability of powders ensure the production of tablets with uniform weight (insignificant weight variation), hence, the analysis of weight variation indirectly evaluates the flowability of a powder.

From figures 3.2 and 3.3 it could be concluded that the filler concentration as well as the mixing time had a significant effect on the weight variation of the tablets.

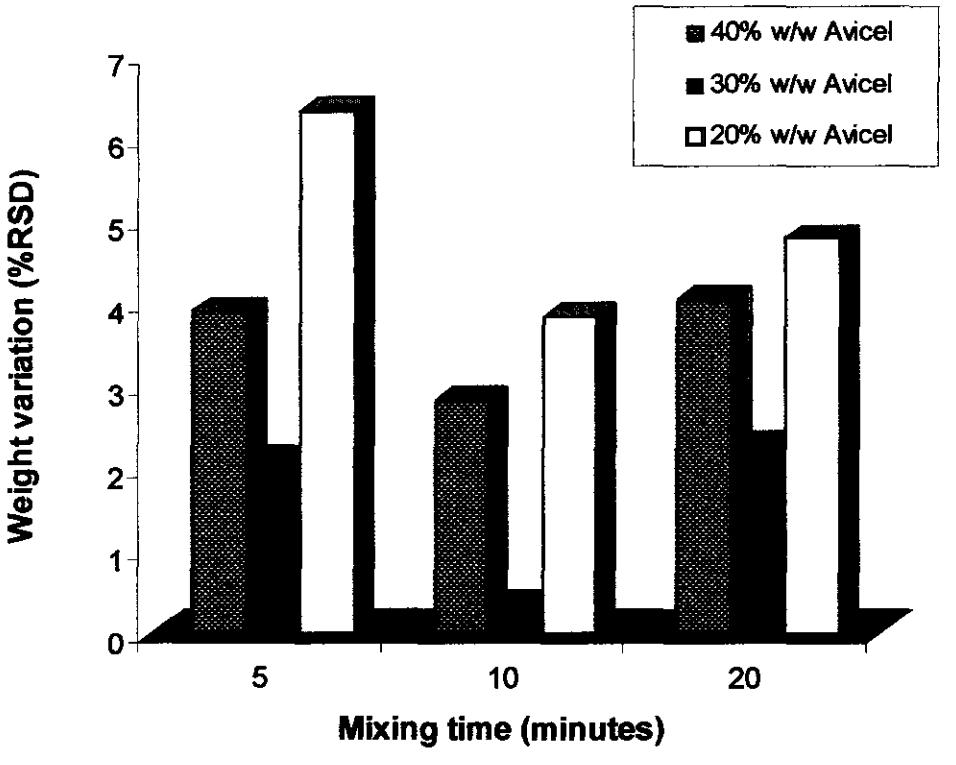


Figure 3.2: *The weight variation (%RSD) of tablets containing different concentrations of Avicel® PH200 in combination with chitosan at different mixing times.*

The mixtures containing 30% Avicel® PH200 produced tablets with the lowest variation in weight at all the mixing times, compared to the mixtures containing 40% or 20% Avicel® PH200 (Figure 3.2). Given that Avicel® PH200 demonstrates gliding properties as well, it could be hypothesized that a concentration of 30% acted as the optimal concentration in combination with chitosan to facilitate improved flow. While, an increase in Avicel® PH200 concentration had the opposite effect (flow properties

worsened) and a decrease to 20% did not have an ample effect to positively influence powder flow.

It is clear that mixing time had a considerable effect on weight variation. Figure 3.2 indicates that a mixing time of 10 minutes produced tablets with the lowest weight variation for all the mixtures. This may be explained in correlation with the fact that an increase in mixing time could result in overmixing of the mixtures (section 1.3.1). Thus, it could be concluded that a mixing time of 5 minutes was too short to ensure adequate mixing of the particles, therefore, indicating no significant improvement in powder flow, whilst a mixing time of 20 minutes resulted in overmixing of the powder. Therefore, having a detrimental effect on the flow properties of the mixtures.

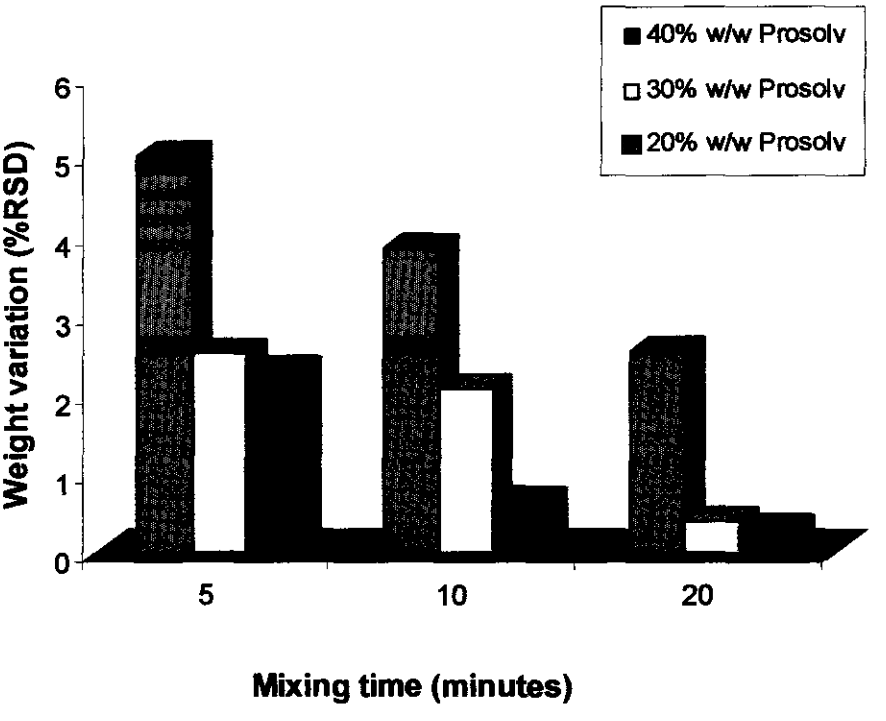


Figure 3.3: *The weight variation (%RSD) of tablets containing varying concentrations of Prosolv® SMCC™ 90 in combination with chitosan vs. different mixing times.*

The mixtures containing Prosolv® SMCC™90 showed a steady decline in weight variation with an increase in mixing time (Figure 3.3). An unexpected decrease in weight variation is indicated with an increase in chitosan concentration. The mixtures containing 20% Prosolv® SMCC™90 signified the least variation in weight compared to other mixtures containing Prosolv® SMCC™90 as well as all the mixtures containing

Avicel® PH200. All the mixtures mixed for 20 minutes showed an unpredicted decrease in weight variation. However, it can be concluded that the optimal mixing time for mixtures comprising of chitosan and Prosolv® SMCC™90 is 20 minutes.

The high degree of weight variation (% RSD) exhibited by both filler combinations could be attributed to the poor flow properties of chitosan raw material, consequently resulting in the variable filling of the die.

The crushing strength showed significant variation corresponding to the mixing time. Figure 3.4 indicate the same trend for all the formulations in terms of the effect of mixing times on crushing strength. Crushing strength initially increased up to 10 minutes followed by a steady decline with prolonged mixing time. Therefore, it was concluded that mixing times exceeding 10 minutes had a detrimental effect on all formulations. With exception, however, the formulation containing 40% Avicel® PH200, which was affected the least by variation in mixing time.

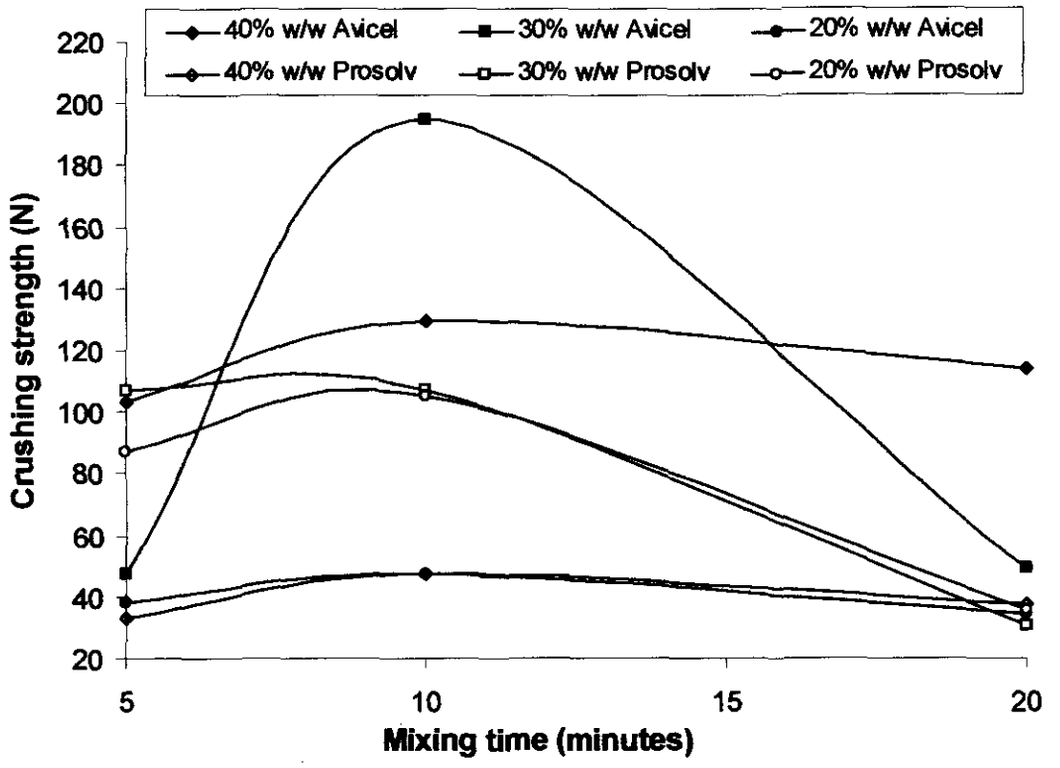


Figure 3.4: *Average crushing strength of tablets containing mixtures of varying concentrations fillers in combination with chitosan vs. varying mixing times.*

The crushing strength of the tablets comprising of Avicel® PH 200 could be correlated to the weight variation (Figure 3.2). The mixture containing 30% Avicel® PH200 (mixed for 10 minutes) produced tablets with the lowest weight variation. Figure 3.4 indicates that the same mixture produced tablets with the highest crushing strength. Thus, a lower weight variation, which indicated uniform filling of the die resulting in a dense packing of the particles. This resulted in efficient compression of the particles to produce tablets with acceptable crushing strength.

From the interpretation of the crushing strength data it could be predicted that the relative low crushing strength of the produced tablets will result in high friability percentages. However, when the crushing strength and friability data are compared (Table 3.2) unexpected low friability percentages were evident.

Tablets consisting of only a filler (Avicel® PH200 or Prosolv® SMCC™90) tend to be hard, exhibited high crushing strengths and during crushing it had a propensity to fracture cleanly. Conversely, the tablets containing filler and chitosan had a propensity to be soft with relative low crushing strengths. During crushing tests these tablets tore apart rather than broke into halves. This was attributed to the inherent "stickiness" of chitosan. Therefore, the ability of chitosan particles to stick to other particles resulted in the production of tablets with low crushing strength but unexpected low friability.

3.3.2 Conclusion

From the results it could be concluded that the characteristics of chitosan raw material significantly influenced the properties of the produced tablets. Given that chitosan raw material exhibits poor flow, its application in direct compressible formulations resulted in the production of tablets that signified considerable weight variation.

Furthermore, poor compression properties of chitosan raw material necessitated the inclusion of a directly compressible filler to facilitate successful tableting. Additionally, it was observed that the inclusion of other excipients had significant effects on weight variation and crushing strength. It is concluded that formulations comprising of 30% Avicel® PH200 and 30% Prosolv® SMCC™ 90 proved most effective in terms of crushing strength. Relatively low friability was obtained despite

the low crushing strength of the tablets. Thus, concluding that interpretation of only the crushing strength data is not an indication of the acceptability of the tablets.

3.4 Direct compression of chitosan in combination with dry binders

The experiments conducted regarding the combination of chitosan with directly compressible fillers indicated that for the production of acceptable tablets, the minimum required concentration of a filler was 20% w/w (section 3.3). However, the objective of the study was to determine the minimum excipient concentration necessary to produce acceptable chitosan tablets.

Minimisation of the quantity of filler might be achieved by inclusion of an additional binder. The binder might substitute the filler from the perspective of both compressibility and binding properties. Additionally, these binders are usually effective at lower concentrations than required for fillers. Therefore, the objective of minimisation is aided by this change.

3.4.1 Direct compression of chitosan combined with a single dry binder

Chitosan mixtures were constituted with either Kollidon® VA-64 or Methocel® K100M as single dry binder. Both binders were included as 4, 5, 7, 10, 15 or 20% w/w fractions. The mixtures were prepared and compressed as described in sections 2.4.1.2 and 2.4.1.3. The tablets were analysed in terms of weight variation, crushing strength, friability and disintegration time according to the procedures described in section 2.5. The results are shown in Table 3.3 with %RSD indicated in parenthesis.

Table 3.3: Results obtained from the physical analyses of tablets containing mixtures of varying concentrations of single dry binders in combination with chitosan.

	Kollidon® VA-64 (% w/w)						
	4	**5**	**7**	**10**	**12**	**15**	**20**
Average weight (mg)	169.4 (2.0)	174.2 (0.9)	179.1 (0.7)	179.7 (1.3)	181.5 (1.4)	187.3 (0.80)	194.8 (1.1)
Crushing strength (N)	24.63 (12.2)	26.55 (10.1)	34.70 (5.7)	40.85 (6.7)	61.99 (7.3)	81.53 (8.1)	124.3 (4.7)
Thickness (mm)	3.1 (1.2)	2.8 (0.6)	2.8 (0.4)	2.8 (0.7)	2.9 (0.6)	2.9 (0.4)	2.9 (0.4)
Diameter (mm)	9.1 (0.2)	9.1 (0.1)	9.1 (0.2)	9.1 (0.1)	9.1 (0.1)	9.0 (0.1)	9.0 (0.1)
Friability (%)	0.7	0.6	0.2	0.1	0.1	0.0	0.0
Disintegration time (min)	3.1	No data	No data	No data	No data	No data	No data
	Methocel® K100M (% w/w)						
	4	**5**	**7**	**10**	**12**	**15**	**20**
Average weight (mg)	165.3 (1.2)	180.3 (1.4)	180.3 (1.4)	177.3 (1.5)	174.8 (3.7)	175.4 (1.2)	180.3 (0.9)
Crushing strength (N)	24.6 (12.2)	12.1 (13.1)	14.4 (15.8)	12.4 (23.4)	37.3 (11.2)	34.3 (10.6)	34.9 (10.4)
Thickness (mm)	3.1 (1.2)	3.4 (1.6)	3.3 (1.1)	6.3 (0.5)	3.1 (0.7)	3.1 (1.4)	3.1 (0.6)
Diameter (mm)	9.1 (0.2)	9.1 (0.2)	9.1 (0.2)	9.5 (0.1)	9.1 (0.1)	9.1 (0.1)	9.1 (0.1)
Friability (%)	0.7	1.4	0.9	1.5	0.9	0.5	0.3
Disintegration time (min)	6.3	0.9	3.7	No data	7.2	No data	No data

The crushing strength of tablets containing Kollidon® was significantly higher at each concentration fraction than the tablets containing Methocel®. Methocel® K100M had an erratic effect on tablet strength and did not produce a significant improvement in crushing strength (Figure 3.7). Its maximum effect was observed at a concentration of 12%. However, the maximum crushing strength of tablets containing Methocel® was approximately 35 N, very weak tablets when compared with the crushing strength of tablets containing Kollidon®. The insignificant effect of Methocel® K100M might be attributed to an insensitivity of chitosan for Methocel® K100M.

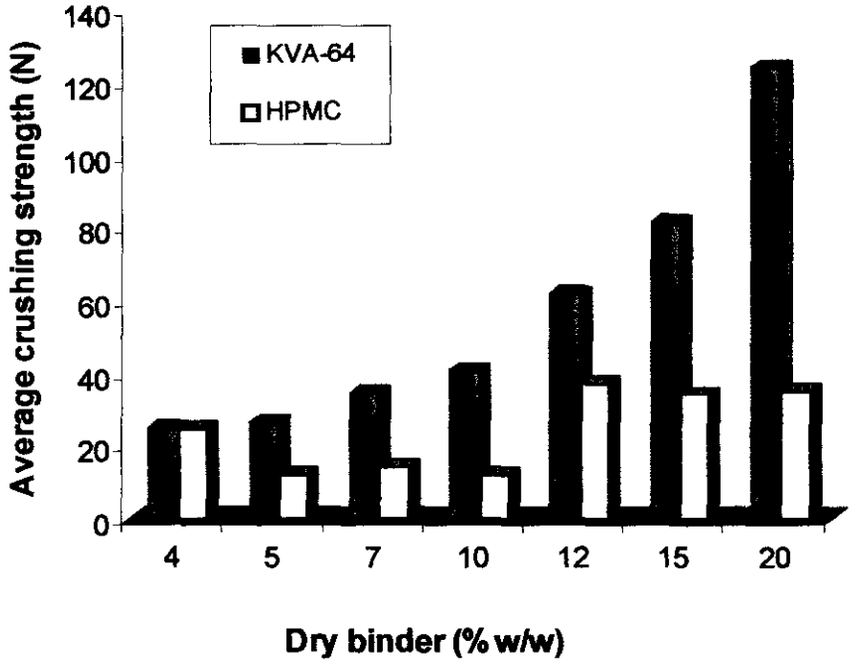


Figure 3.7: *Average crushing strength of tablets containing varying concentrations of Kollidon® VA-64 and Methocel® K100M.*

Kollidon® had a pronounced effect on crushing strength. Further analysis of the data revealed a strong positive exponential dependency of crushing strength on the Kollidon® concentration. Log transformation of the data illustrated the linear relation (Figure 3.8). It could be concluded that a minute differential in concentration effected a significant differential in crushing strength. This illustrated the high efficiency of Kollidon® as a binder. Furthermore, it illustrated the sensitivity of chitosan to Kollidon® as binder, perhaps suggesting an advantageous interaction. It is

concluded that Kollidon® VA-64 is without question a suitable binder in chitosan mixtures.

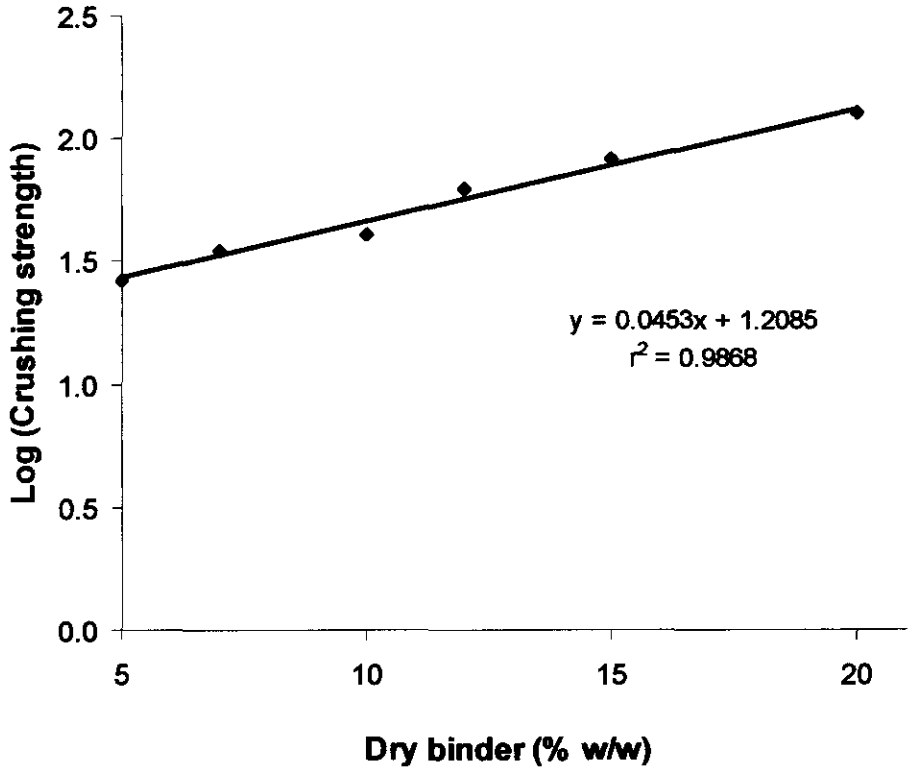


Figure 3.8: *The correlation between the crushing strength of chitosan tablets containing varying concentrations of Kollidon® VA-64.*

Extrapolation of the line (to 0% Kollidon®), with necessary exponential transformation, suggested that tablets comprised of pure chitosan raw material would produce mechanically weak tablets (15.8 N). Confirmation of this weak binding interaction was illustrated (section 3.3). This argument therefore motivated the inclusion of either fillers or binders to improve tabletability.

Figure 3.9 shows the percentage friability of the chitosan tablets. Mixtures containing chitosan in combination with Kollidon® delivered tablets with friability less than 1%, while the formulations containing Methocel® as binder showed friability varying from 0.33 to 1.51%. These formulations also had the lowest crushing strength values. Figure 3.9 also indicates that the formulations containing Kollidon® had a gradual decrease in the percentage friability with an increase of the binder concentration.

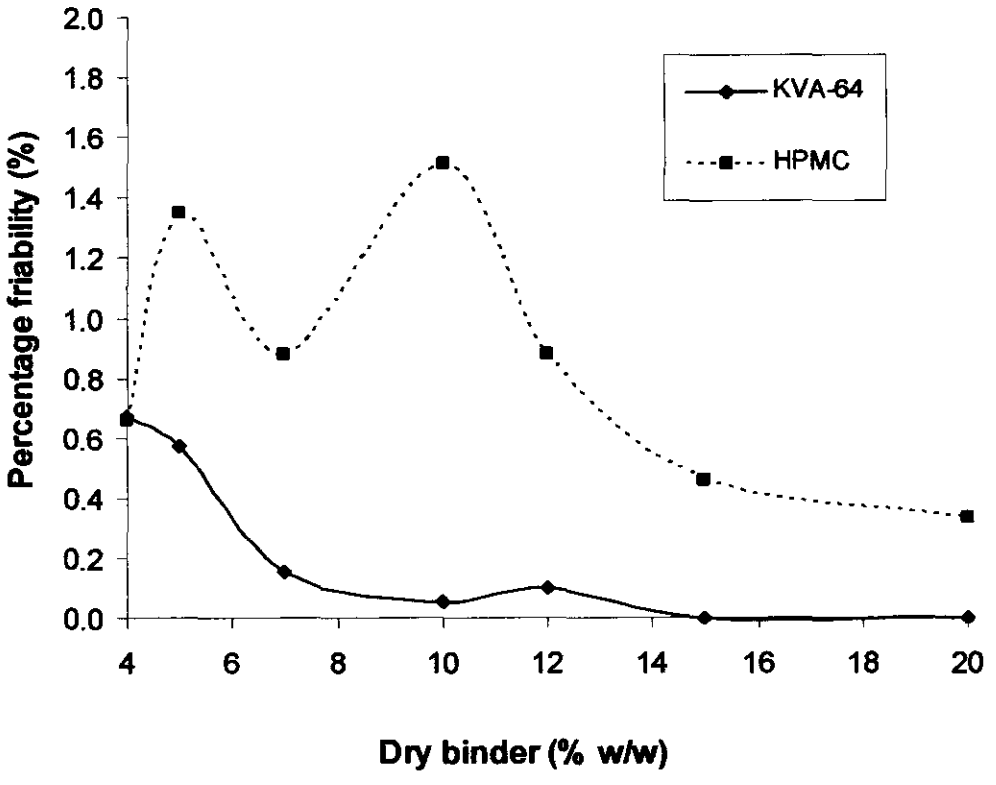


Figure 3.9: *The percentage friability (%) of directly compressed tablets containing various concentrations dry binders in combination with chitosan.*

The efficiency of a binder can be quantified by the measurement of hardness and friability. Therefore, the calculation of hardness–friability ratios will be a clear indication of the efficiency of the two binders.

Figure 3.10 depicts the calculated hardness-friability ratios of tablets containing varying concentrations of Kollidon® and Methocel®. From the results it was evident that higher crushing strength values and lower friability percentages resulted in higher hardness-friability ratios (HFR). HFR-values for the formulations containing 15% and 20% Kollidon® were omitted from the graph because a HFR could not be calculated due to the fact that the percentage friability was zero. The significant higher HFR for formulations containing Kollidon® could be ascribed to the high crushing strength and low friability of these formulations. Therefore, it was evident that the low crushing strength and high friability of formulations containing Methocel® resulted in marked low HFR.

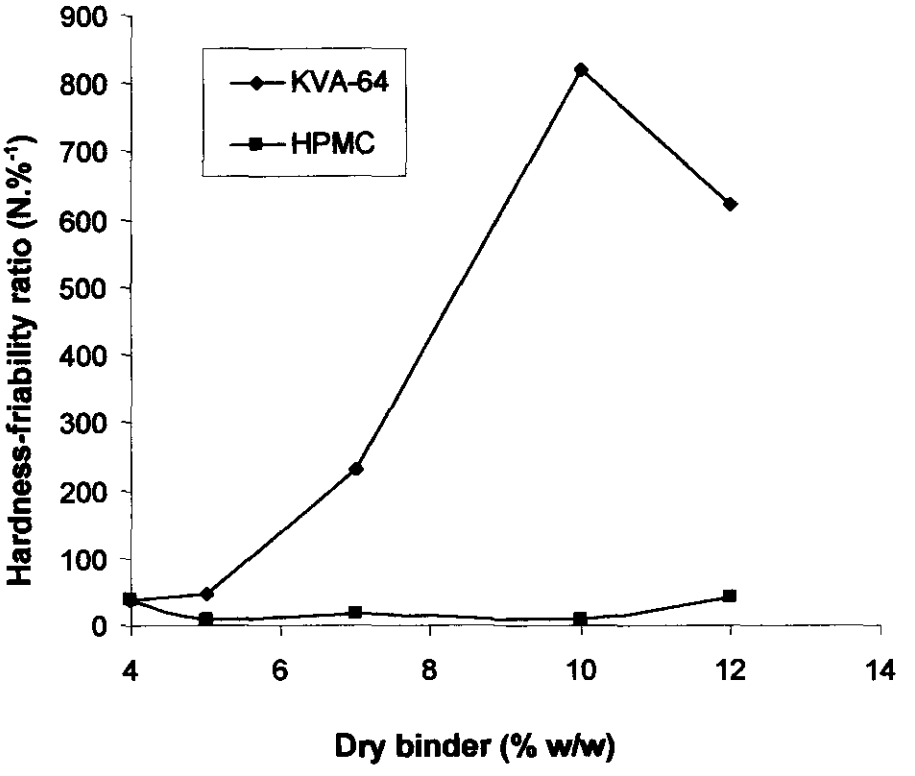


Figure 3.10: *The hardness-friability ratio (HFR) of directly compressed tablets containing various concentrations dry binders in combination with chitosan.*

The tablets produced from the mixtures containing Kollidon® exhibited no disintegration, whilst the formulations containing 4, 5, 7 and 12% Methocel® disintegrated (Table 3.4). Methocel® K100M is a cellulose derivative (1.5.3.2) with properties like film formation, gelation and swellability. These properties could influence the water penetration and consequently the disintegration of tablets. On contact with water Methocel® K100M hydrates readily followed by swelling (Prasad, 1988:147 and Siepman *et al.,* 2000:140).

Kollidon® VA-64, however, does not swell on contact with water. This excipient aids the transport of water into the tablet through intraparticular capillary spaces, followed by wetting of the tablet interior with subsequent disintegration of the tablet. Thus, it could be predicted that tablets comprising of Kollidon® would indicate relative rapid disintegration. However, only the formulation containing 3% Kollidon® disintegrated. This may be explained in correlation with figure 3.8. It was already concluded that an increase in Kollidon® concentration resulted in an increase in crushing strength. Therefore, an increase in binder concentration will result in the formation of stronger and more effective particle bonding, thereby, decreasing interparticular spaces

(voids). This might lead to a decrease in the amount of water transported into the tablets, resulting in slower or even no disintegration of the tablets.

Conversely, Methocel® K100M did not have a significant effect on the crushing strength (Figure 3.7). Therefore, hydration and swelling of the tablets would be faster, resulting in the disintegration of the tablets. Subsequently, the inclusion of both binders in mixtures might produce mechanically strong tablets that disintegrate on contact with water.

3.4.2 Direct compression of chitosan combined with combinations of dry binders

Combinations of the two binders, Kollidon® and Methocel®, were used as excipients in formulations intended for the directly compression of chitosan. The rationale for the inclusion of binder combinations was to determine whether the combination will result in the potentiation of the binding effect, thus, resulting in the application of a lower binder concentration during the direct compression of chitosan. Furthermore, to determine if the disintegration properties of the tablets will improve, since it was clear from section 3.4.1 that the presence of Methocel® K100M had a positive effect on the disintegration of the tablets. Whereas, the presence of Kollidon® VA-64 had a positive effect on the binding of chitosan, but a negative influence on the tablet disintegration. Table 3.4 summarises the results.

Table 3.4: *Results obtained from the physical analyses of tablets containing various concentration ratios of dry binders in combination with chitosan.*

Ratio	1% Methocel® K100M: 1% Kollidon® VA-64			3% Methocel® K100M: 1% Kollidon® VA-64			1% Methocel® K100M: 3% Kollidon® VA-64		
Total binder concentration (% w/w)	**2**	**6**	**10**	**4**	**12**	**20**	**4**	**12**	**20**
Average tablet weight (mg)	172.0	165.3	167.1	166.7	175.9	179.9	166.8	174.2	188.1
Weight variation (%)	1.2	1.1	1.9	1.5	1.5	1.1	1.3	1.2	1.0
Crushing strength (N)	15.5 (11.1)	11.3 (24.1)	17.2 (23.3)	15.1 (19.2)	33.8 (13.5)	50.83 (8.3)	15.8 (19.9)	38.7 (20.5)	56.3 (13.2)
Thickness (mm)	3.5 (0.8)	3.6 (2.0)	3.5 (1.9)	3.5 (0.8)	3.2 (0.9)	3.0 (0.9)	3.5 (0.8)	3.1 (1.2)	3.2 (0.8)
Diameter (mm)	9.1 (0.2)	9.1 (0.4)	9.1 (0.1)	9.1 (0.1)	9.1 (0.1)	9.1 (0.1)	9.1 (0.1)	9.1 (0.1)	9.1 (0.1)
Friability (%)	4.2	8.9	2.1	3.3	1.0	2.1	3.8	5.3	0.08
Disintegration time (min)	1.0	0.4	0.7	2.1	3.4	No data	1.0	0.8	No data

From Table 3.4 it is evident that the combination 3% Methocel® : 1% Kollidon® produced tablets with crushing strengths of nearly the same magnitude than the tablets containing the 1% Methocel® : 3% Kollidon® combination. However, the latter resulted in tablets with higher crushing strengths at each total binder concentration. Furthermore, a total binder concentration of 20% resulted in no disintegration, irrespective of the binder combination. The tablets containing 3% Methocel® : 1% Kollidon® revealed slower disintegration times than the 1% Methocel® : 3% Kollidon® combination. Therefore, it could be concluded that the presence of Methocel® in these combinations did not enhance disintegration.

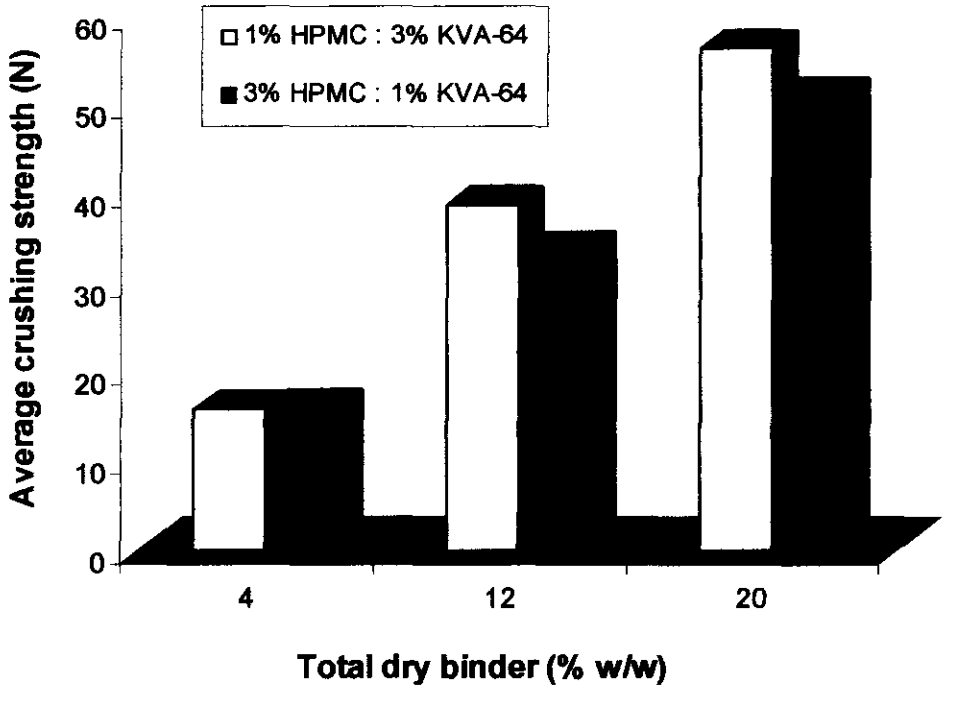


Figure 3.11: *The average crushing strength (N) of tablets containing binder combinations of 1% Methocel®: 3% Kollidon® and 3% Methocel®: 1% Kollidon®.*

Figure 3.11 illustrates the average crushing strength of tablets containing combinations of the two binders. In comparison, insignificant differences occurred in terms of crushing strength. However, the formulations containing a higher concentration Kollidon® (1% Methocel®: 3% Kollidon®) produced tablets with higher crushing strengths than the formulations containing higher concentrations of Methocel®. This can be correlated to the exponential dependency of crushing strength on the Kollidon® concentration (Figure 3.8), that is higher concentrations Kollidon® resulted in higher crushing strengths of the tablets.

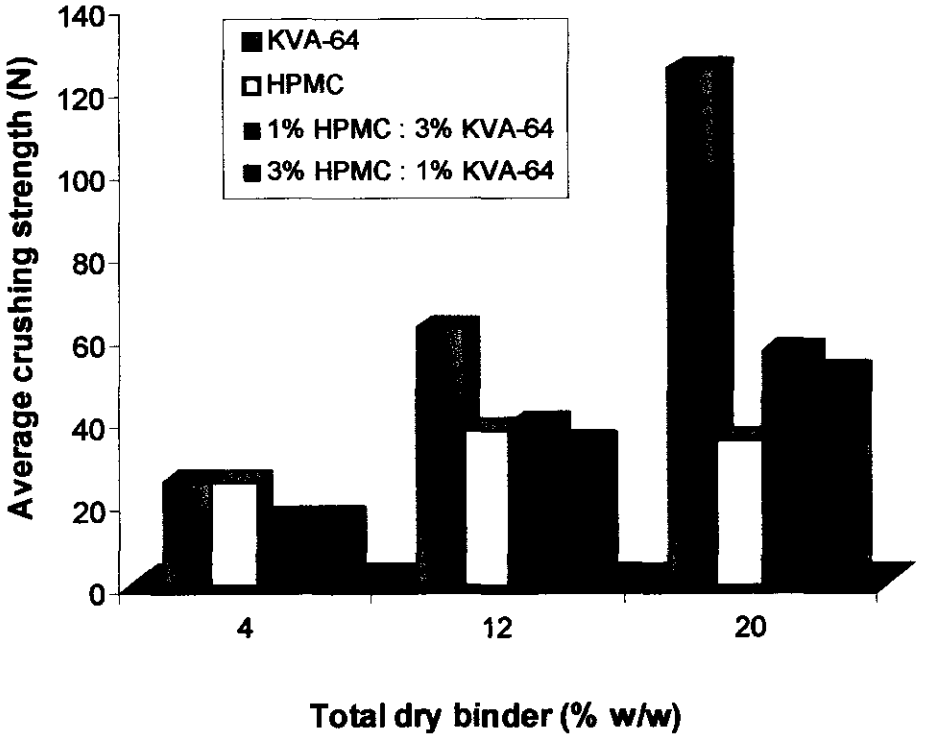


Figure 3.12: *The average crushing strength (N) of tablets containing binder combinations of 1% Methocel® K100M : 3% Kollidon® VA-64 and 3% Methocel® K100M : 1% Kollidon® VA-64 as well as formulations containing either Kollidon® VA-64 or Methocel® K100M as binder.*

Figure 3.12 depicts the average crushing strength of tablets containing combinations of the binders as well as mixtures consisting of corresponding concentrations of single binders (Table 3.3). The formulations comprising of single dry binders produced tablets with higher crushing strengths than the formulations containing the dry binder combinations. However, combination formulations (with a total binder concentration of 20%) showed an increase in crushing strength, compared to the mixtures containing binder combinations of lower concentrations. Once more this could be attributed to the exponential correlation indicated previously (Figure 3.8). Thus, the mixtures containing higher concentrations Kollidon® VA-64 produced tablets with higher crushing strengths.

The mixture comprising of single dry binder (Kollidon® VA-64) with a concentration of 20% resulted in tablets with crushing strength of 124.3 N, compared to the combination mixtures with a total binder concentration of 20% which effected tablet

crushing strengths of ~ 56.3 N. Therefore, it could be concluded that combinations of the dry binders did not potentiate the binding effect of chitosan during compression and since chitosan exhibited sensitivity for Kollidon® it resulted in formation of strong bonds between the two materials during compression.

The formulations containing the binder combinations produced tablets with relative high friability which were markedly higher in comparison with the friability of the tablets containing the single binders.

The presence of Methocel® in the binder combination did improve the disintegration of the tablets to some extent, but it also had a negative effect on the friability and hardness of the tablets. Even at high concentrations Methocel® (15% w/w) disintegration could not be initiated. Therefore, in comparison with the formulations containing single binders, the binder combinations did not potentiate the binding effect of chitosan particles and although the presence of Methocel® did improve disintegration, the tablet friability was a drawback.

3.5 Conclusion

From the characterisation of chitosan raw material it could be concluded that chitosan is a fairly cohesive powder that exhibit poor flow. From this and the results of the preliminary studies regarding the direct compression of tablets containing pure chitosan raw material, it was clear that the characteristics of the powder make direct compression thereof a difficult task. Therefore, it was obvious that chitosan have to be combined with other tablet excipients in order to be directly compressed. From the direct compression experiments it could be deduced that the minimum excipient concentration to be combined with chitosan varies from 10% to 30% w/w. The formulations containing single dry binders produced acceptable tablets containing lower concentrations of excipients when compared to the formulations containing fillers.

However, the aim of the study was to assess the tableting properties of chitosan by adding the least amount of excipients to the formulations. Thus, in order to achieve this goal the basic characteristics of chitosan had to be improved first, since these characteristics have a considerable influence on the tabletability of chitosan powder.

CHAPTER 4

WET GRANULATION OF CHITOSAN AND TABLET COMPRESSION

4.1. INTRODUCTION

The third phase of the study dealt with the wet granulation of chitosan raw material. Sections 3.2 and 3.3 demonstrated that chitosan raw material exhibits poor flowability with a subsequent high degree of weight variation. Due to the poor compressibility of chitosan it was not possible to compress chitosan without the presence of a directly compressible filler or binder (sections 3.3 and 3.4). Therefore, the aim of this phase was to improve the flowability and compressibility of chitosan employing the process of wet granulation. The granulation was investigated in two sections i.e. low and high speed granulation.

4.2. PRELIMINARY STUDIES

The granulation method investigated various experimental variables i.e. the type and concentration of the binders, volume of the binder solutions, mixing speed as well as mixing time. Therefore, a series of preliminary experiments had to be conducted in order to determine the optimal granulation conditions for chitosan. The preliminary experiments illustrated that it was impossible to compress tablets consisting only of the produced chitosan granules. The compacted granules crumbled on ejection from the die. Therefore, the addition of external binders to the granules was necessitated, even obligatory.

4.3. LOW SPEED GRANULATION OF CHITOSAN

The low speed granulation of chitosan with Kollidon® VA-64 and Methocel® K100M was conducted according to the methods explained (sections 2.4.5.1 and 2.4.5.2), Annexure B, Tables B1.1-B1.4 contain the data that were recorded through the physical analyses of the tablets.

Figures 4.1 and 4.2 depicts SEM–micrographs of chitosan raw material and Kollidon® VA-64 granulate respectively. The micrographs do not distinguish clearly between

the raw material and the granulate, however Figure 4.2 indicates larger particles (granules) as well as chitosan particles that did not form granules.

Figure 4.1: *SEM micrograph of chitosan raw material.*

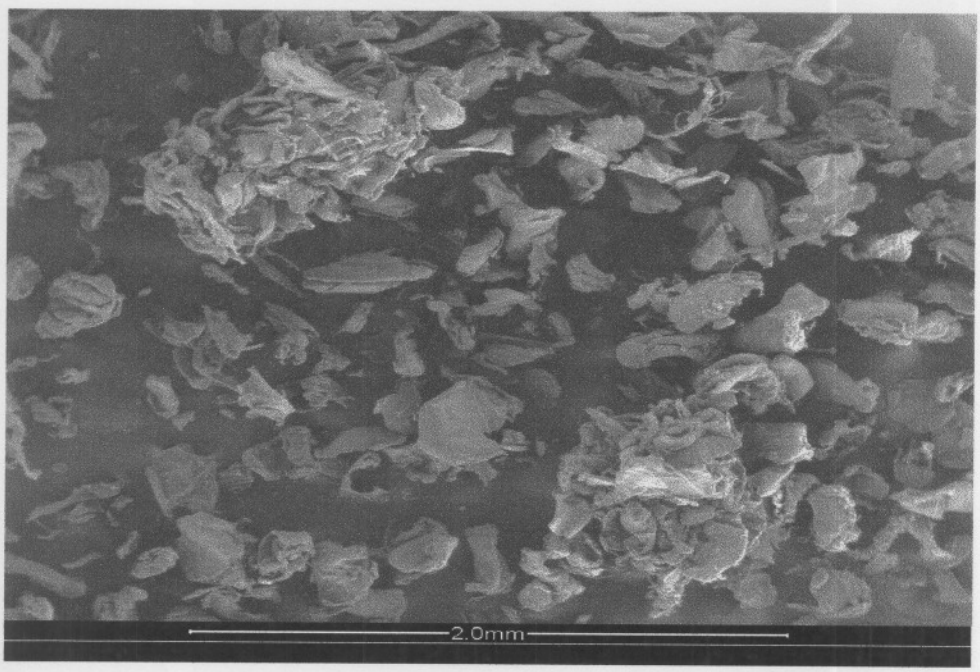


Figure 4.2: *SEM micrograph of chitosan granules obtained by granulation, utilising Kollidon® VA-64 as binder.*

4.3.1. Weight variation

Section 3.4.1 illustrated that the poor flowability of chitosan had a detrimental effect on the weight variation of tablets containing high proportions of chitosan. Therefore, the aim of the granulation process was to improve the flowability of chitosan raw material, consequently decreasing the variation in tablet weight.

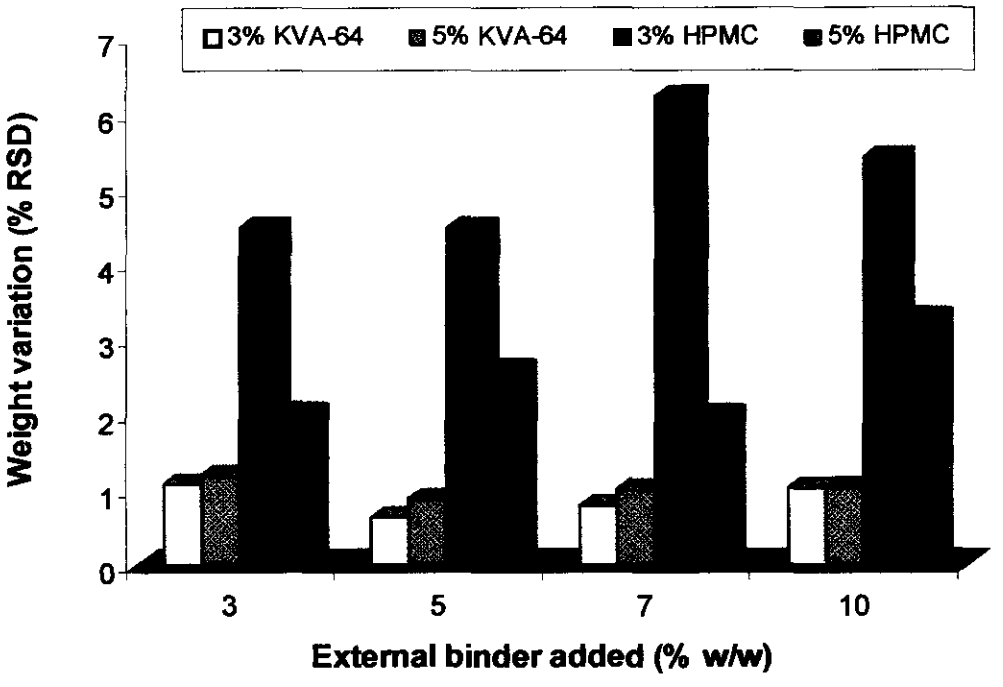


Figure 4.3: *The weight variation (%RSD) of tablets containing Kollidon® VA-64 or Methocel® K100M granulate (3 and 5 % w/w) respectively combined with various concentrations of external binder.*

From figure 4.3 it is evident that the mixtures comprising of the Kollidon® granulate (3 and 5% w/w) produced tablets with the least variation in terms of tablet weight. It should be noted that weight variation (Kollidon® tablets) assumed a virtually equivalent magnitude, regardless of the quantity of external Kollidon® added. It may be suggested that the observed variation was not dependent on concentration but that the mere presence of Kollidon® induced low weight variation in all systems.

Slight discrepancies were noted for the 3 and 5% w/w granulates compounded with an additional 5 and 7% w/w external Kollidon®. It may be concluded that the

interparticle interaction in these systems were at a minimum and produced the best flowability from the perspective of weight variation.

All the Methocel® formulations exhibited a higher weight variation in comparison with Kollidon®. The 3% granulate showed a significantly higher weight variation compared to the systems evaluated. Additionally, this granulate superseded values recorded for the 5% granulate systems. It could be concluded that the presence of Methocel® induced a high variation, contradicting the findings observed for Kollidon®. It could be suggested that chitosan-Methocel® particle interaction were at a maximum; ascribed to their chemical structure similarities. Thus, concluding that the type of binder had a profound influence on flowability, regardless of the binder concentration.

4.3.2 Crushing strength and friability

Results from sections 3.3 and 3.4 indicated that the poor compressibility of chitosan is a characteristic that detrimentally affects the tabletability of the material. Therefore, the crushing strength and friability of the tablets were also assessed to determine the effect of granulation on the compressibility of chitosan.

Figure 4.4 clearly depicts the differences in terms of crushing strength. It is evident that the tablets comprising of the Kollidon® granulate revealed the highest crushing strength, irrespective of the concentration external binder. The tablets consisting of Methocel® granulate (3%) indicated an increase in crushing strength (increase of ~ 10 N) with an increase in the concentration external binder. In comparison, the mixtures comprising of Methocel® granulate (5%) did not indicate significant changes in crushing strength with varying concentrations external binder.

Furthermore, figure 4.4 indicated a relatively consistent tablet strength for all Kollidon® tablets. A slight increase in strength is observed that coincides with an increase in percentage of total binder. The explanation for the consistent strength might be a consequence of upper punch displacement in relation to Kollidon® plasticity properties. The compression load was maintained at a set volume. Therefore, a compression threshold of the specific systems could not be observed. It might be suggested that a critical load may be applied, resulting in a maximum characteristic strength of each system.

The slight increase in tablet strength noted with the increase in binder concentration might be attributed to energetics of the system. The larger proportion of binder might harness the work of compression to a larger extent than observed for lower binder proportions. Therefore, the work of compression might be transformed to bonding energy of greater magnitude.

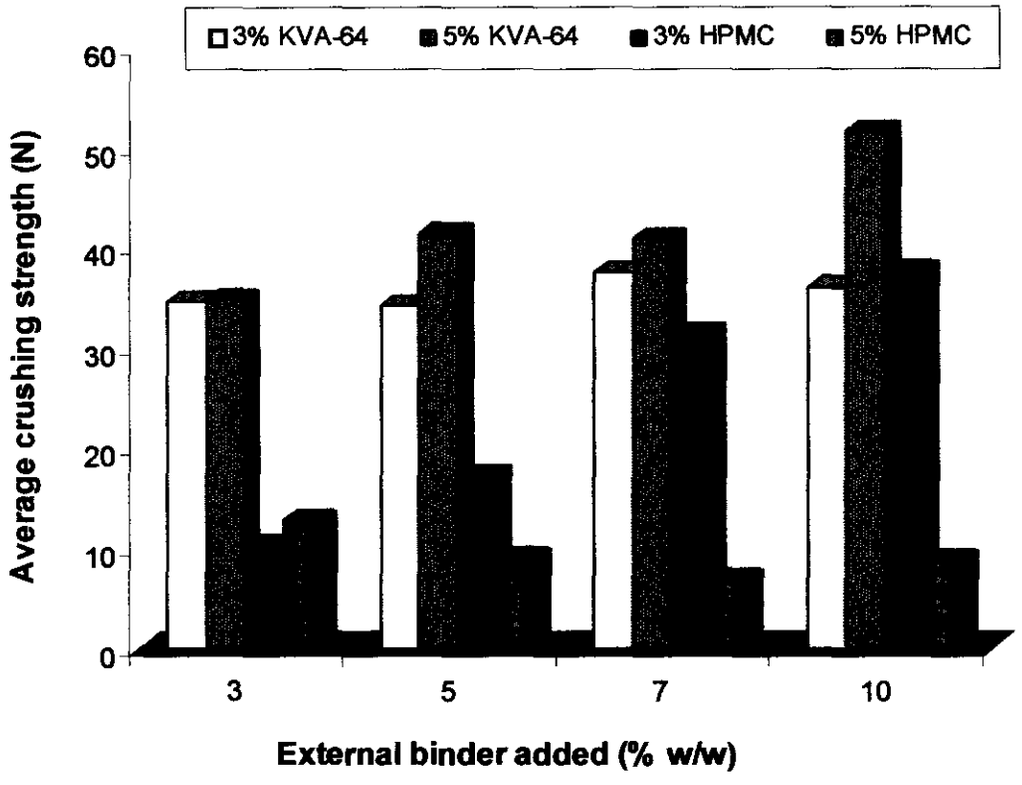


Figure 4.4: *The average crushing strength (N) of tablets containing Kollidon® VA-64 or Methocel® K100M granulate (3 and 5 % w/w) respectively combined with various concentrations of external binder.*

Furthermore, the Kollidon® tablets indicated the lowest weight variation, coinciding with better flowability. This indicated the superior packing density compared to Methocel®. Packing density plays an important role in compressibility of materials (section 1.2). It is unclear what the relationship is between flowability (weight variation) and packing density (crushing strength) for Methocel® tablets. The 3% Methocel® tablets proved superior in strength compared to the 5% formulation. These results for crushing strength reaffirmed the erratic effects of Methocel® on crushing strength (section 3.4.1)

In addition, it may be suggested that the 5% may not have been compressed optimally. The threshold of compression for this system may be reached by an increase in compression load; however this load could not be achieved within the normal tablet press operational parameters. Finally it is deduced that Kollidon® confirmed its suitability to formulation with chitosan with regards to the crushing strength.

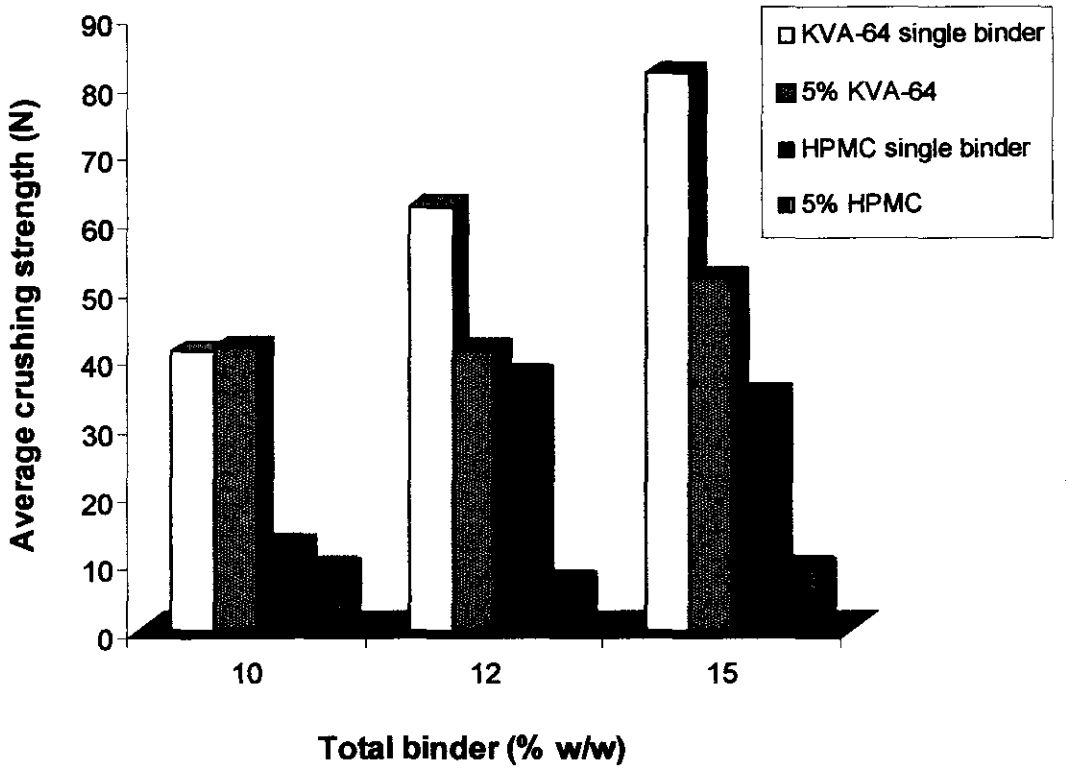


Figure 4.5: *A comparison between the crushing strength of tablets containing corresponding concentrations of single dry binders (direct compression) with the crushing strength of tablets comprising of granulate (Kollidon® or Methocel®) and external binder.*

If the crushing strength of tablets comprising of Kollidon® granulate were compared to the crushing strength of tablets containing single dry binders (direct compression), of the same total binder concentration, it could be concluded that the granulate resulted in a decrease in crushing strength. Figure 4.5 depicts a marked decrease in crushing strength of the tablets containing the Methocel® granulate. This decrease may be due to the change in particle individuality produced by the wet granulation of chitosan. Given that both chitosan and Methocel® particles exhibit irregular particle shapes and surface roughness, the wet granulation process may cause these particles to fuse together or hook into each other. This fusion of the particles may

decrease the surface area available for further bonding of external binder, thus affecting the compaction of the granules. (Gustafsson *et al.*, 1999:171).

Furthermore, the strength of a tablet depends on the area of intimate contact between particles and the adhesive strength over the whole area. Therefore, it is clear that the strongest bonds are formed between clean surfaces. The film formation induced by the wet granulation of chitosan utilising Methocel®, may result in the presence of a physical barrier between the granule and the added external binder, interfering with the adhesive bond between the granules and the external binder (Asker *et al.*, 1975:30).

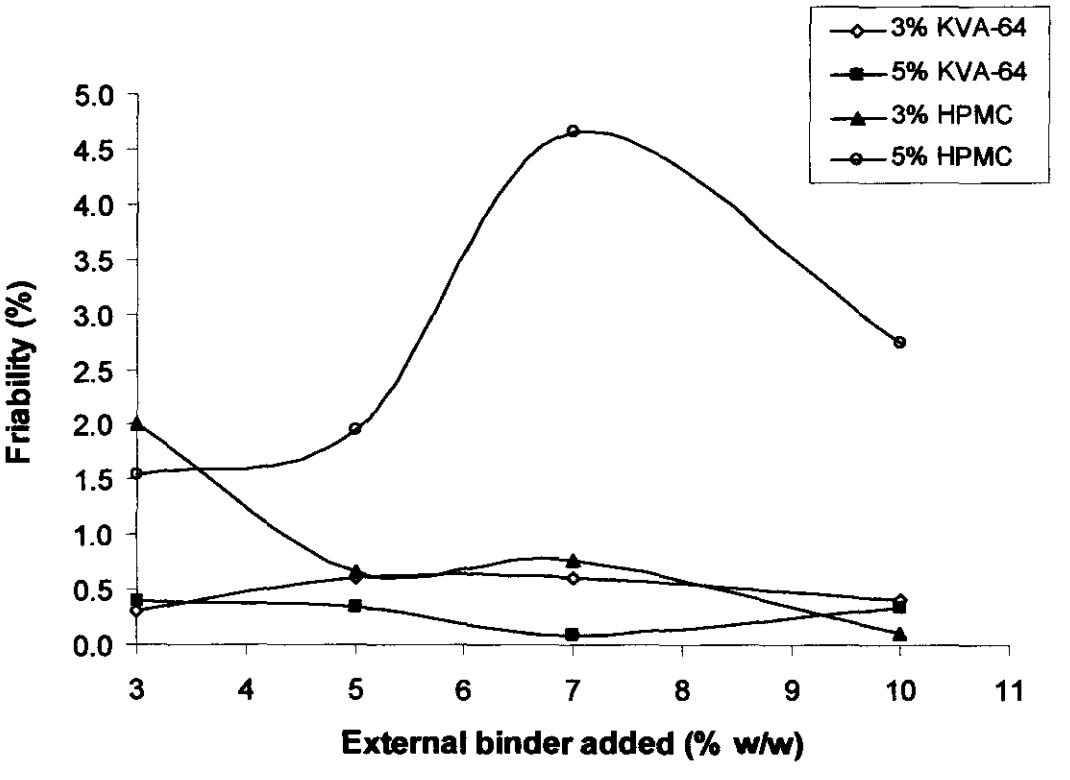


Figure 4.6: *The friability (%) of the formulations containing 3 or 5% w/w Kollidon® VA-64 or Methocel® K100M granulate with varying concentrations of external binder.*

Tablets consisting of Methocel® granulate (5%) revealed friability values exceeding 1% (Figure 4.6). In comparison the tablets containing 3% Methocel® granulate revealed significantly lower friability percentages. Furthermore, all the tablets containing the Kollidon® granulate indicated very low friability (< 1%). Again the

inherent "stickiness" of chitosan is evident when the friability and crushing strength are compared. Tablets that are relative weak in terms of mechanical strength revealed low friability, indicating the resistance of chitosan tablets to surface fragmentation. Comparison of the friability of tablets that consists of the granulates (Annexures B1.1 and B1.4) with tablets containing single dry binders (Table 3.3) revealed no significant differences.

4.3.1 Conclusion

Considering the weight variation, crushing strength and friability of tablets containing chitosan granules, it could be concluded that the wet granulation process improved the flowability of the raw material (Figure 4.3). However, in comparison with the directly compressible formulations (sections 3.3 and 3.4) it was demonstrated that granulation impeded the compressibility of chitosan (Figure 4.5). Additionally, the preliminary experiments (section 4.2) illustrated that the speed of granulation had a significant effect on the granules. Therefore, a high speed granulation process was implemented to investigate the effect of mixing speed on the granulation of chitosan.

4.4. HIGH SPEED GRANULATION

The data obtained from the low speed granulation method revealed that the inherent characteristics of chitosan powder still affected the tabletability of the material. The low speed granulation was not as effective in circumventing all the problems encountered during compression. Therefore, a high speed granulation method was examined. This method consisted of a series of preliminary studies that were conducted in order to eliminate formulations and variables that had no positive effects on the tabletability of chitosan.

Chitosan was granulated using Kollidon® (Figure 4.7) as well as Methocel® (Figure 4.8) according to the methods explained (sections 2.4.5.3 and 2.4.5.4). Additionally, both Kollidon® and Methocel® were utilised as external binders in mixtures containing Kollidon® or Methocel® granulate. The rationale for the combination of binders was to determine if it would potentiate their binding effects and which binder produces more acceptable results as an intragranular binder and which as an external binder.
Tables B2.1 to B2.8 (Annexure B2), contain the data of the physical analyses of the tablets that were produced. Firstly, the results obtained from the formulations containing the Kollidon® granulate will be discussed, followed by the results of the

formulations consisting of the Methocel® granulate. Finally a comparison will be made of the superior formulations obtained from both granulates as well as a comparison of the low speed granulation method with the high speed granulation method.

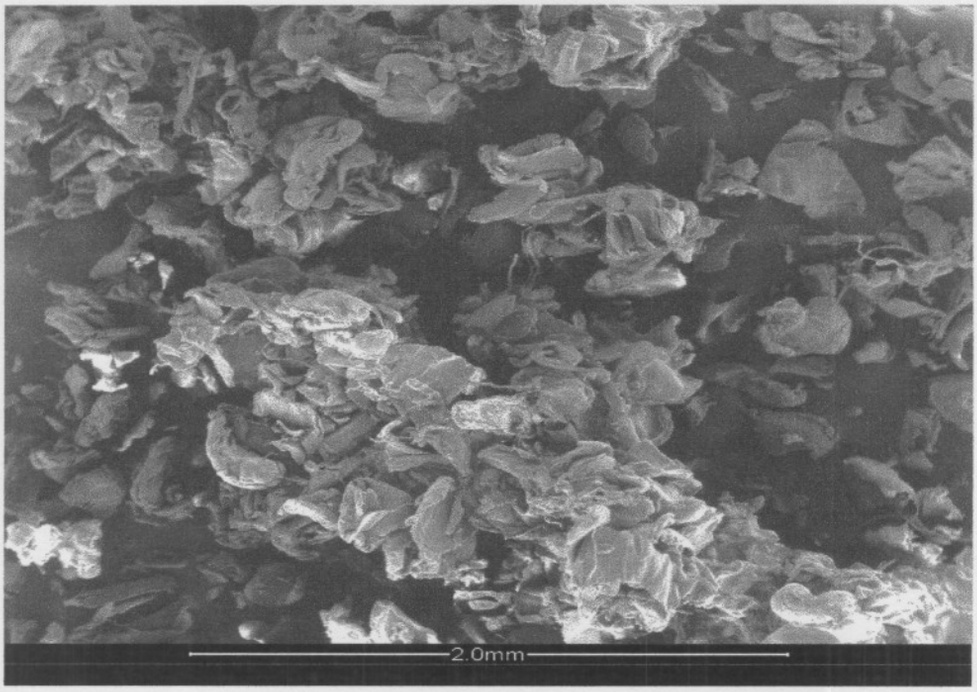


Figure 4.7: *A SEM-micrograph of granulate obtained from the granulation of chitosan with Kollidon® VA-64.*

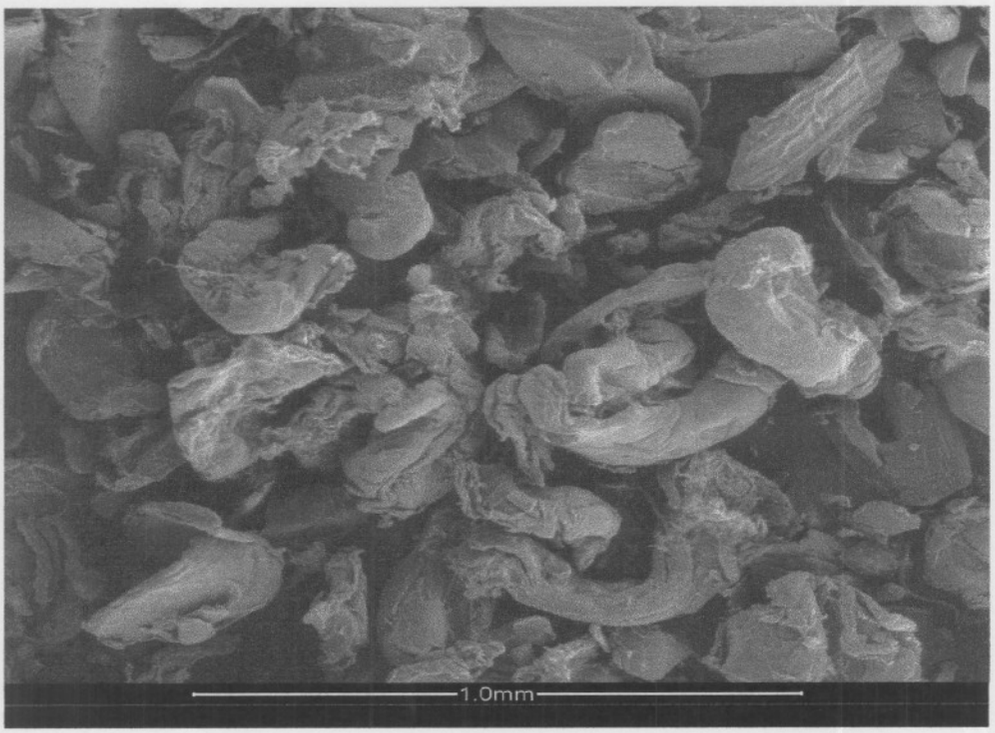


Figure 4.8: *A SEM-micrograph of granulate obtained from the granulation of chitosan with Methocel® K100M.*

Comparison of figures 4.7 and 4.8 with figures 4.1 and 4.2 it is apparent that the high speed granulation method resulted in the occurrence of a larger degree of chitosan particle bonding than during the low speed granulation method. Therefore, it can be suggested from the SEM-micrographs that the high speed granulation method was more superior to the low speed method. However, the physical analyses of the tablets provided the ultimate assessment of the applicability of granulation on chitosan tabletability.

4.4.1. Weight variation

Interpretation of the weight variation of tablets containing Kollidon® granulate combined with various concentrations of externally added Kollidon® or Methocel® did not indicate any significant correlation to the granulate, type or external binder concentration (Figure 4.9). It was, however, evident that the tablets comprising of Kollidon® granulate (5%) and Methocel® as external binder exhibited a decrease in weight variation with an increase in the external binder concentration.

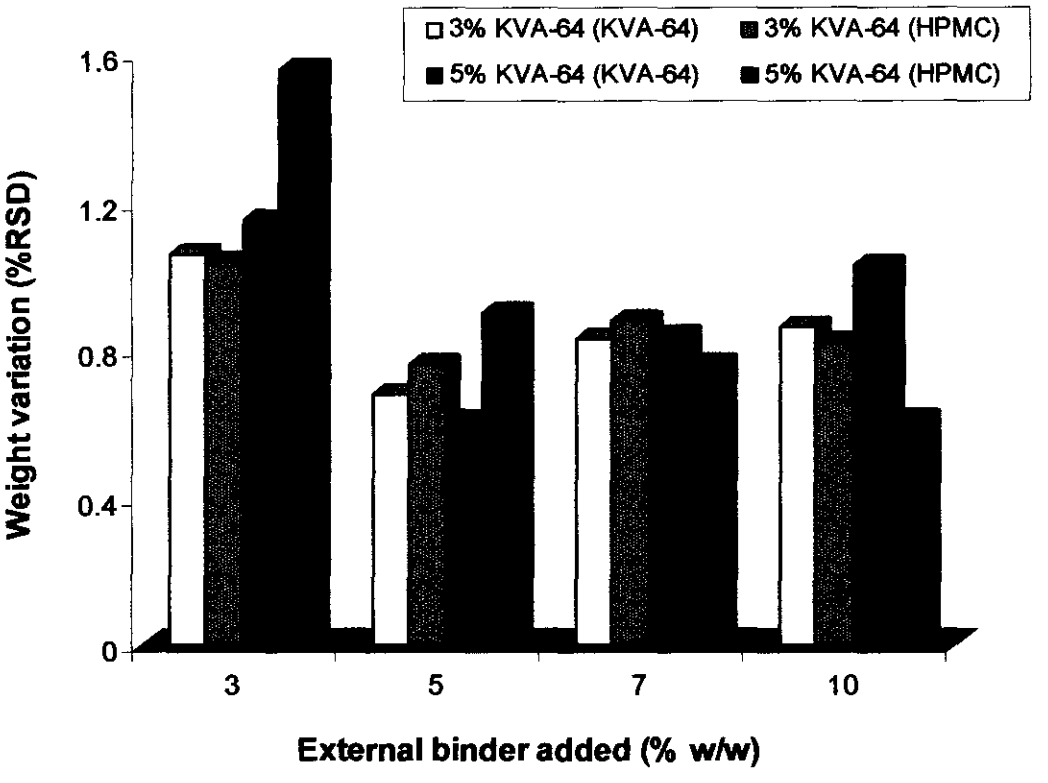


Figure 4.9: *The average weightvariation (% RSD) of the formulations containing Kollidon® VA-64 granulate and various concentrations (% w/w) of external binder added with the type of external binder added indicated in parenthesis.*

Furthermore, comparing weight variation of all the formulations, except 5% Kollidon® granulate (Methocel® as external binder), it is clear that a concentration of 5% external binder, induced the least weight variation in terms of tablet weight. Comparison of the weight variation obtained from the high speed granulation process with that obtained with the low speed granulation process indicated a slight decrease in weight variation. Therefore, it could be concluded that the increase in granulation speed augmented the flowability of the granules.

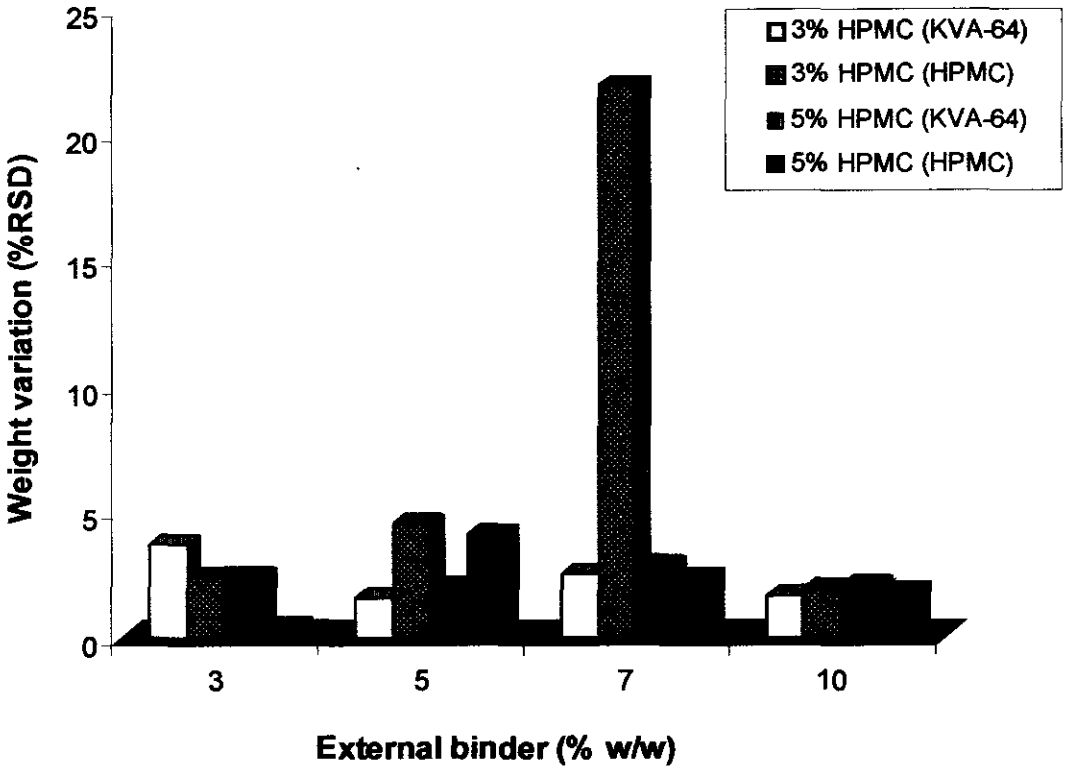


Figure 4.10: *The average weight variation (% RSD) of the formulations containing Methocel® K100M granulate and various concentrations (% w/w) of external binder added with the type of external binder added indicated in parenthesis.*

From figure 4.10 it is impossible to distinguish a clear correlation between the granulate, type, concentration external binder and weight variation. Nonetheless, if the weight variation of tablets containing Methocel® granulate were compared to that of tablets containing the Kollidon® granulate (Figure 4.9), it is clear that the Methocel® granulate produced tablets with a higher degree of weight variation. This increase in weight variation occurred irrespective of the type and concentration of the external binder. Thus, it is concluded that the wet granulation of chitosan and Methocel® resulted in a decrease of the flowability of the granules when compared to the granules obtained from the wet granulation with Kollidon®. These facts affirmed the trend that the presence of intragranular Kollidon® induces acceptable flowability and Methocel® alters flow (section 4.3.1).

4.4.2. Crushing strength and friability

Another property that might indicate the suitability of the granulation method to improve compressibility of chitosan is the crushing strength. The crushing strength

and friability are two important properties of tablets that describe the extent of consolidation during compression, particle deformation and bond formation.

Figure 4.11 illustrates the average crushing strength values of tablets containing Kollidon® granulate and various concentrations of Kollidon® and Methocel® as external binders. The graph clearly indicates that the tablets containing 5% Kollidon® granulate produced tablets with the highest crushing strength, irrespective of the concentration of external binder. The 5% granulate probably harnessed the work of compression more effectively than the 3% granulate. This trend is confirmed by the previous findings (section 4.3.2). The 5% tablets were harder compared to the 3% tablets. The log linear relation of crushing strength and percentage Kollidon® might explain this phenomenon (section 3.4.1). The effect of Methocel® as external binder, however, were contradictory.

The 3% Kollidon® formulations (Methocel® as external binder) produced tablets of decreasing strength with an increase in binder concentration. The suggestion could be made that the granules were more plastic in nature than Methocel® particles. The increase in Methocel® concentration might result in an overall mixture plasticity. Consequently, work of compression was harnessed to a lesser degree with an increase in external binder. These tablets were the weakest of all.

The 5% Kollidon® tablets exhibited a significant contradiction in behaviour, regarding the response to Methocel®. In all cases these tablets proved superior in crushing strength. The higher quantity of Kollidon® would harness work of compression to a larger extent as a result of a small increase in concentration (log linear relation, section 3.4.1). Kollidon® as an external binder confirmed trends and arguments reported (section 4.3.2). It seemed rather unexpected that Methocel® as external binder produced harder tablets compared to Kollidon®. However, the compression threshold of Methocel® might be attained to lower compression loads than for Kollidon®. Consequently, a maximum degree of deformation of Methocel® could be achieved, resulting in a higher bonding surface area compared to Kollidon®. The suggestion could be repeated that Methocel® formulations might have reached their threshold crushing strength; however, Kollidon® might still achieve this threshold. Studies exceeding normal press operation might confirm this assumption.

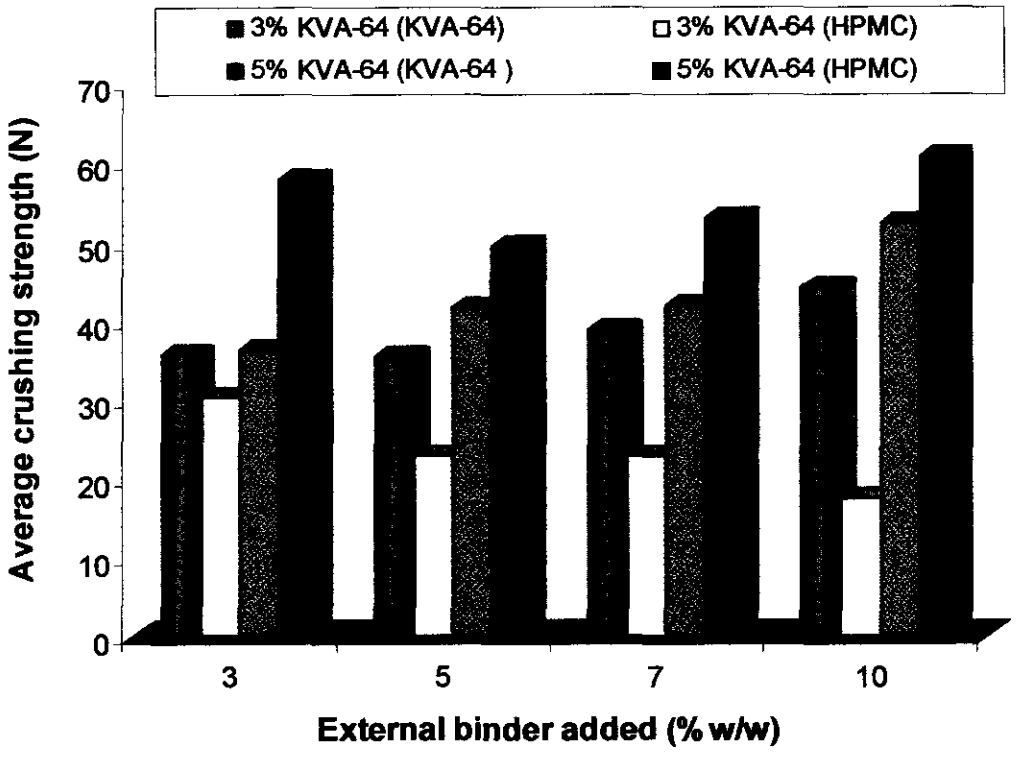


Figure 4.11: *The average crushing strength (N) of the formulations containing Kollidon® VA-64 granulate and various concentrations (% w/w) of external binder added with the type of external binder added indicated in parenthesis.*

In comparison with figure 4.11, figure 4.12 indicates the average crushing strength of tablets containing Methocel® granulate. The graph clearly indicates that the formulation containing 5% Methocel® granulate and Kollidon® as external binder resulted in tablets with the highest crushing strengths.

Addition of external Kollidon® affirmed its significant binding capacity. The increase in crushing strength occurred in good agreement with the log-linear relation (section 3.4.1). The erratic effect of Methocel® on crushing strength was yet again observed. Thus, it is evident that the type of binder that is added externally to the formulation greatly influenced the physical properties of the obtained tablets. Initially it would be suspected that the type of binder that was utilised as the intragranular binder should also be used externally. However, from the results it was clear that utilising a different type of binder externally, potentiated the binding effect of the granules subjected to compression. Another variable that has to be considered is the concentration of binder used internally and externally. The formulations containing 3% binding agent

intragranular did not exemplified the same trends as the formulations containing 5% intragranular binder.

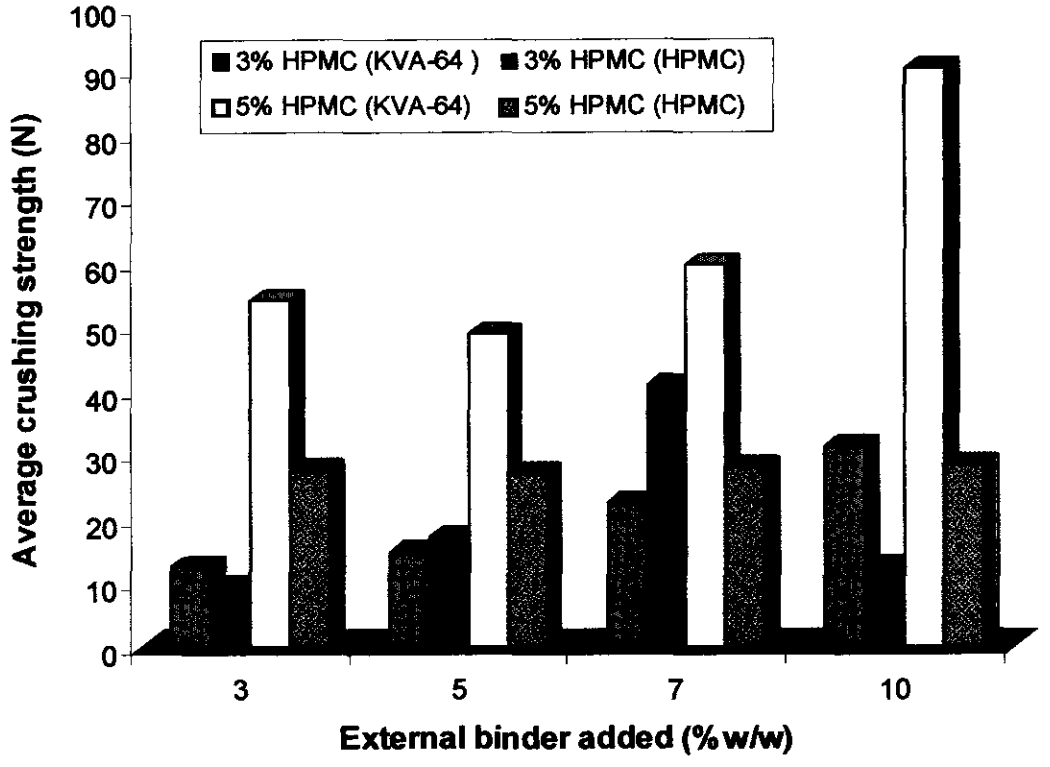


Figure 4.12: *The average crushing strength (N) of the formulations containing Methocel® K100M granulate and various concentrations (% w/w) of external binder added with the type of external binder added indicated in parenthesis.*

Figure 4.13 shows a comparison of the crushing strength values of 5% Kollidon® granulate and 5% Methocel® granulate. The graph indicates that the formulations containing 5% Kollidon® granulate combined with 3 and 5% Methocel® externally had higher crushing strength values than the tablets containing 5% Methocel® granulate and the same concentrations external binder (Kollidon®). The formulations containing 5% Methocel® granulate combined with 7 and 10% external binder (Kollidon®) delivered higher crushing strengths than the tablets compressed from 5% Kollidon® granulate. Therefore, it can be concluded that the concentration of Kollidon® in the tablet formulation, i.e. internally or externally, markedly influenced the crushing strength of the tablets. Therefore, the higher the overall concentration of Kollidon® the higher the crushing strength of the tablets.

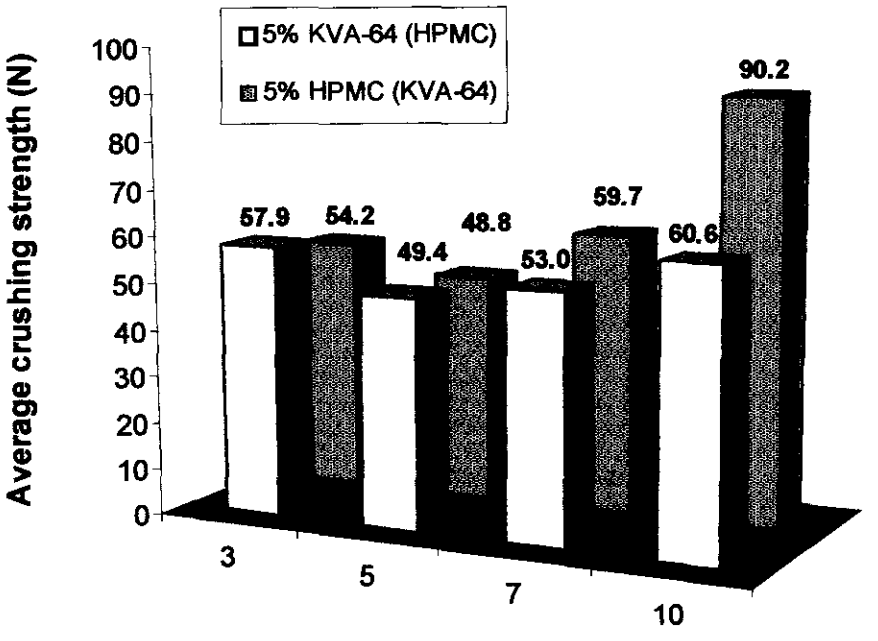


Figure 4.13: *A comparison of the average crushing strength (N) of tablets containing 5% w/w Kollidon® or Methocel® granulate respectively as a function of the percentage external binder (% w/w) that was added to the formulations.*

Figure 4.14 clearly indicated that the types of external binder were able to potentiate the crushing strength of the tablets. This may be concluded from the fact that the formulations containing 5% Kollidon® granulate with varying concentrations of Kollidon® as external binder resulted in tablets with lower crushing strengths than the tablets containing 5% Kollidon® granulate with the same concentrations of Methocel® as external binder. Once again the maximum degree of deformation, resulting in a higher bonding surface area of Methocel® was illustrated. Therefore, the crushing strength threshold of the Methocel® formulations might have been reached.

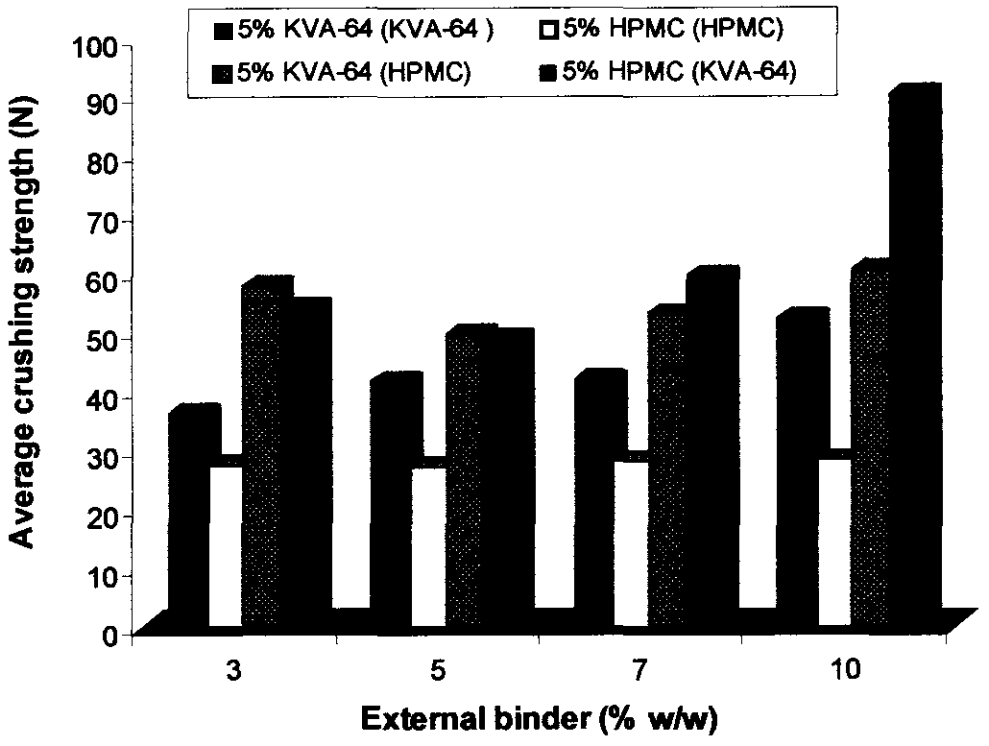


Figure 4.14: *A comparison of the average crushing strength (N) of tablets containing 5% w/w Kollidon® or Methocel® granulate respectively as function of the percentage external binder (% w/w) that was added to the formulations.*

The same argument could be applied to the formulations containing 5% Methocel® granulate. The formulations containing 5% Methocel® granulate and varying concentrations of Kollidon® as external binder delivered tablets with much higher crushing strength values than the tablets containing the same granulate with the only difference being that the external binder is Methocel®. Thus, it may be concluded from figures 4.12 and 4.14 that not only the concentration of the external binder played a role in the crushing strength of the chitosan tablets but also the type of external binder.

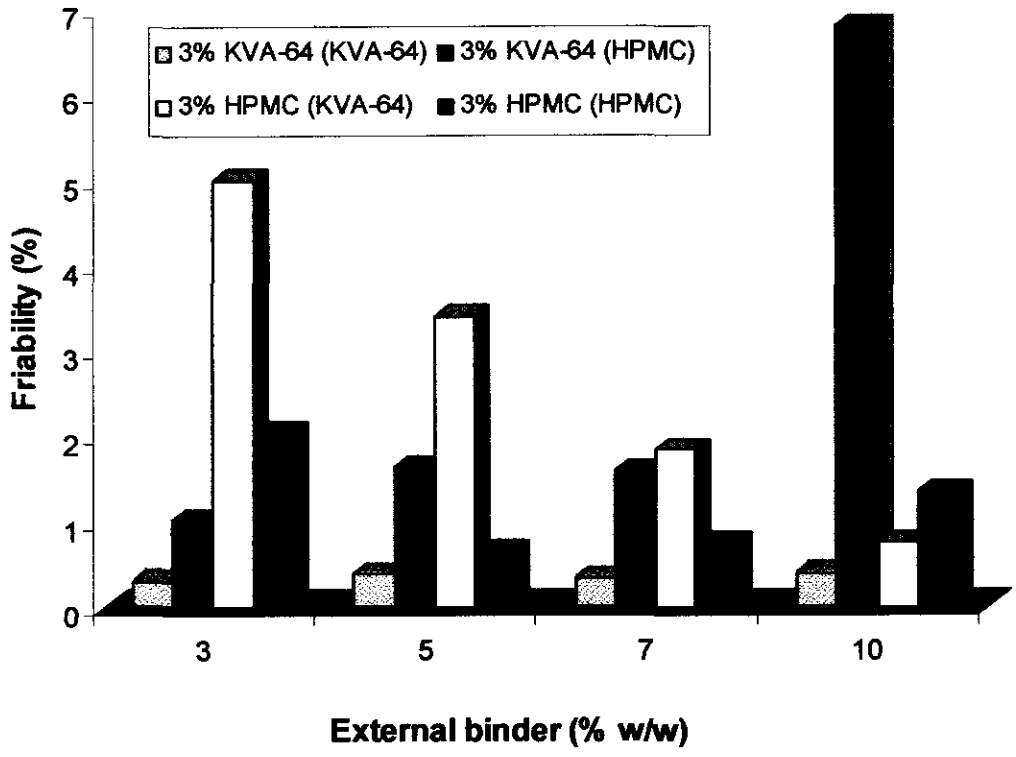


***Figure 4.15**: Friability (%) of tablets containing Kollidon® or Methocel® (3% w/w) granulate respectively as a function of. the percentage external binder (% w/w) that was added to the formulations.*

From figure 4.15 it is clear that tablets comprising of 3% Methocel® granulate and Kollidon® external binder resulted in a decrease in friability. In comparison the tablets consisting of 3% Kollidon® and Methocel® showed an increase in friability. Since friability is also a measure of the mechanical strength of tablets, a correlation exists between the crushing strength and friability of tablets. Therefore, the tablets that exhibited low crushing strength indicated higher friability.

Comparison of figures 4.15 and 4.16 indicated a decrease in friability for the formulations consisting of 5% Kollidon® and Methocel® granulate. All the formulations containing 5% granulate revealed friability percentages less than 1%. Therefore, it is concluded that the 5% Kollidon® and Methocel® granulate produced optimal results. An explanation for this might be that Kollidon® tend to be more plastic than Methocel® therefore revealing more resistance to shock as the tablets impact the friabilator wall, resulting in less surface fragmentation.

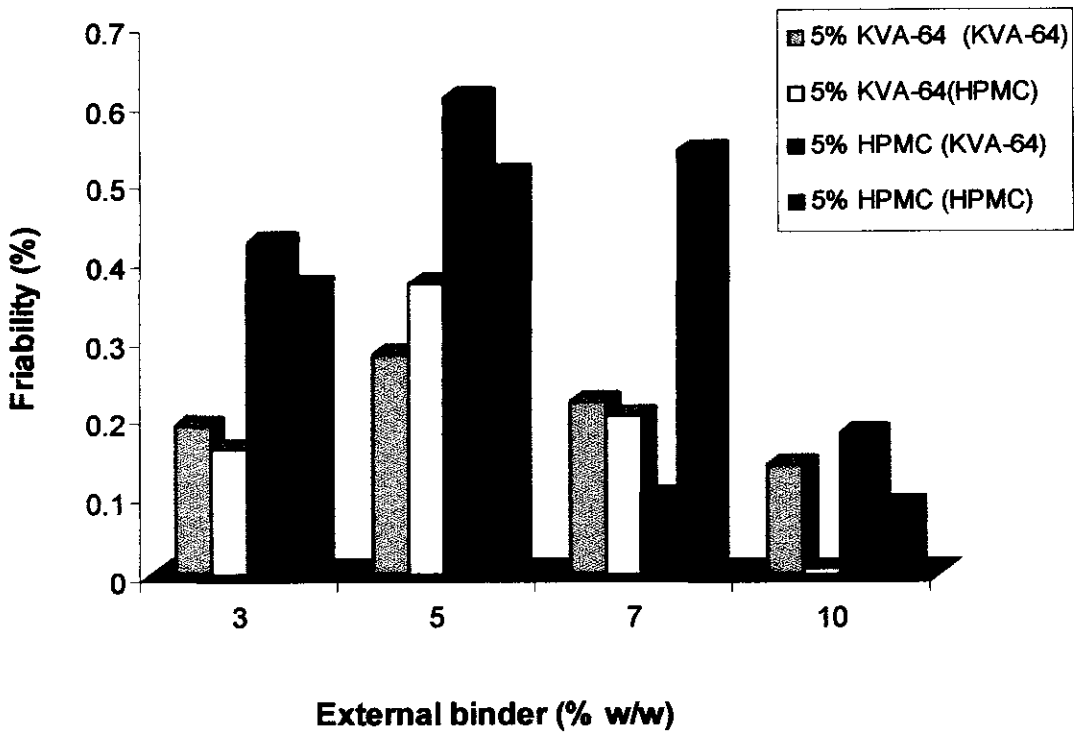


Figure 4.16: *Percentage friability of tablets containing Kollidon® or Methocel® (5% w/w) granulate as a function of the percentage external binder (%w/w) that was added.*

4.4.3. Comparison of the low speed granulation and high speed granulation method

Sections 4.3.1 and 4.3.2 indicated that the flowability of chitosan raw material improved, to some extent, as a result of the low speed granulation method. However, it is paramount to compare the low speed granulation with the high speed granulation method to determine the best process for the improvement of the flowability and compressibility of chitosan.

All the formulations containing Kollidon® granulate (high and low speed) revealed the same tendency in terms of weight variation (Figure 4.17). Thus, it is concluded that the high speed granulation method did not significantly enhance the flowability in comparison with the low speed method.

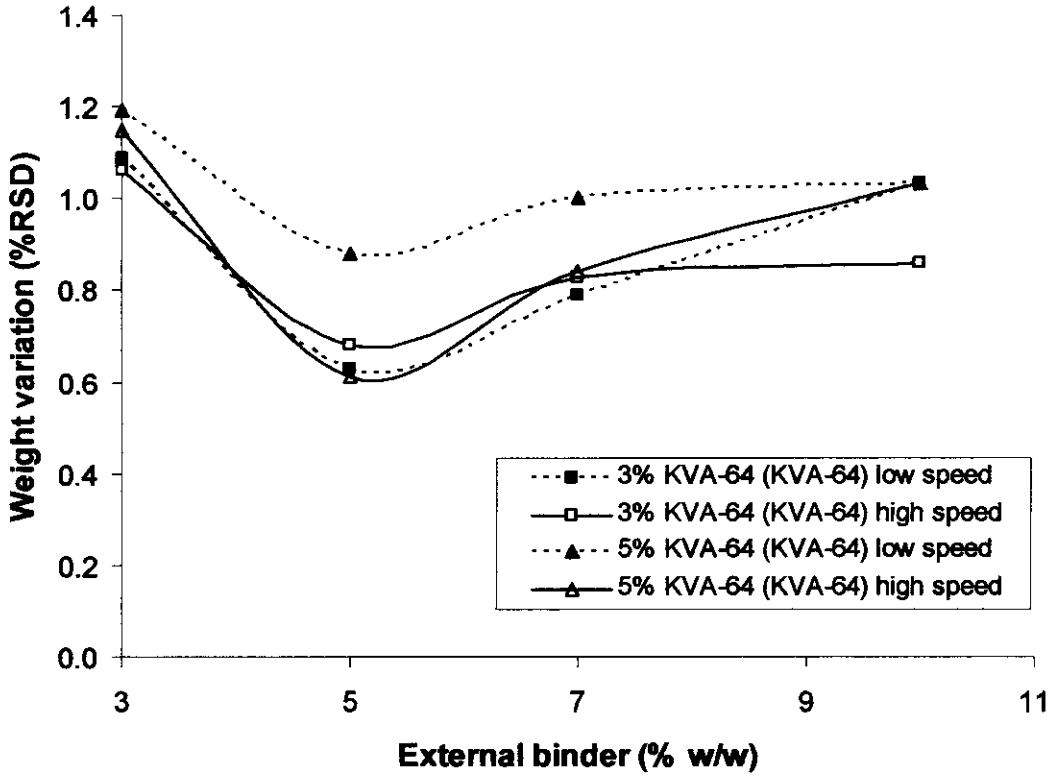


Figure 4.17: *Comparison of the weight variation (% RSD) of tablets containing 3 or 5% w/w Kollidon® granulate obtained from low and high speed granulation methods respectively with various percentage external binder (% w/w) that added.*

In comparison with the Methocel® granulate it is evident that the Kollidon® granulate produced optimum results in terms of weight variation (Figure 4.18). The weight variation obtained for Kollidon® granulate containing tablets was considerably lower than for the Methocel® granulate. Furthermore, the low speed granulation method signified a higher degree of weight variation compared to the high speed method. This suggested that an increase in mixing speed resulted in relatively lower weight variation, indicating the enhancement of the flowability of the raw material. This could be ascribed to better homogeneity of all the components during the mixing process.

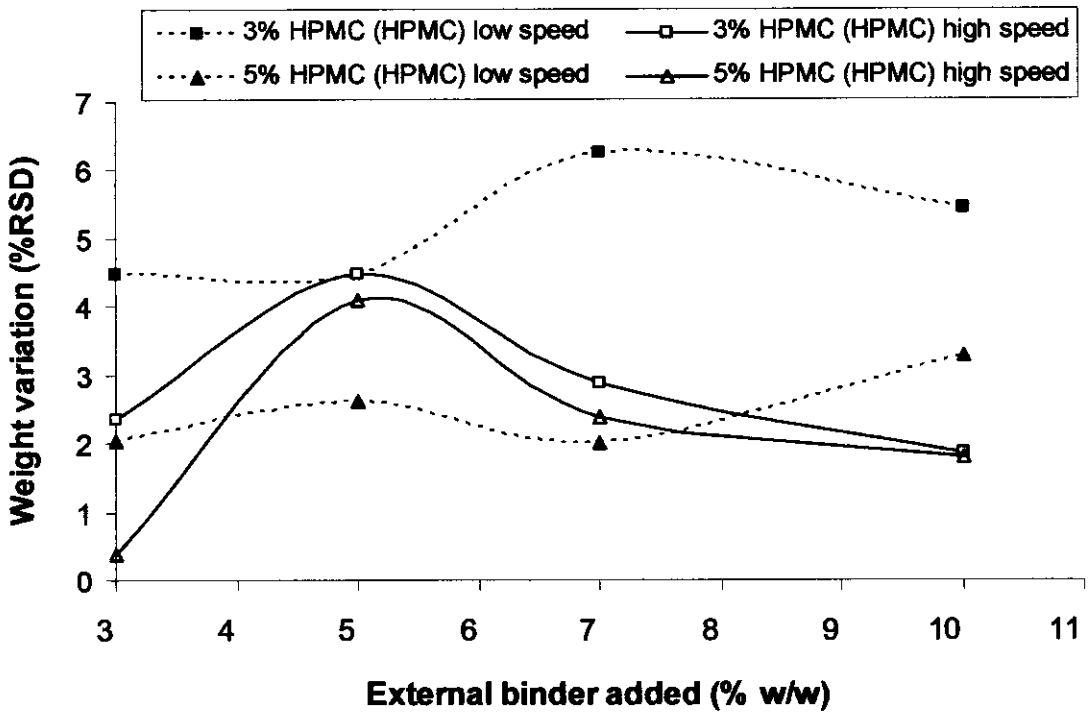


Figure 4.18: *Comparison of the weight variation (% RSD) of tablets containing 3 or 5% w/w Methocel® granulate obtained from low and high speed granulation methods respectively with various percentage external binder (% w/w) that added.*

Figure 4.19 compares the crushing strength values of the formulations containing Kollidon® granulate that was obtained through the low as well as the high speed granulation method. The graph indicates that there was no significant increase or decrease in the crushing strength as would have been expected. This may suggest that the binding potential of Kollidon® in combination with chitosan has been saturated, independent of the mixing speed during granulation. Furthermore, it could be suggested that the applied load of the press was not sufficient to achieve the crushing strength threshold for the system. Therefore, in the case of the application of Kollidon® as a binding agent the concentration of binder superseded the effect of mixing speed during granulation.

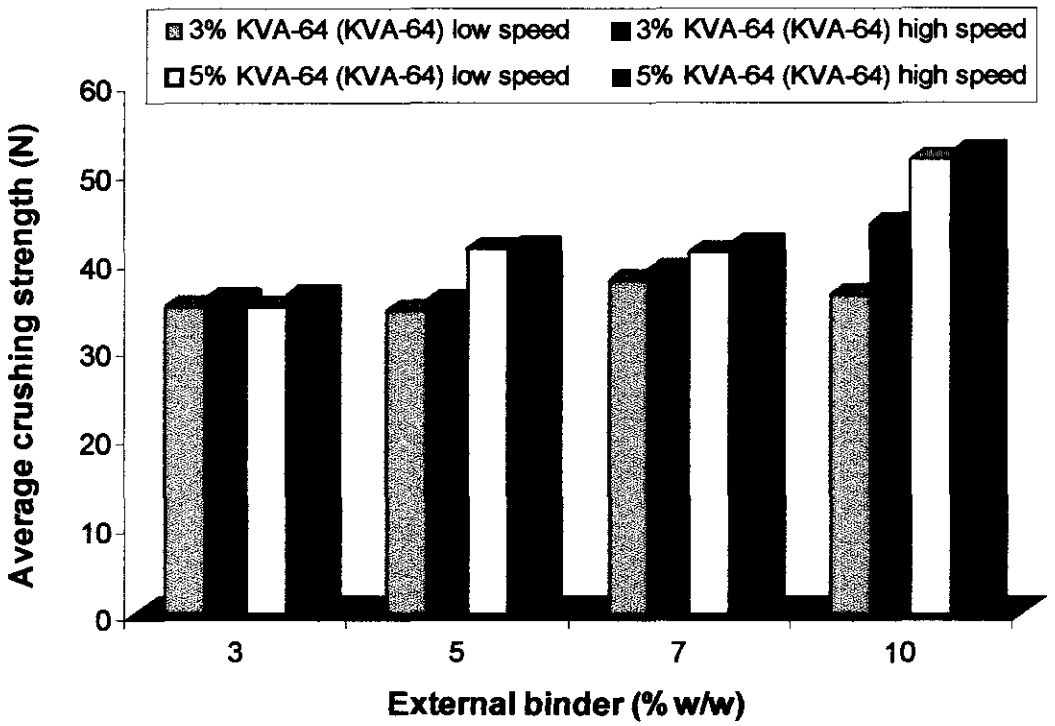


Figure 4.19: *Comparison of the average crushing strength of tablets containing 3 or 5% w/w Kollidon®* granulate *obtained through the low and high speed granulation methods respectively.*

In comparison Methocel® resulted in a large increase in crushing strength as the low speed method was changed to the high speed method (Figure 4.20). This may be an indication that the high speed method resulted in homogenous distribution of the binding solution in chitosan. Thus, wetting all the particles with Methocel® solution, resulted in an increase the contact surface of the Methocel® with the chitosan particles and consequently, resulting in a uniform distribution of the binder. This may also indicate that Methocel® is an effective binder to use during the granulation of chitosan, if the granulation method was adequately modified.

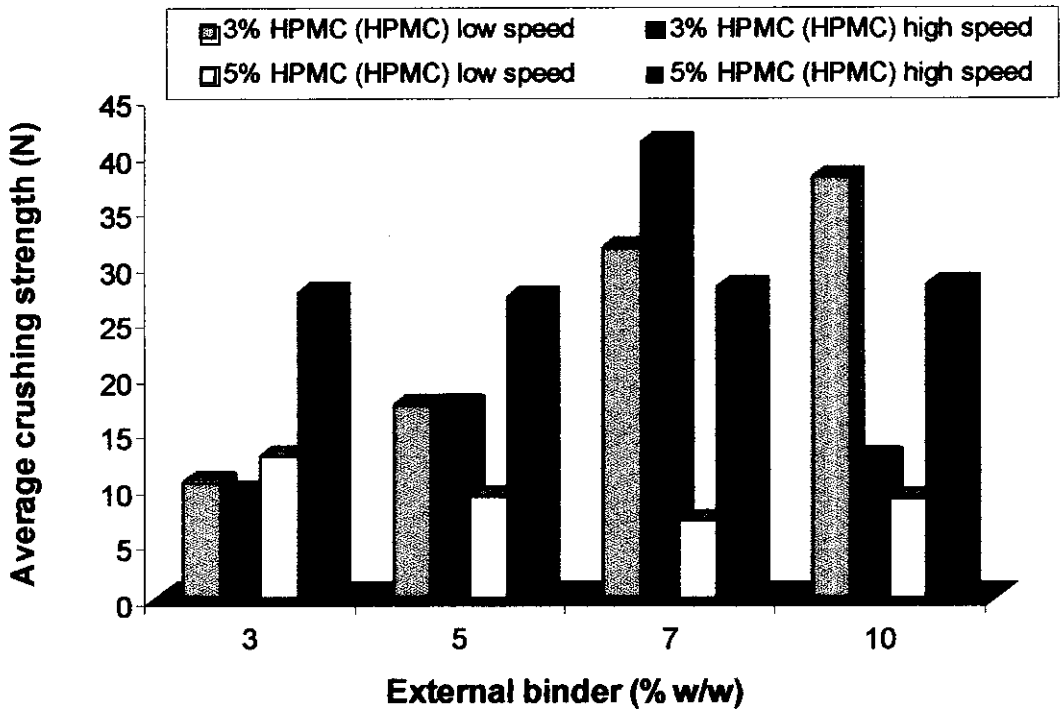


Figure 4.20: *Comparison of the average crushing strength of tablets containing 3 or 5% w/w Methocel® granulate obtained through the low speed and high speed granulation methods respectively.*

It is clear that the Kollidon® granulate produced tablets with low friability. Furthermore, it was evident that the high speed granulation method was more advantageous in terms of friability than the low speed method, since a decrease in friability was obvious with an increase in mixing speed (Figure 4.21). If the friability results obtained from tablets containing Methocel® granulate (Figure 4.22) were compared it could be concluded that the 5% Methocel® granulate produced improved results, since these formulations produced tablets with significant low friability (< 1%). Furthermore, if figure 4.21 were compared with figure 4.22 it could be concluded that the Kollidon® granulate produced optimum results in terms of friability.

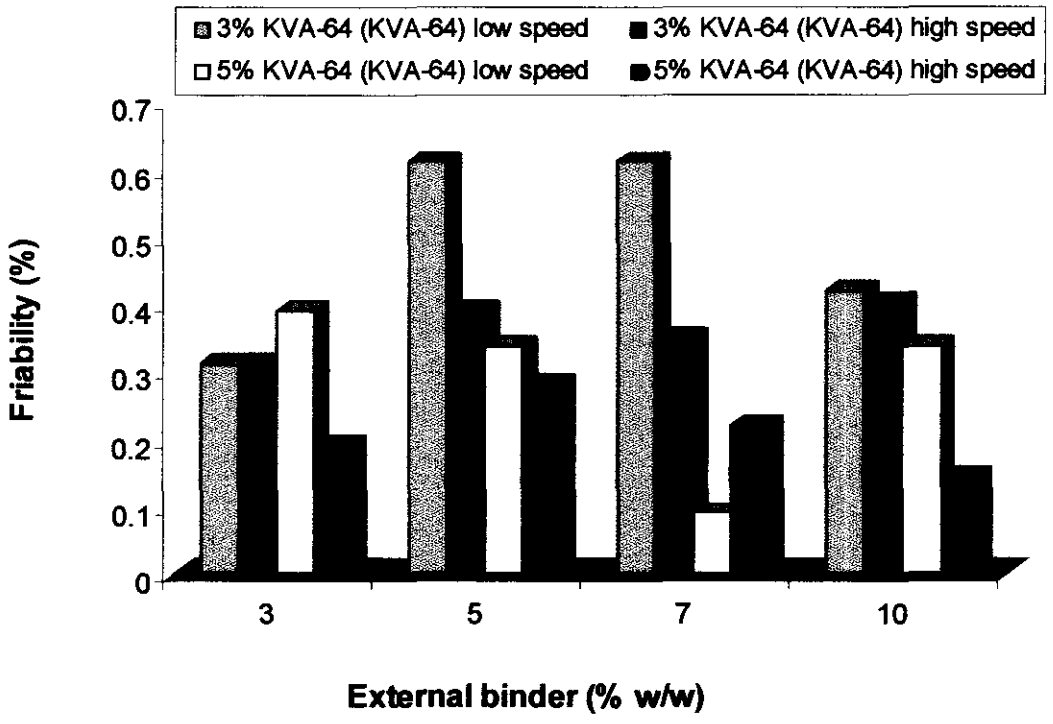


Figure 4.21: *Comparison of the friability (%) of tablets containing 3 or 5% w/w Kollidon® granulate obtained through the low speed and high speed granulation methods respectively.*

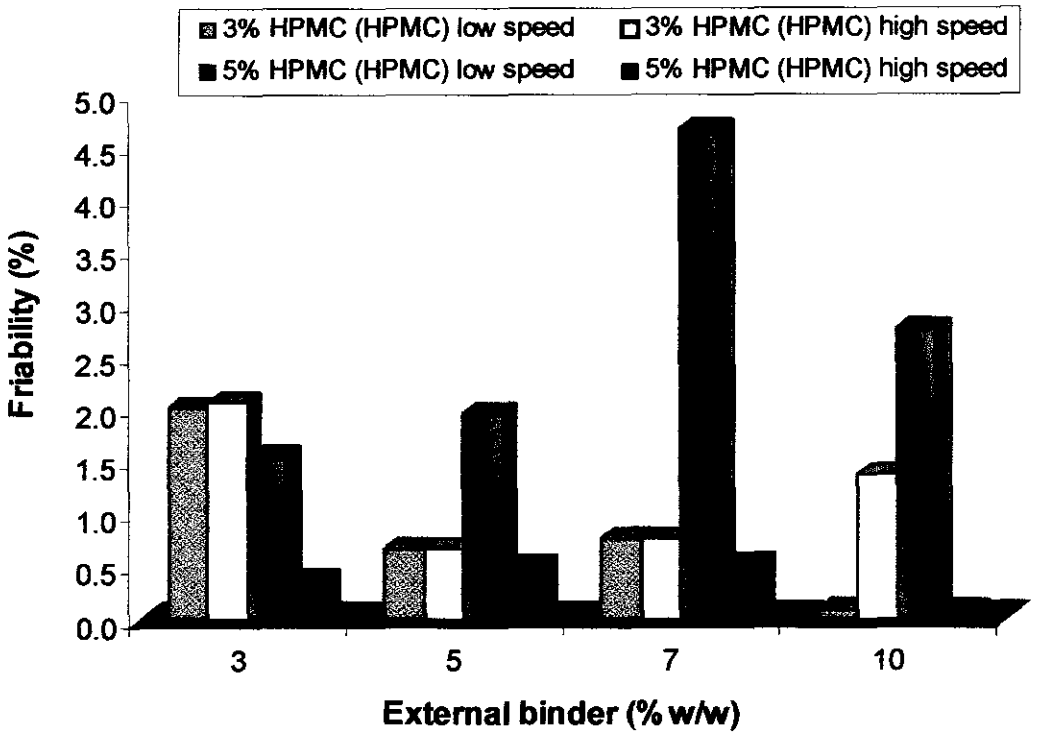


Figure 4.22: *Comparison of the friability (%) of tablets containing 3 and 5% w/w Methocel® granulate obtained through the low speed and high speed granulation methods respectively.*

4.5. Conclusion

The following conclusions could be made regarding the granulation of chitosan, the application of different types and concentrations of binders as well as the speed of granulation.

The granulation of chitosan improved the flowability and compressibility, however, the inherent characteristics of the powder tended to reside in the tabletability of chitosan despite granulation. The granulation of chitosan produced tablets with a higher percentage (% w/w) chitosan content than with the directly compressible formulations (formulations containing fillers). Therefore, it was clear that the granulation process improved the tabletability of chitosan raw material, since it was possible to compress larger quantities of chitosan into a tablet with the aid of selected binders.

The slight increase in the crushing strength of tablets containing Kollidon® granulate, indicated that granulation improved the compressibility of chitosan powder as well as crushing strength.

The Methocel® granulate obtained by high speed granulation produced tablets with significantly higher crushing strength and lower friability compared to low speed granulation. This indicated that the high speed granulation method was better suited for application of Methocel® as binding agent than the low speed method. Homogenous distribution of the binding solution in chitosan had a considerable influence on the properties of the granules. Thus, it could be recommended that Methocel® granules necessitate adequate mixing in order to produce acceptable granules, resulting in a positive effect on the compressibility of chitosan powder. In comparison with the Kollidon® granulate, the mixing process did not have a significant effect on the tabletability but rather the concentration of the binder in the formulations.

Comparison of the directly compressible formulations to the formulations containing the granulate, it was apparent that the crushing strength values was higher for directly compressible formulations. However, the decrease in crushing strength did not imply that the tablets containing the chitosan granules were unacceptable. This was evident from the friability values that were less than 1% for the majority of formulations containing the granulate.

Therefore, it is clear that the granulation of chitosan raw material improved the basic characteristics of the powder and that it was possible to compress tablets containing mainly chitosan as an excipient. In this regard, Kollidon® VA-64 might be the better suited binder to apply as granulation binder, compared to Methocel® K100M. Furthermore, the effect of machine operation parameters should be considered to select appropriate formulation and processing variables.

CHAPTER 5

DISSOLUTION PROFILES OF CHITOSAN TABLETS

5.1 INTRODUCTION

Chitosan is a cationic polyelectrolyte which has been found to interact with anionic compounds (Nigalaye *et al.*, 1990:449). Therefore, the possibility exists that chitosan may interact with either the drug or excipients, consequently influencing the dissolution of the drug or even that of chitosan. Furthermore, chitosan forms a gel structure in acidic pH. Therefore, dissolution studies were imperative in order to determine the effect that the inherent properties of chitosan will have on drug release.

The formulations that produced optimal physical tablet characteristics were selected from the direct compression and wet granulation processes. Furosemide was incorporated into these formulations to aid as a hydrophobic, poorly water soluble tracer drug and were subsequently subjected to dissolution tests. The rationale for the addition of a tracer drug was to determine the effect of pharmaceutical excipients as well as chitosan on the dissolution profile of a drug. The dissolution profile of chitosan was also determined during this phase, since the inclusion of excipients (binders) and the granulation process may influence the dissolution of chitosan. In turn, the dissolution of chitosan might affect the dissolution of the tracer drug.

5.2 SELECTION OF OPTIMAL FORMULATIONS AND UTILISATION IN DISSOLUTION STUDIES

The direct compression formulation that were chosen comprised of 20% w/w Kollidon® VA-64 (section 3.4.1) and the wet granulation formulations included 5% w/w Kollidon® and Methocel® granulate. The selection of these formulations was based on the results that were obtained in terms of weight variation, crushing strength and friability. Subsequently, the tracer drug, furosemide, was added during the compression phase (section 2.4.2.3) of these formulations and physical analyses were performed. The data obtained are tabulated in table C1 (Annexure C). After physical analyses, dissolution studies were initiated (section 2.5.5).

5.2.1 Dissolution profile of furosemide suspension

Annexure C.2 contains the dissolution data and figure C.2.1 shows the dissolution profile of a furosemide suspension. The dissolution profile of furosemide suspension was used as a reference profile, since the suspension dissolution will be optimal compared to tablets. Optimal furosemide dissolution is facilitated due to the optimal surface area evidenced for the suspended particles. Therefore, a comparatively larger quantity of the particles was in contact with the dissolution medium. To compare the different formulations, two parameters i.e. AUC (extent of dissolution) and DR_i (initial rate of dissolution) were normalised against the suspension as reference. Equations 5.1 and 5.2 were the equations utilised to normalise the dissolution parameters.

$$(AUC)_n = \frac{AUC_{formula}}{AUC_{suspension}} \qquad (5.1)$$

Where AUC_n = normalised AUC, $AUC_{formula}$ = AUC of formulation and $AUC_{suspension}$ = AUC of reference.

$$(DR_i)_n = \frac{(DR_i)_{formula}}{(DR_i)_{suspension}} \qquad (5.2)$$

Where $(DR_i)_n$ = normalised DR_i , $(DR_i)_{formula}$ = DR_i of formulation and $(DR_i)_{suspension}$ = DR_i of reference.

5.2.1 Dissolution profile of furosemide from chitosan tablets

Annexure C.3 contains the dissolution data of furosemide from chitosan tablets. The dissolution parameters are summarised in table 5.1. From the data it is evident that both the $(AUC)_n$ and $(DR_i)_n$ values of all the formulations were lower than that of the furosemide suspension. These results indicated that the presence of chitosan and binders decreased the rate and extend of drug dissolution. The formulations consisting of Methocel® granulate (Kollidon® externally) and 20% Kollidon® single dry binder revealed the lowest $(AUC)_n$ values, whilst the formulation consisting of Kollidon® granulate and Methocel® external binder revealed relative similar $(AUC)_n$ results in comparison to the suspension.

The formulation comprising of Kollidon® granulate (Kollidon® external binder) revealed the highest value in terms of $(DR_i)_n$, whilst the formulation consisting of Methocel® granulate and Kollidon® externally revealed a significantly lower value, therefore, indicating that the type and concentration of intragranular and extragranular binder affected the initial dissolution rate of the drug.

Table 5.1: *Dissolution parameters of formulations containing furosemide as tracer drug (% RSD indicated in parenthesis).*

Parameters	Furosemide suspension	20% w/w KVA-64	5% w/w Kollidon® granulate		5% w/w Methocel® granulate	
			External binder (10% w/w)			
			KVA-64	HPMC	KVA-64	HPMC
AUC × 10^2 ($\mu g.min.cm^{-3}$)	3.7 (0.2)	2.0 (1.8)	2.5 (4.5)	3.6 (2.2)	2.0 (0.4)	1.5 (0.5)
$(AUC)_n$	1.00 (1.2)	0.53 (0.4)	0.66 (0.0)	0.53 (0.0)	0.54 (0.0)	0.40 (0.0)
DR_i ($\mu g.cm^{-3}.min^{-1}$)	0.002 (0.01)	0.087 (37.4)	0.002 (0.00)	0.005 (0.00)	0.001 (0.60)	0.002 (0.01)
$(DR_i)_n$	1.000 (0.02)	43.56 (0.02)	8.56 (4.60)	2.47 (0.01)	4.08 (0.01)	9.98 (0.02)

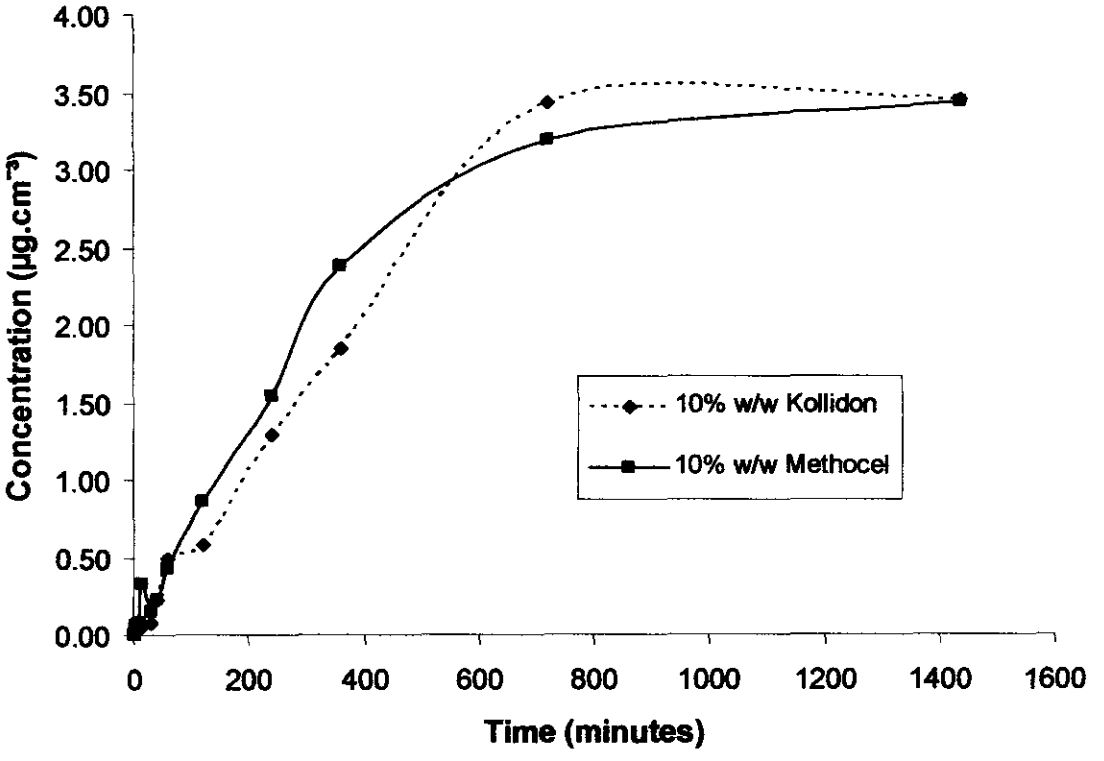


Figure 5.1: *Dissolution profiles of furosemide from tablets containing 5% w/w Kollidon® VA-64 granulate and 10% w/w Kollidon® or Methocel® as external binder.*

Figure 5.1 depicts the dissolution profiles of furosemide from tablets containing chitosan granulate (5% w/w Kollidon® VA-64 intragranular) and 10% w/w Kollidon® VA-64 or Methocel® K100M external. Compared to the dissolution profile of the suspension it was apparent that the initial dissolution rate from the tablets were significantly slower. The formulation consisting of 5% w/w Kollidon® granulate and 10% Kollidon® external binder indicated an increase in the concentration of the drug dissolved at 720 minutes followed by a plateau, whilst the formulation containing 10% w/w Methocel® externally still indicated an increase in dissolved drug concentration after 1440 minutes. In comparison, both the formulations containing Methocel® granulate (Figure 5.2) indicated a degree of saturation after 360 minutes followed by a plateau. This observation may be correlated to the $(AUC)_n$ and $(DR_i)_n$ values (Table 5.1).

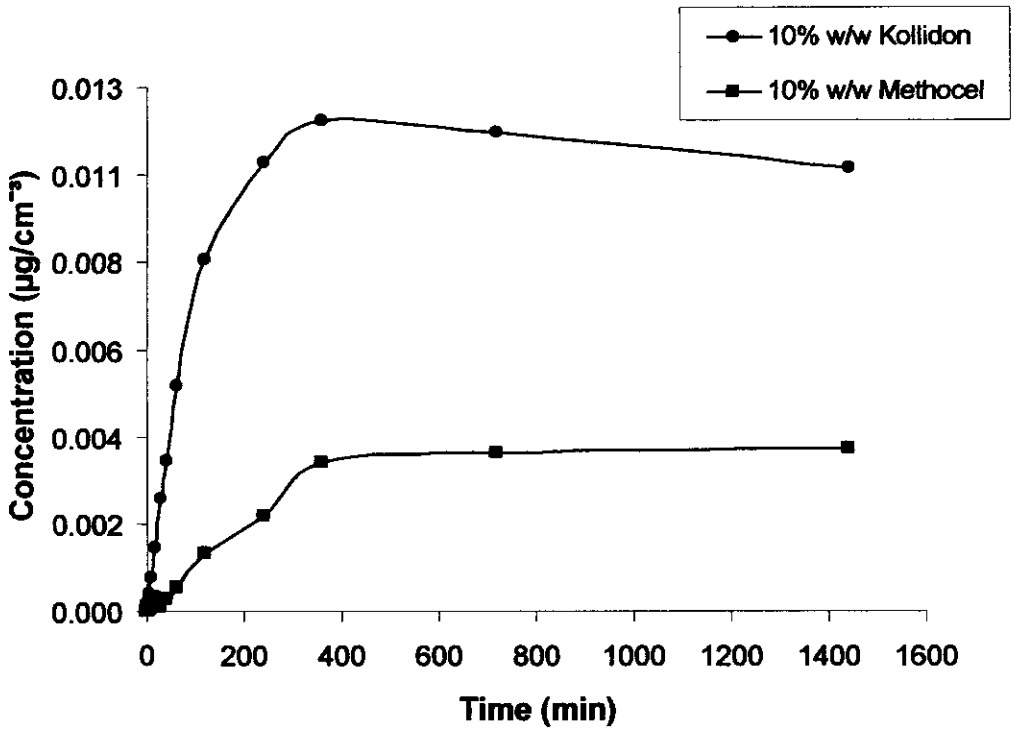


Figure 5.2: *Dissolution profiles of furosemide from tablets containing 5% w/w Methocel® granulate and 10% w/w Kollidon® or Methocel® as external binder.*

Subsequently, it is imperative to compare the $(AUC)_n$ and $(DR_i)_n$ values of the two formulations containing different types of external binders, since this will be an indication of the extent to which dissolution was influenced by the presence of different excipients in the formulations.

The $(AUC)_n$ and $(DR_i)_n$ values of Methocel 10% w/w (externally) were markedly lower compared to the values of the formulation containing Kollidon® as external binder. This decrease in $(DR_i)_n$ could be attributed to the inherent characteristics of Methocel®. Upon contact of Methocel® with the dissolution medium a gel layer forms followed by swelling, due to polymer chain relaxation and volume expansion. The gel layer posses a diffusion barrier and its thickness governs the release kinetics of the drug. Subsequently, a sparingly soluble drug will additionally influence the dissolution rate since, in the outer gel layer, the drug is completely dissolved whilst in the inner gel layer undissolved drug particles still exist. Thus, it is evident that all these characteristics will influence the dissolution profile of the drug (Grassi *et al.*, 2004:106 and Siepmann *et al.*, 2001:140).

Both Kollidon® intragranular and Methocel® intragranular formulations revealed substantial differences in terms of the calculated $(AUC)_n$ values (Figure 5.3). Both formulations containing Methocel® as external binder revealed lower $(AUC)_n$ values than the formulations containing Kollidon® as external binder. This may be correlated to the low $(DR_i)_n$ value calculated for the formulations containing Methocel® externally (Figure 5.4). It is also clear that any combination of Kollidon and Methocel (internal or external) result in a low $(DR_i)_n$ value. The low $(AUC)_n$ and $(DR_i)_n$ values may be attributed to the gel forming ability of Methocel®. The gel layer increases the viscosity of the diffusion layer, therefore, resulting in a slower onset of dissolution and longer duration of drug dissolution. Furthermore, the formulation containing Kollidon® intragranular (Kollidon® external binder) revealed a significantly higher $(AUC)_n$ value than the formulation consisting of Kollidon® intragranular (Methocel® external binder). This phenomenon may be ascribed to the solubilisation effect of copolyvidone (Kollidon® VA-64). It might be possible that Kollidon® formed a soluble complex with furosemide, resulting in more extensive dissolution of the tracer drug.

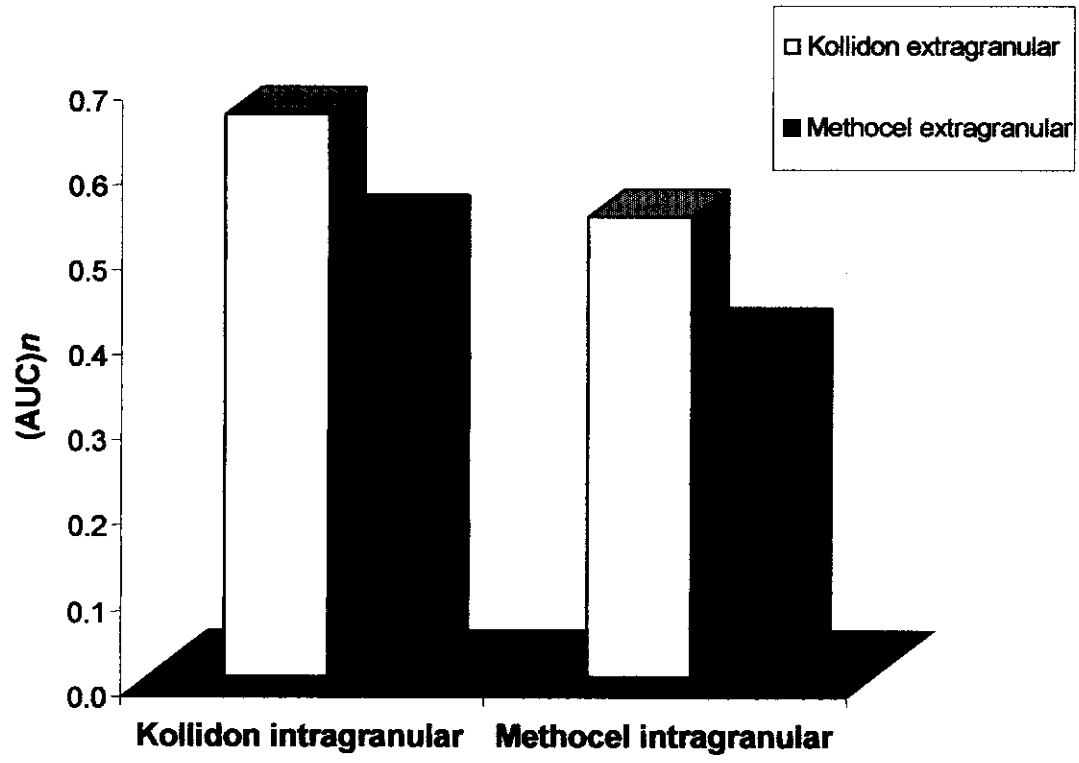


Figure 5.3: *Comparison of the $(AUC)_n$ values of formulations containing 5% w/w Kollidon® or Methocel® granulate and 10% w/w Kollidon® or Methocel® as external binder.*

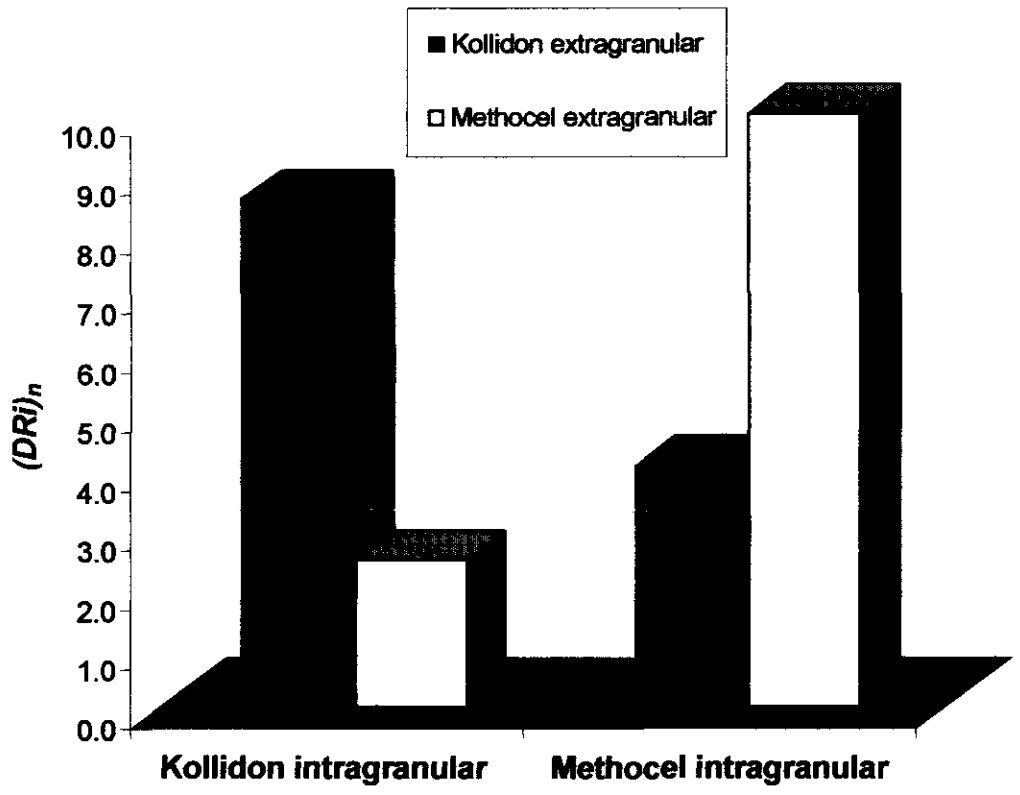


Figure 5.4: *Comparison of the $(DR_i)_n$ values of formulations containing 5% w/w Kollidon® or Methocel® granulate and 10% w/w Kollidon® or Methocel® as external binder.*

The formulation containing Methocel® granulate combined with Methocel® external binder revealed a higher $(DR_i)_n$ value as the formulation containing Kollidon® externally. Therefore, it could be concluded that despite the gel layer formed by Methocel®, the dissolution micro-environment is still more hydrophilic as for Kollidon® utilised as external binder. In comparison with the formulations consisting of granulate, the formulation containing 20% w/w Kollidon® as single dry binder revealed significantly higher dissolution parameters values (Table 5.1). This may also be attributed to the solubilisation effect of copolividone (Kollidon® VA-64).

5.5.2 Dissolution profiles of chitosan

The dissolution profile of chitosan from a suspension was utilised as a reference profile, as described in section 5.2.1. The normalised dissolution parameters, $(AUC)_n$ and $(DR_i)_n$, were calculated according to the given equations (section 5.2.1). Annexure C.3 contains the data of the dissolution of chitosan from tablets containing

chitosan granules as well as tablets containing 20% w/w Kollidon® (single dry binder). The calculated chitosan dissolution parameters are summarised in Table 5.2.

Table 5.2: *Dissolution parameters of chitosan in various formulations.*

Parameters	Chitosan suspension	20% w/w KVA-64	5% w/w Kollidon® granulate		5% w/w Methocel® granulate	
			External binder (10% w/w)			
			KVA-64	HPMC	KVA-64	HPMC
AUC × 10^2 ($\mu g.min.cm^{-3}$)	2.1 (0.3)	1.9 (1.8)	0.3 (0.9)	0.1 (0.2)	0.5 (10.3)	0.5 (2.3)
$(AUC)_n$	1.00 (1.2)	0.90 (8.6)	0.10 (1.7)	0.05 (0.2)	0.23 (9.8)	0.24 (2.3)
DR_i × 10^{-3} ($\mu g.cm^{-3}.min^{-1}$)	22.0 (0.1)	8.7 (12.4)	2.2 (1.3)	2.1 (0.09)	4.6 (21.6)	2.1 (19.6)
$(DR_i)_n$ × 10^{-3}	1.0 (0.2)	0.4 (0.02)	0.1 (1.7)	0.1 (0.6)	0.2 (21.7)	0.1 (17.6)

The formulation containing Kollidon® intragranular (10% w/w Kollidon® external), revealed higher $(AUC)_n$ and $(DR_i)_n$ values in comparison with the tablets consisting of Methocel® as external binder (Table 5.2). This might be attributed to the solubilisation of Kollidon®. A high concentration Kollidon® possibly resulted in the formation of a soluble complex with chitosan, thus improving the dissolution of the polymer.

Conversely, the considerable low $(AUC)_n$ and $(DR_i)_n$ values obtained from formulations containing Methocel® (intra- or extragranular) might be ascribed to the gel forming effect of both Methocel® and chitosan. On contact with the dissolution medium both polymers form a gel layer on the surface of the tablet, resulting in a slow initial dissolution rate as well as a low $(AUC)_n$. Thus, it is concluded that the combination of chitosan with Methocel resulted in a sustained release system regarding chitosan dissolution.

The formulation containing 20% w/w Kollidon® (single dry binder) revealed an unexpectedly low $(DR_i)_n$ value. It would be expected that the formulation would

indicate virtually the same dissolution profile as obtained for the furosemide dissolution (due to the solubilisation effect of Kollidon®). However, the unexpected decrease in the initial dissolution rate (Table 5.2) might be due to the gel forming ability of chitosan. It might be possible that the gel forming capacity of chitosan superseded the solubilisation capacity of Kollidon®, therefore, resulting in a slower onset of dissolution.

Since both chitosan and Methocel® were proven to be promising polymers for the application in the formulation of matrix tablets, it could be suggested that all the formulations utilised in the dissolution studies could have delivered matrix tablets. According to the Highuci equation, if the percentage of the drug release versus the square root of time delivers a straight line ($r^2 \geq 0.9999$), the tablets signify matrix like dissolution (Rinaki *et al.*, 2003:199-201). However, it was not possible to plot a straight line with a linear regression of $r^2 \geq 0.9999$ ($r^2 \sim 0.9897$ were obtained). Therefore, the formulations did not produce matrix tablets but only tablets with sustained release profiles. The subsequent linear regression coefficient of $r^2 \sim 0.9897$ indicated, to some extent, matrix formation, however, a higher total concentration of Kollidon® or Methocel® might produce matrix tablets.

5.3 Concluding remarks

The primary aim of the study was to develop formulations that will allow the compression of chitosan, without the addition of high concentrations of other pharmaceutical excipients. Furthermore, it was envisaged to incorporate a drug, either hydrophobic or hydrophilic, into these formulations.

From the dissolution studies, it was evident that the formulations containing chitosan granules and external binder resulted in the sustained release of the incorporated drug (24 hour period). The ability of chitosan to form a gel layer on contact with water or biological fluid renders it a useful excipient in the development of sustained release or matrix tablets. It is concluded that chitosan is a polymer that may be used with success in the formulation of sustained or controlled drug delivery systems. Since it was not possible to formulate chitosan tablets containing smaller concentrations excipients (binders), it would be a difficult task to produce tablets containing chitosan without sustained drug release profiles. However, the incorporation of disintegrant might result in immediate drug release. The effects of disintegrant might be addressed in future studies.

Furthermore, the combination of chitosan with Methocel® not only aided in the compression of acceptable tablets containing large amounts of chitosan, but also assisted in the manufacturing of tablets that exhibited prolonged drug release. Therefore, it can be concluded that the combination of chitosan and Methocel® may lead to a vast amount of possibilities regarding the formulation of tablets with altered drug release profiles.

CHAPTER 6

INFLUENCE OF TEMPERATURE AND HUMIDITY ON CHITOSAN STABILITY

6.1. INTRODUCTION

An imperative factor for the application of chitosan in tablet formulations would be the extent of polymer degradation as function of time. The stability behaviour of chitosan was investigated by method of short-term exposure of the raw material to elevated temperatures as well as by long-term stability evaluation.

6.2. Short-term stability: effect of temperature and moisture

Chitosan raw material was exposed to 30 °C, 40 °C, 50 °C and 60 °C for periods of 1, 2, 4 and 8 hours. Samples were collected at these intervals for tableting (section 2.4.3), Karl Fischer titration (section 2.3.5) and TGA (section 2.3.4) analyses. The tablets were analysed in terms of crushing strength and friability (section 2.5). These results are summarised in Annexure D.

Temperature and time are two imperative variables which influence the moisture content of chitosan raw material. It is clear that time dependent exposure of chitosan to elevated temperatures resulted in dehydration (Figure 6.1). Moisture content is an important parameter that influences the tabletability of a material. A common observation after tableting is the variation in tablet strength associated with the presence of water in the powder mass. It is possible that sorbed water may affect the volume reduction of a powder mass as well as the interparticulate bonding in the tablet (Ahlneck *et al.*, 1989:131). The moisture content of the powder mass before compaction may influence the tablet strength indirectly by affecting the volume reduction of the powder mass.

The presence of moisture may aid in the binding of particle during compression by means of the formation of liquid bridges between the particles. Furthermore, it may also aid as a lubricant, resulting in better consolidation of particles. However, a high degree of dehydration or significantly high moisture content may have the opposite effect, resulting in mechanically weak tablets. Therefore, a distinct correlation exists between the moisture content and physical properties of the produced tablets.

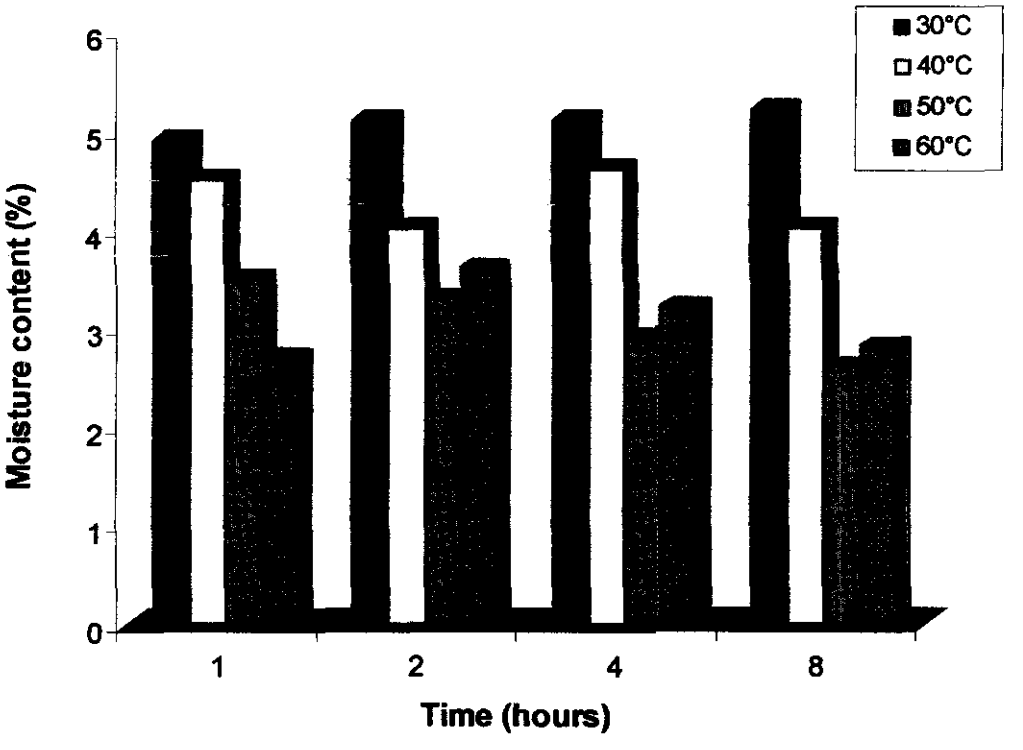


Figure 6.1: *Illustration of the effect of elevated temperatures on the moisture content (%) of chitosan raw material.*

It is clear that temperature had an effect on crushing strength with an increase in time (Figure 6.2). The 30 °C sample revealed a pronounced detrimental effect on the crushing strength of compressed tablets. In comparison the 40 °C condition indicated the lowest degree of variation in terms of crushing strength with time lapse. Additionally, the 40 °C samples produced the strongest tablets of all the elevated temperatures.

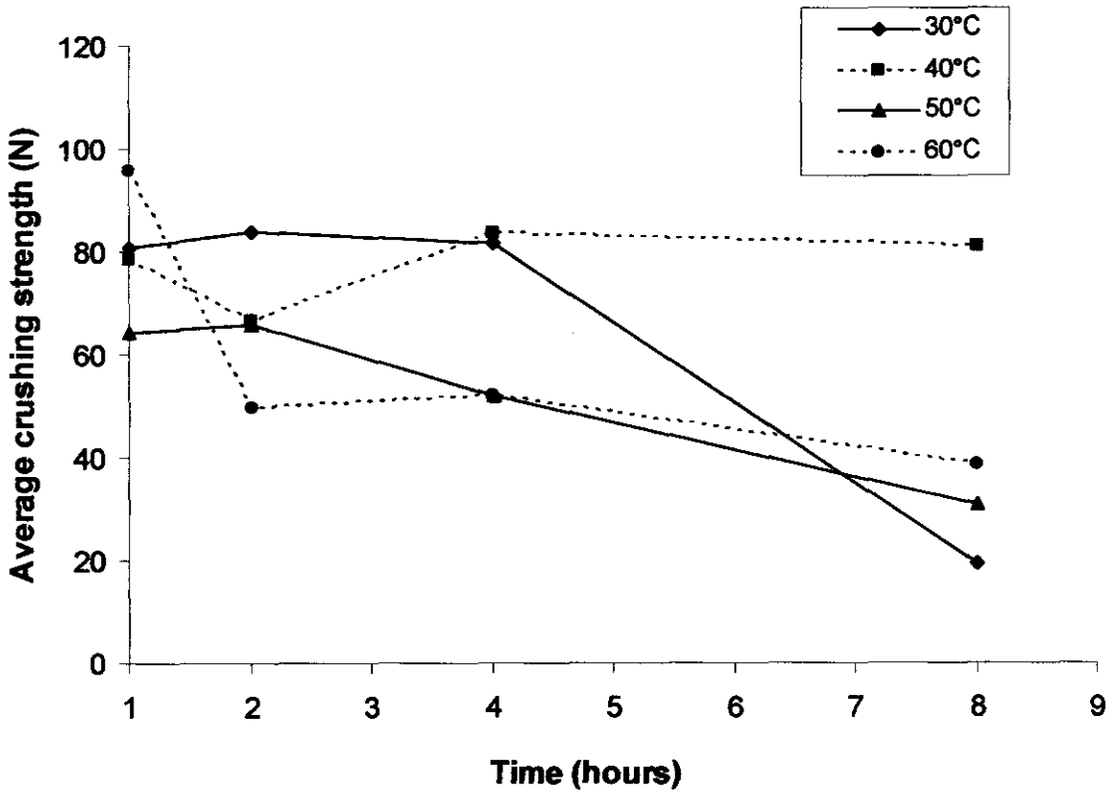


Figure 6.2: *The average crushing strength of tablets containing chitosan exposed to elevated temperatures as a function of time.*

Temperature had a significant effect on the crushing strength. Figure 6.3 indicates that 50 °C had a detrimental effect on crushing strength, irrespective of time. Another observation could be made regarding the 8 hours condition. It was clear that the 30 °C (8 hour) sample produced tablets with the weakest mechanical strength compared to the other tablets. Therefore, it could be concluded that the moisture content influenced the tabletability of chitosan. A fine distinction was observed in terms of crushing strength and the percentage moisture present. Higher percentage moisture could result in poor mechanical strength and too low moisture content could also produce mechanically weak tablets. Therefore, it is evident that the 40 °C condition resulted in the least variation in terms of crushing strength of the tablets, therefore, having the least detrimental effect on the raw material. This might be attributed to the possibility that a temperature of 40 °C influence moisture loss to such an inconsequential manner that enough moisture still exist in the material that particle bonding is enhanced during compression. Furthermore, is might be that the percentage moisture content of the 40 °C samples result in optimal elasticity and plasticity of the material, consequently enhancing the compression of chitosan.

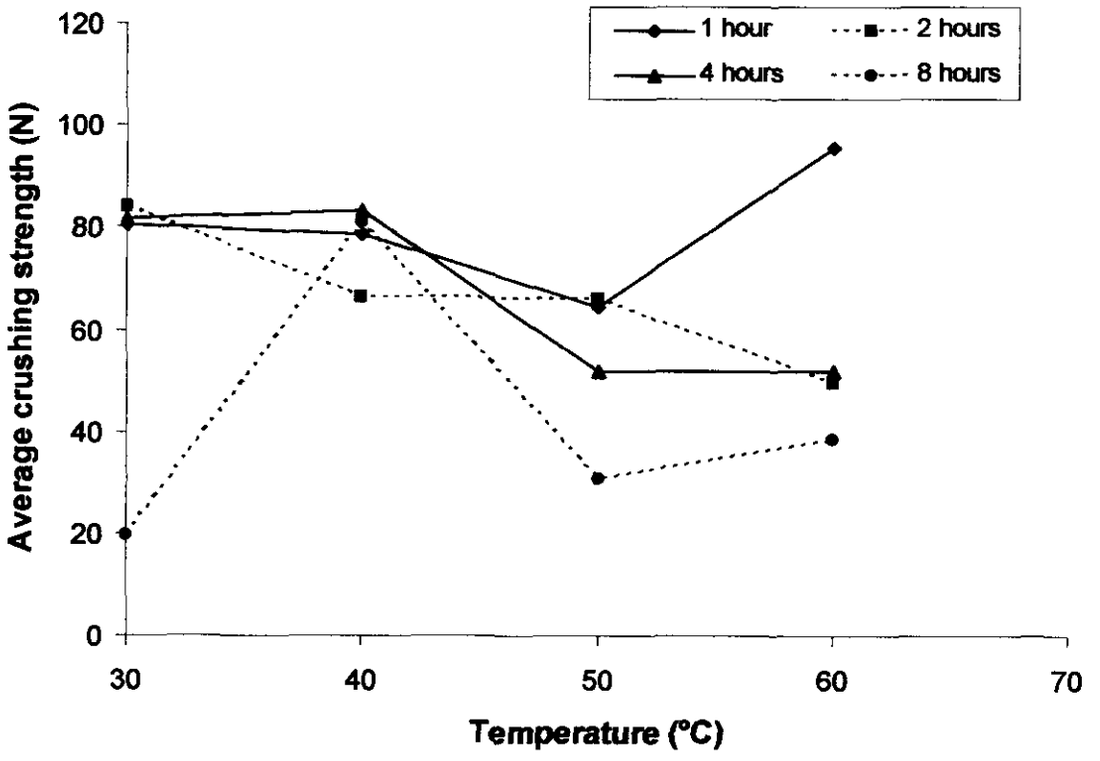


Figure 6.3: *The average crushing strength of tablets containing chitosan exposed to elevated temperatures.*

In addition, the exposure of chitosan to elevated temperatures affected friability in a time-dependent mode (Figure 6.4). The 60 °C (2 hour) sample indicated a significant increase in friability followed by a marked decline in friability. Conversely, the 50 °C sample indicated a decrease in friability at 2 hours interval with a subsequent increase from 0.05% (4 hours) to 1.4% (8 hours), comprising an increase of 28 fold. *The 30 °C sample also revealed a marked increase from 4 hours (0.0%) to 8 hours* (0.41%), comprising a total increase of 41.0%. It is evident that the 40 °C sample did not vary significantly in terms of friability, consequently illustrating the correlation that exists with crushing strength (Figure 6.2).

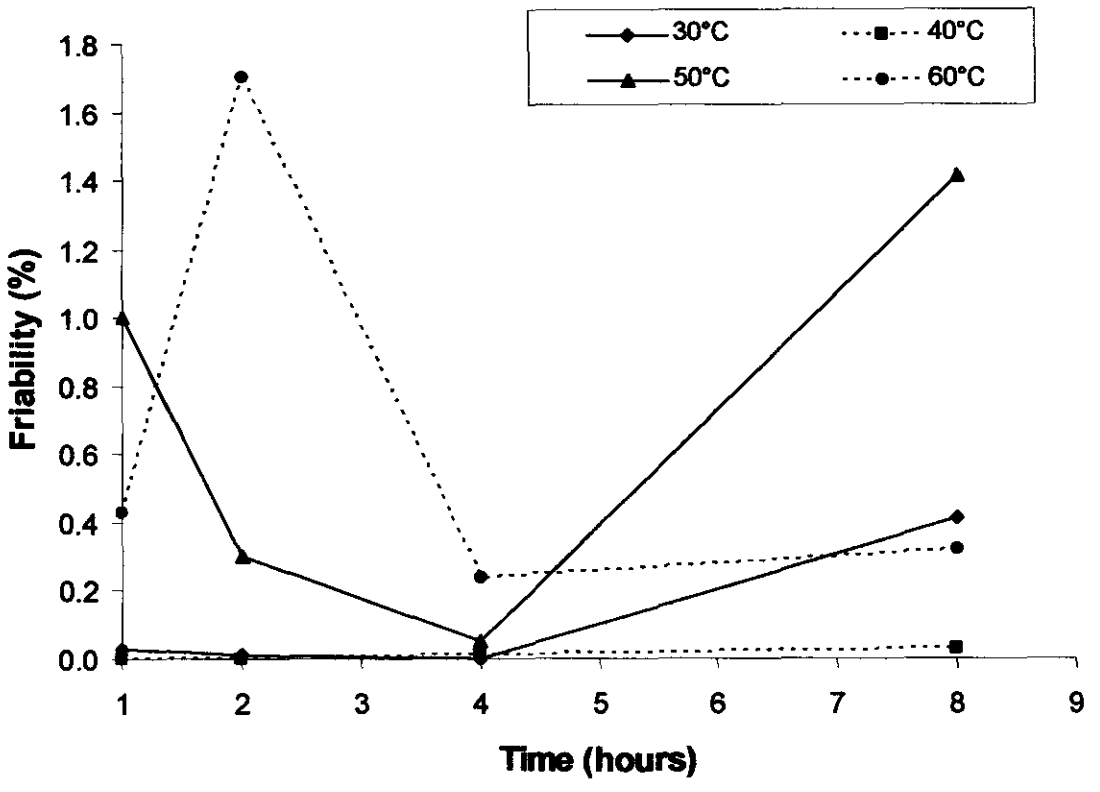


Figure 6.4: *The friability of tablets containing chitosan exposed to elevated temperatures as a function of time.*

Both hardness and friability are parameters that could be utilised in the measurement of the mechanical strength of tablets. Therefore, the hardness-friability ratio (HFR) may be applied to quantify the effect of time - dependent exposure of chitosan to elevated temperatures on hardness and friability (Table 6.1). High crushing strength results in low friability, subsequently resulting in a higher HFR. It is evident that the 30 °C (2 hour) and 60 °C (4 hour) samples revealed the highest HFR values. However, the HFR of the samples with friability of 0.0% could not be defined. It could be concluded that these tablets signify maximum crushing strength according to the HFR. Overall the tablets from the 30 °C and 40 °C samples revealed optimal results in terms of the HFR.

Table 6.1: *The calculated hardness-friability ratio ($N.\%^{-1}$).*

Temperature (°C)	Time (hours)			
	1	2	3	4
30	2690.0	8400.0	0.0	47.3
40	0.0	0.0	8330.0	2696.7
50	64.4	219.7	1038.0	21.7
60	222.3	29.2	216.3	120.3

6.2.1 Concluding remarks

It is clear that the exposure of chitosan to elevated temperatures for a period of 8 hours resulted in marked differences in the physical properties of the tablets. In addition, it is evident that the presence of moisture (sorbed water) had a considerable influence on the tabletability of chitosan raw material. Furthermore, it could be deduced that chitosan is a polymer that exhibits time-dependent tableting performance sensitivity to temperature fluctuation.

6.3. Long-term stability

Long term stability tests simulate ambient stresses to which pharmaceutical products might be exposed during storage. These simulated stresses include the exposure of a material or pharmaceutical product to elevated temperatures and high relative humidities. These accelerated tests are useful in comparison of the physical stability of tablets of different formulations.

The stability behaviour of chitosan was investigated on a long term basis according to the procedure explained in section 2.6. Subsequently the stability of chitosan raw material, chitosan tablets containing Avicel® PH200 (30% w/w) as well as tablets containing chitosan granules (10% w/w external binder) were assessed. The physical stability of the tablets and raw material were determined by method of crushing strength and friability evaluations. The data are summarised in Annexure D2.

6.3.1 Chitosan raw material and chitosan tablets

Tablets consisting of 30% w/w Avicel® PH200 and 70% w/w chitosan as well as chitosan raw material were stored at 25 °C / 60% relative humidity (RH) and 40 °C / 75% RH. Samples were collected monthly. Subsequently, the raw material samples were compressed after co-formulation with 30% w/w Avicel® PH200 (section 2.6.1). Both the sampled chitosan tablets and compressed raw material of both sets of stress conditions were analysed to assess the influence of elevated temperature and relative humidity on the physical properties of chitosan tablets and chitosan raw material.

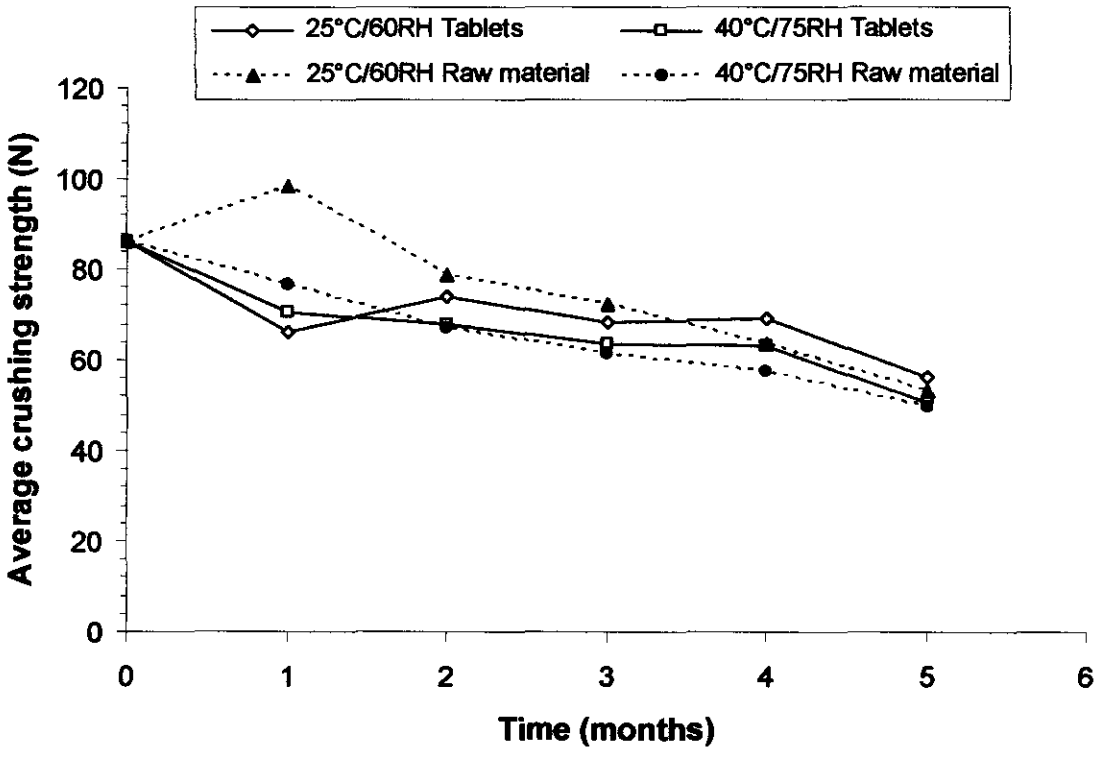


***Figure 6.5:** Average crushing strength of chitosan tablets and raw material subjected to 25 °C / 60% RH and 40 °C / 75% RH stress conditions for a period of 5 months.*

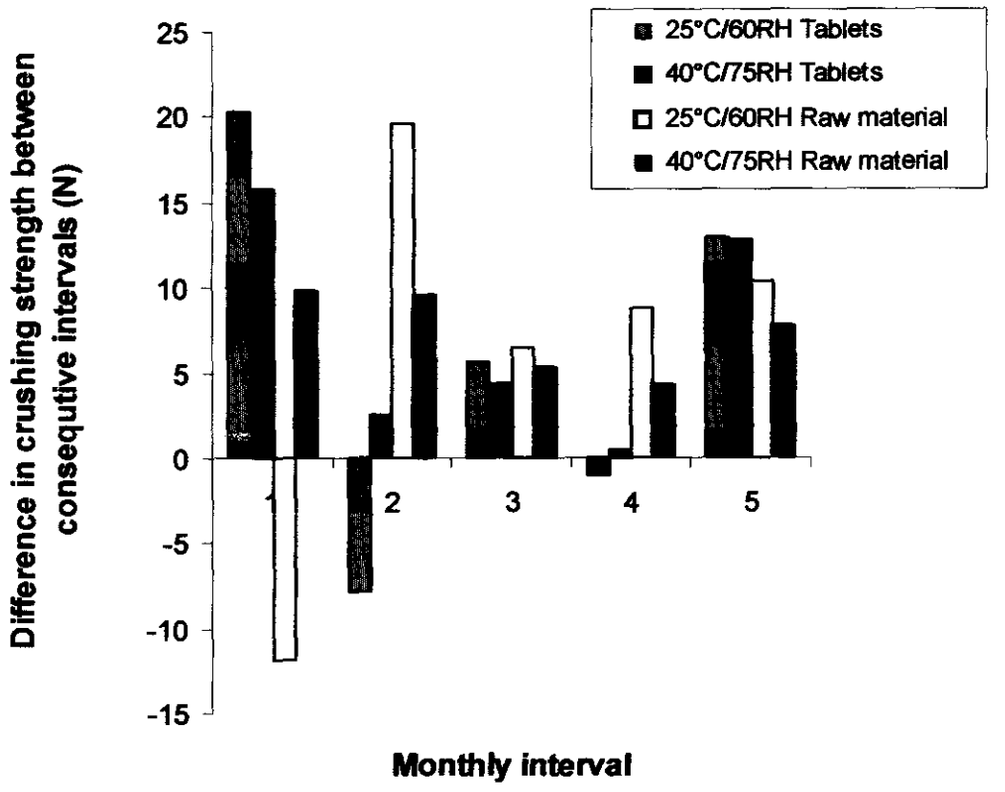


Figure 6.6: *Difference in crushing strength between consecutive monthly intervals.*

Both sets of conditions had a detrimental effect on the crushing strength over a period of 5 months. The tablets stored at both sets of conditions showed a comparable pattern of deterioration. The raw material subjected to 40 °C / 75% RH signified a distinct decrease in crushing strength from month 0 - 5 (Figure 6.5). The difference in crushing strength (Figure 6.6) was calculated by subtraction of the crushing strength of consecutive months. It was shown that the first monthly interval (month 0 - 1) produced the most marked decrease in terms of crushing strength. The raw material subjected to 40 °C / 75% RH showed the most significant decrease of crushing strength, with a total decrease of 36.6 N from month 0 - 5. The deterioration of tablet strength could be attributed to changes in the bonding of particles due to the aging and dehydration of the particles. The effect of elevated temperatures was illustrated by the relative larger decrease in crushing strength for the higher temperature condition. It could be observed, with exception of the first month, that both tablets and raw material deterioration was in good agreement. It could be concluded that neither conditions favoured the raw or compacted material state. Therefore, under these conditions, the manufacturer may choose to manufacture tablets or store the material until necessary without a difference in quality. However,

it should be considered that a time-dependent decay in product quality is observed the material or tablets are exposed to ambient conditions.

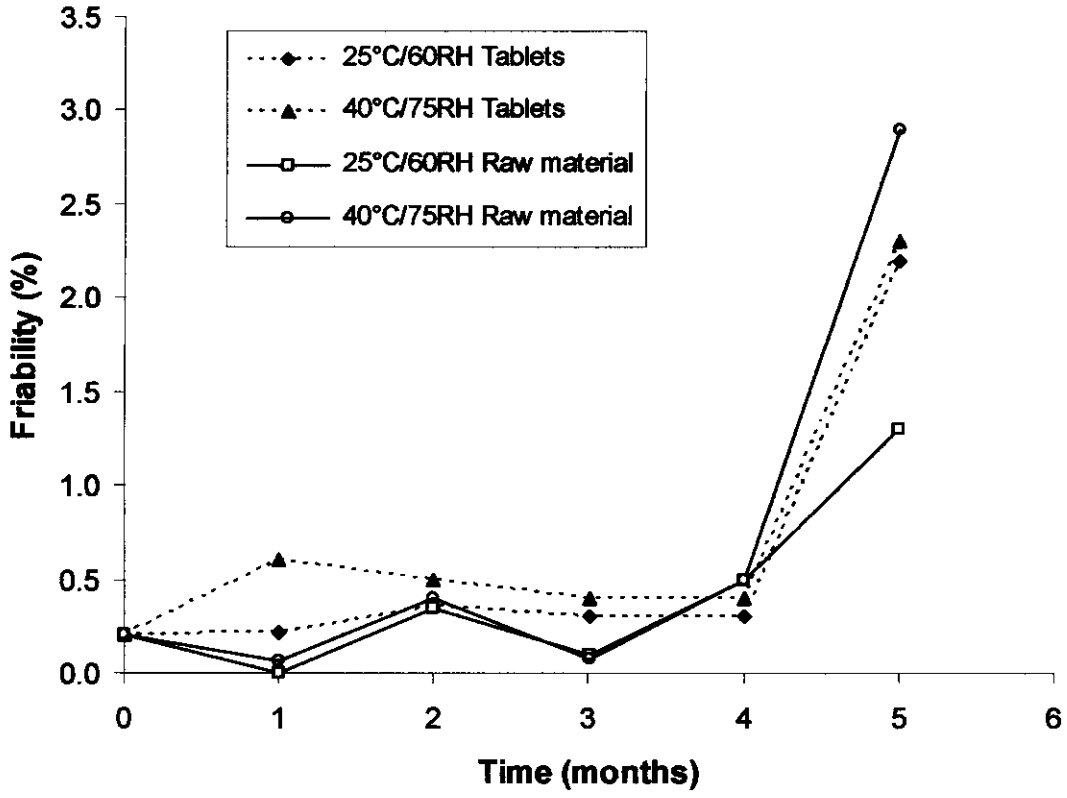


Figure 6.7: *Friability of chitosan tablets as time-dependent parameter.*

Tablets produced from raw material samples prior to analyses follow the same trend regarding fluctuation in the magnitude of friability (Figure 6.7). An upwards shift is seen at the 5th month, with the 40 °C / 75% RH product demonstrating a value double that of 25 °C / 60% RH product. The tablet samples follow a similar trend to those produced from stored raw material. The final values are in close proximity and no condition is significantly favoured. It could be suggested that stored tablets posed a slight advantage with regards to variation in tablet quality as time-dependent function. However, a general conclusion could be made if the maximum limit of friability was set at 1% w/w. Regardless of the material state unacceptable tablets were produced or sampled after 4 months. This would suggest that the direct compression method offers a limited shelf-life of the product regarding friability. Furthermore, a complex, time-dependent detrimental interaction of moisture loss and mechanical strength could be observed.

6.3.2 Concluding remarks

The stability of chitosan raw material seemed to be affected by stress conditions (elevated temperatures and relative humidities). It seemed clear that the stability of chitosan raw material deteriorated to a greater extent than the chitosan tablets that were also subjected to the stress conditions. The dehydration of chitosan raw material influenced the bonding mechanisms of the particles during compression. Furthermore, the decrease of crushing strength and increase of friability occurred due to the dehydration of the polymer.

6.3.3 Long- term stability of chitosan granules

The stability of chitosan raw material was assessed in the previous section. It is, however, imperative that the stability of chitosan granules should be assessed to determine the effect that excipients i.e. Kollidon® and Methocel® would have on the stability of tablets comprising of chitosan. Tablets containing Kollidon® and Methocel® granulate (3% and 5% w/w) were stored at 25 °C / 60% RH and 40 °C / 75% RH. Monthly samples were collected with the subsequent physical analyses of the tablets.

The long-term stability evaluation of tablets containing Kollidon® granulate (3% or 5% w/w) indicated a decrease in crushing strength over a period of 5 months (Figure 6.8). The 3% w/w Kollidon® tablets (25 °C / 60% RH) indicated a significant increase in crushing strength over the first monthly interval, compared to tablets containing 5% w/w Kollidon® granulate and 3% w/w Kollidon® granulate (40 °C / 75% RH). It is evident that the crushing strength of all the tablets containing Kollidon® granulate were detrimentally affected. In these evaluations no clear dependence of crushing strength on percentage binder could be seen as in chapter 3 and 4. A time dependent decay was observed regardless of the percentage binder.

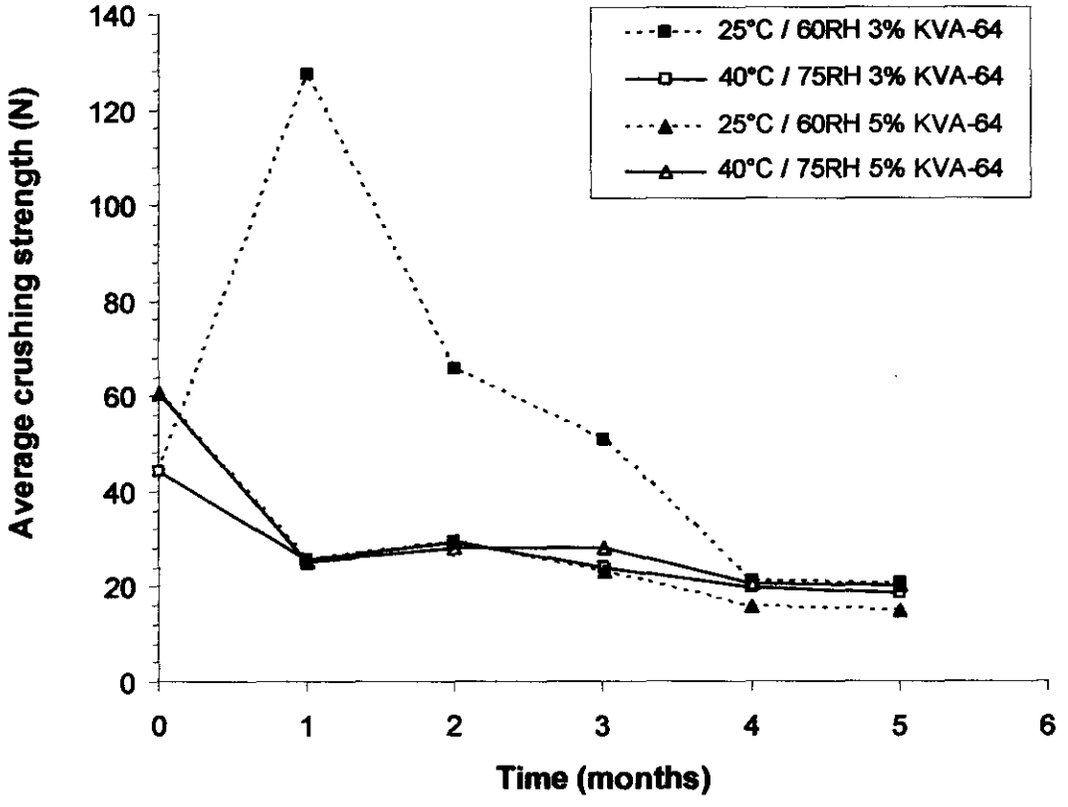


Figure 6.8: *Crushing strength of tablets containing Kollidon® granulate (3% and 5% w/w) stored at two sets of stress conditions.*

Tablets containing Methocel® granulate (3% or 5% w/w) revealed a significant decrease in crushing strength over a period of 4 months. The tablets deteriorated to such an extent that additional analysis was precluded (Figure 6.9). All tablets containing Methocel® granulate, for both condition sets, became brittle and crumbled on handling. The tablets containing 3% w/w Methocel® granulate (stored at both conditions) revealed an initial increase in crushing strength. The performance of Methocel® was proven inferior to Kollidon® and it could be ascribed to its hygroscopic properties. Moisture sorption of Methocel® most probably alleviated bonding interaction, resulting in low strength tablets. This phenomenon illustrated that crushing strength was not the sole determinant of mechanical strength. In comparison the tablets containing 5% w/w Methocel® granulate revealed a distinct decrease in crushing strength from month 0 - 4. Both formulations (3% and 5% w/w Methocel® granulate) stored at 40 °C / 75% RH revealed a decrease in crushing strength up to a period of 3 months (Figure 6.9). On the fourth monthly interval the tablets were too brittle to analyse. Therefore, it could be concluded that the tablets

containing Methocel® granulate was detrimentally affected and to a greater extent by elevated temperatures and relative humidities.

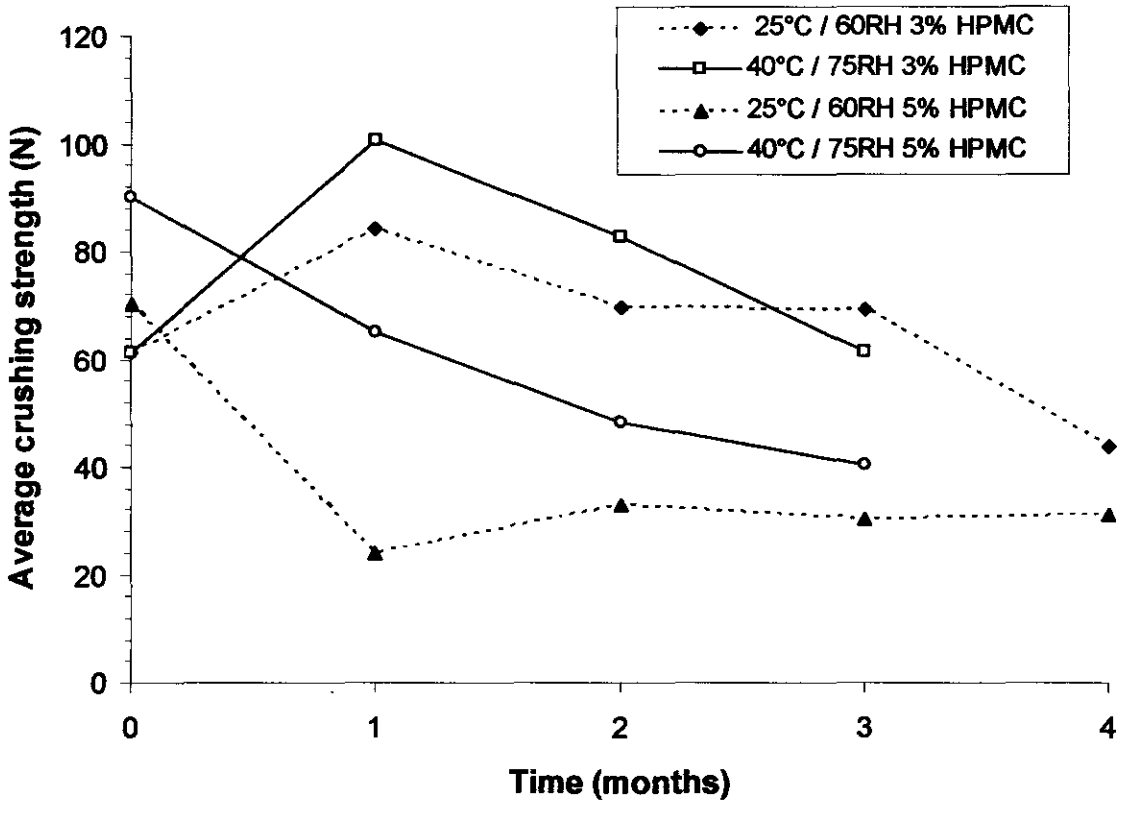


Figure 6.9: *Crushing strength of tablets containing Methocel® (HPMC) granulate (3% and 5% w/w) stored at two sets of stress conditions.*

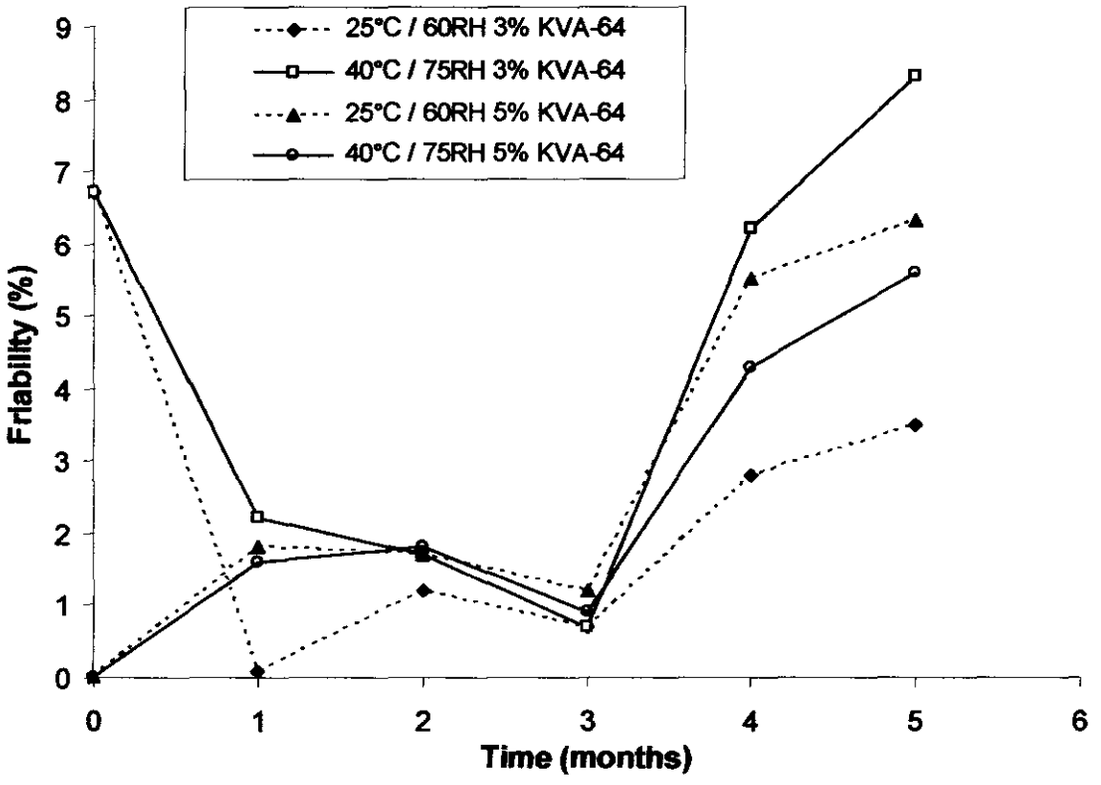


Figure 6.10: *Friability of tablets containing Kollidon ® granulate (3% and 5% w/w) stored at two sets of stress conditions.*

The relation that exists between the crushing strength of tablets and friability is clear from Figure 6.8 and 6.10. The tablets containing 3% Kollidon® granulate (both conditions) revealed a decrease in friability (first monthly interval). This decrease in friability could be attributed to the increase in crushing strength that occurred in the same interval (Figure 6.8). Furthermore, all tablets showed a significant increase in friability. The formulation containing 3% Kollidon granulate (40 °C / 75% RH) exhibited the highest friability, therefore, concluding that the conditions was far too extreme to maintain effective bonding of the tablets.

All the formulations containing 3% Methocel® granulate (both conditions) showed a significant increase in friability (Figure 6.11). Furthermore, the tablets containing 5% w/w Methocel® granulate deteriorated to such an extent that friability analyses of the 4 months interval was impossible.

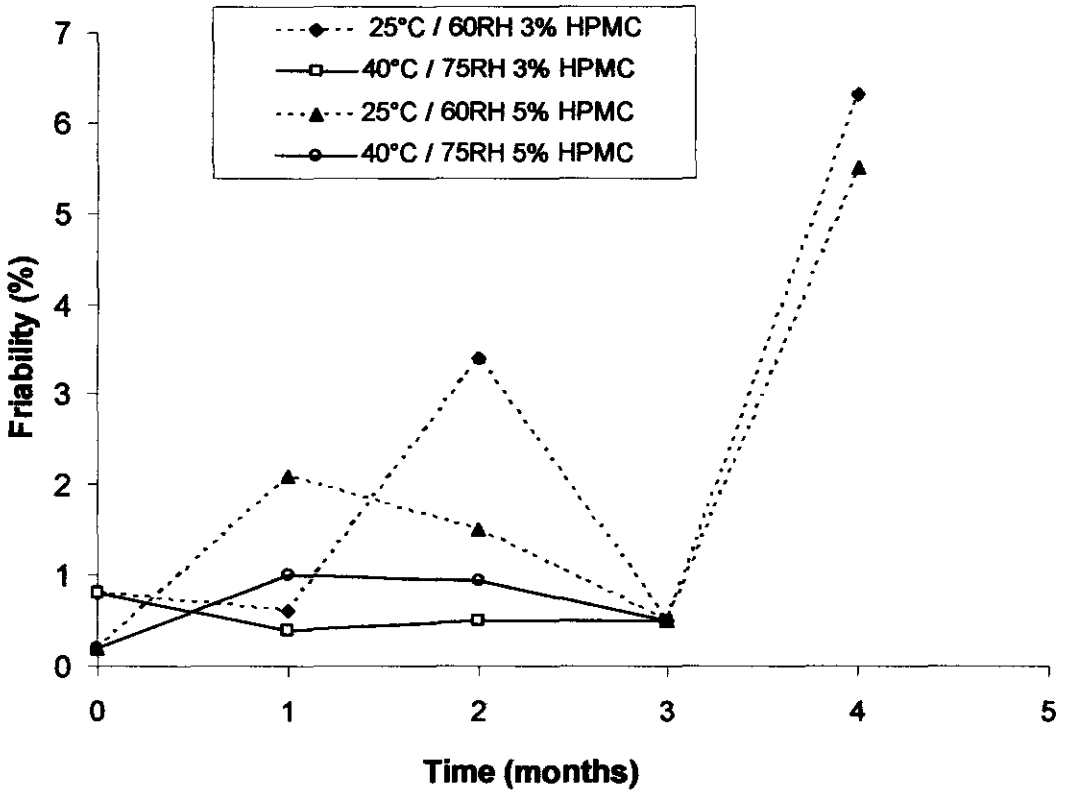


Figure 6.11: *Friability of tablets containing Methocel ® granulate (3% and 5% w/w) stored at two sets of stress conditions.*

The analyses of tablets containing granulate in terms of crushing strength and friability revealed that subjection to stress conditions resulted in deterioration of these physical properties (Figure 6.11). Both types of granulate indicated a significant decrease of crushing strength and increase of friability. It was also clear that 40 °C / 75% RH resulted in the highest degree of deterioration. Furthermore, it was clear that Methocel® was more sensitive to the stress conditions than Kollidon®. This was deduced from the observation that after a period of 3 months the deterioration of the Methocel® tablets were so severe that handling caused it to crumble, making physical analyses impossible.

6.4 Conclusion

Chitosan raw material exhibited sensitivity towards elevated temperatures and loss of moisture content. Lower moisture content detrimentally affected the compressibility

of chitosan raw material. Therefore, indicating that a balance exist between moisture content and tabletability.

Furthermore, chitosan tablets and raw material indicated sensitivity towards stress conditions. It could be concluded that 40 °C / 75% RH had detrimental effects on chitosan tablets and the raw material. Additionally, it was evident that the presence of excipients influenced the stability of chitosan tablets. In comparison with the tablets comprising of Avicel® PH200 and Kollidon®, the tablets containing Methocel® revealed the most deterioration in terms of crushing strength and friability. The compression of raw material with Avicel® PH200 revealed the best results. Therefore, it could be concluded that direct compression produced the optimal system in terms of product stability. From chapters 3 and 4 it were obvious that the addition of binders allow the exclusion of Avicel® PH200 from chitosan formulations, however, the formulations consisting of binders (granulate) revealed poor stability. Therefore, future studies on the long-term stability of the directly compressible and wet granulated systems discussed might provide decisive answer on the manufacturing process as well as stability of chitosan tablets.

CHAPTER 7

CONCLUSION

The natural abundance, low toxicity, biocompatibility and relative low cost associated with chitosan could result in the successful application of this polymer in the pharmaceutical industry. Although chitosan is present in various pharmaceutical preparations, little if any is known about its tabletability as well as its function in tablets formulations.

Chitosan possessed poor flow properties, resulting in variable filling of the die cavity and pronounced tablet weight variation. It was found that certain interventions were necessary in order to improve the tabletability of chitosan raw material. The poor compressibility of the polymer necessitated the inclusion of a directly compressible filler to facilitate successful tableting. A concentration of 30% w/w Avicel® PH200 or Prosolv® SMCC™ 90 proved sufficient to facilitate direct compression of chitosan. An optimal mixing time of 10 minutes was determined in all instances.

The direct compression of combinations of chitosan and single dry binders proved an additional alternative to improve the poor compressibility of chitosan raw material. A concentration of 20% w/w Kollidon® VA-64 produced optimal results in terms of crushing strength and friability. A clear log-linear correlation existed between chitosan and Kollidon® VA-64 in terms of crushing strength. Therefore, a distinct sensitivity of chitosan for Kollidon® VA-64 was exemplified. The chitosan / Kollidon® VA-64 combinations revealed optimal crushing strength and friability results, whilst the chitosan / Methocel® K100M combinations posed advantageous to tablet disintegration. Formulations containing dry binder combinations of different concentration ratios did not potentiate the binding effect of chitosan during compression and a detrimental effect on tablet friability was considered a significant drawback of these combinations. Comparison of all the formulations tableted through direct compression revealed that Kollidon® VA-64 as single dry binder was superior to all the other investigated formulations.

Wet granulation of chitosan was investigated as an additional method to improve the flowability of chitosan raw material. This method improved the flowability as well as the

compressibility of the polymer, however, the inherent characteristics of the raw material still resided in the tabletability despite the granulation. Therefore, the inclusion of extragranular binders was required. The granulation of chitosan produced tablets with a higher percentage (% w/w) chitosan content than with the directly compressible formulations. Therefore, the granulation process improved the tabletability since it was possible to compress larger quantities of chitosan into tablets with the aid of selected binders. From a comparison of the directly compressible formulations to the formulations containing granulate, it was apparent that the crushing strength was higher for the directly compressible formulations. However, the majority of formulations comprised of granulate produced friability percentages less than 1%. This could be ascribed to the inherent stickiness of chitosan. This characteristic evidently influenced the tablet properties and resulted in the production of tablets with low crushing strength but low friability as well. This attribute also indicated that the crushing strength was not the only parameter to quantify the mechanical strength of chitosan tablets.

Furthermore, the wet granulation of chitosan was investigated in two sections i.e. low and high speed granulation. The Methocel® K100M granulate obtained through high speed granulation produced tablets with significantly higher crushing strength and low friability compared to the low speed granulation. This indicated that the homogenous distribution of the binding solution in chitosan had a considerable influence on the granules. In comparison with the Kollidon® granulate, the mixing process did not have a significant effect on the tabletability but rather the concentration of the binder in the formulations. Additional comparison of the two granulate types revealed that Kollidon® VA-64 proved to be a superior binder to Methocel® K100M in terms of chitosan granulation.

Dissolution of selected chitosan formulations indicated that formulation variables and excipients had a considerable effect on drug release. All the formulations resulted in the sustained release of the tracer drug, furosemide. This drug release profiles were attributed to the gel-forming ability of chitosan in acidic pH. The formulations that contained Methocel® either intragranular or extragranular also revealed sustained drug release. This resulted from the ability of Methocel® K100M to form a gel layer on contact with water or biological fluid. Since both chitosan and Methocel® K100M possessed the ability to form a gel layer, matrix like dissolution profiles was expected, however, the dissolution profiles of these formulations did not reveal matrix like

dissolution. Therefore, it was evident that a higher concentration Methocel® K100M was necessary to achieve such dissolution profiles.

Chitosan raw material exhibited sensitivity towards elevated temperatures and loss of moisture content. Lower moisture content had a detrimental effect on the compressibility of the polymer. Chitosan tablets and chitosan raw material also exhibited sensitivity towards stress conditions. It was evident that the presence of excipients influenced the stability of chitosan tablets. In comparison, the tablets comprised of Avicel® PH200 was more resistant to ambient conditions than the tablets comprised of Kollidon® VA-64 or Methocel® K100M granulate. The tablets comprised of Methocel® K100M revealed the most deterioration in terms of crushing strength and friability. Therefore, it was concluded that chitosan raw material or chitosan tablets had to be stored at temperatures beneath 25 °C and relative humidity not exceeding 60%.

The improvement of basic characteristics of chitosan raw material i.e. flowability and compressibility seemed relatively intricate. The study proved that a systemic optimisation of the raw material could render the polymer useful in tablet formulations. The cost-effectiveness of chitosan as well as its biological advantages also could result in the successful application thereof in tablet formulations. From this perspective the optimisation and development of a multipurpose excipient seems an achievable and applicable objective.

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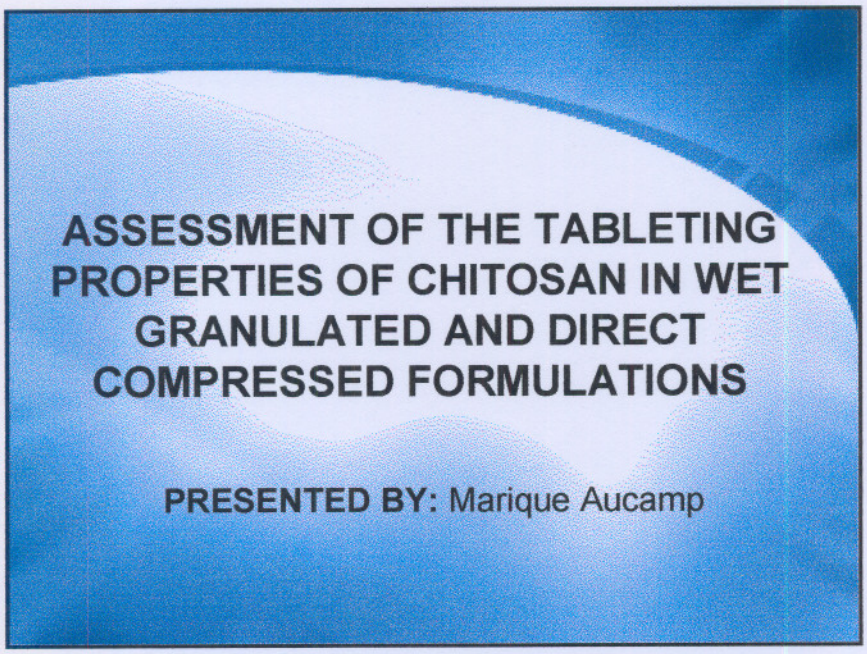
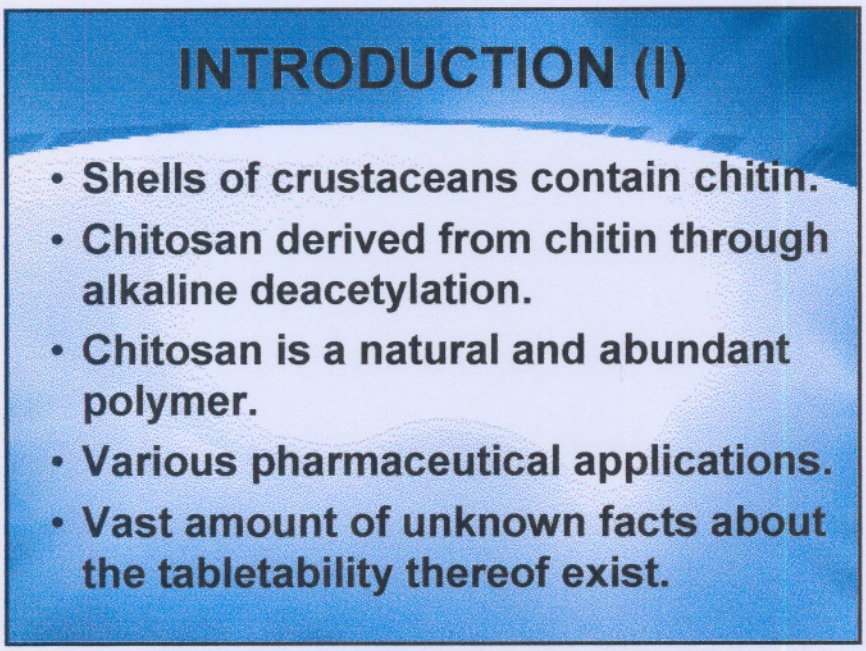


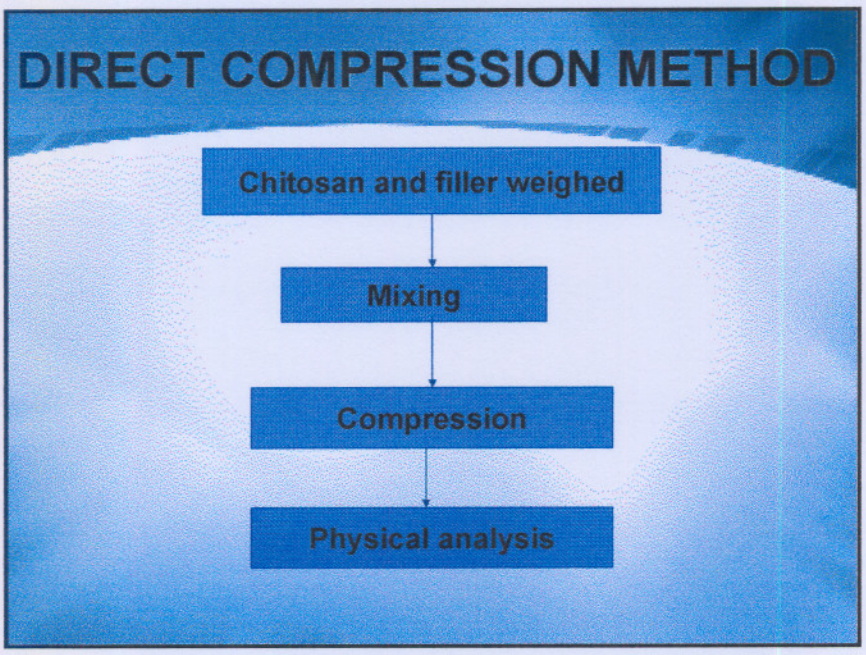


CHARACTERISTICS

- Poor flow
- Poor compressibility
- Irregular particle shape
- Large distribution of particle size
- Negative influence on tabletability
- Processes had to be implemented to improve tabletability

DIRECT COMPRESSION

- Phase II
- Chitosan compressed in combination with Avicel® PH200 and Prosolv® 90.
- Combination of different ratios (Fig. 1).



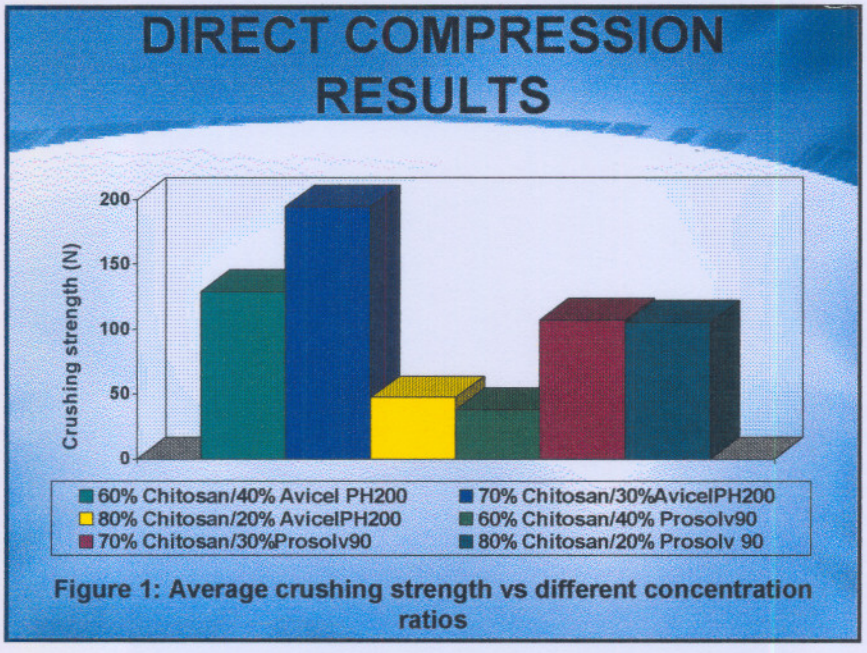
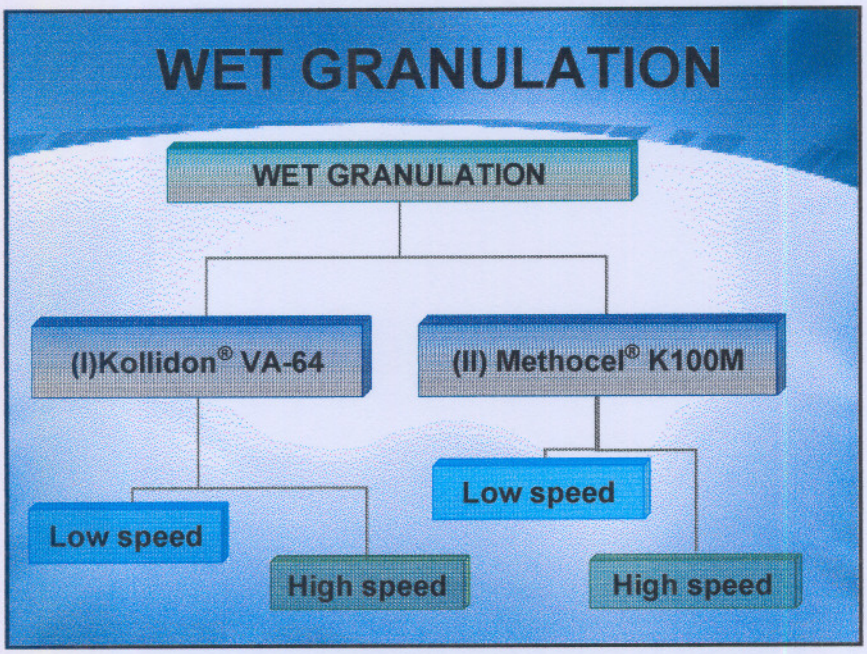
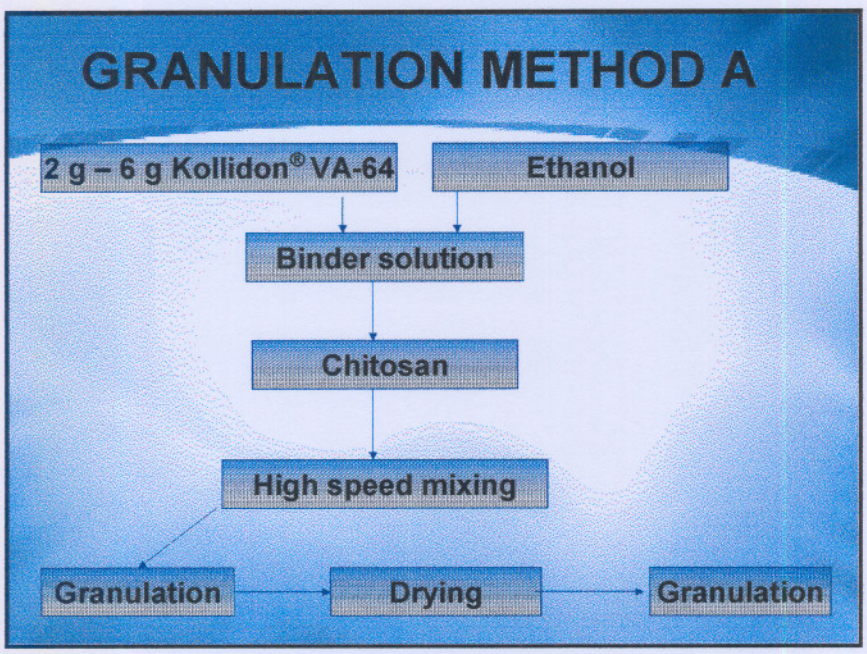
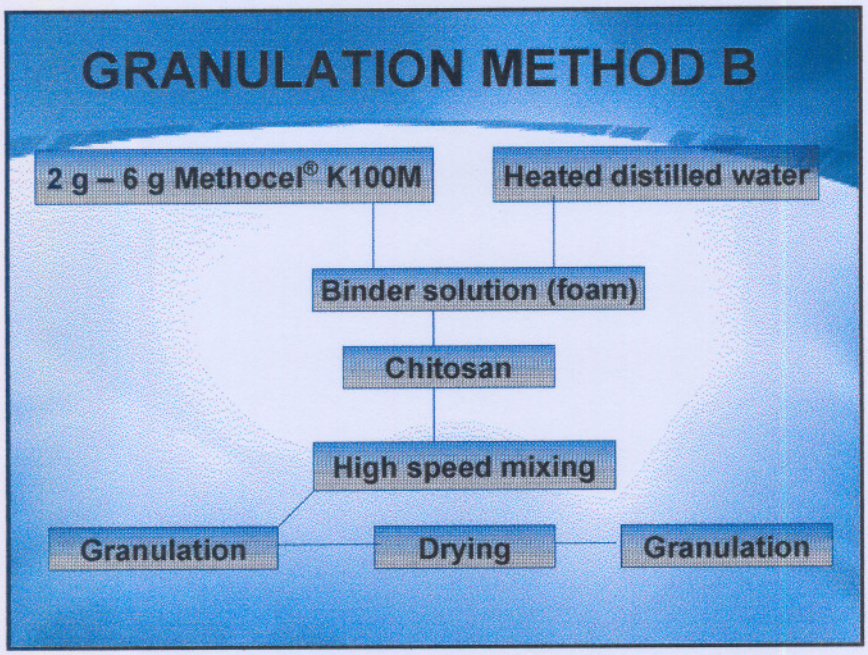


Figure 1: Average crushing strength vs different concentration ratios


WET GRANULATION
WET GRANULATION
(I)Kollidon® VA-64
(II) Methocel® K100M
Low speed
High speed
Low speed
High speed


GRANULATION METHOD A
2 g – 6 g Kollidon® VA-64
Ethanol
Binder solution
Chitosan
High speed mixing
Granulation
Drying
Granulation



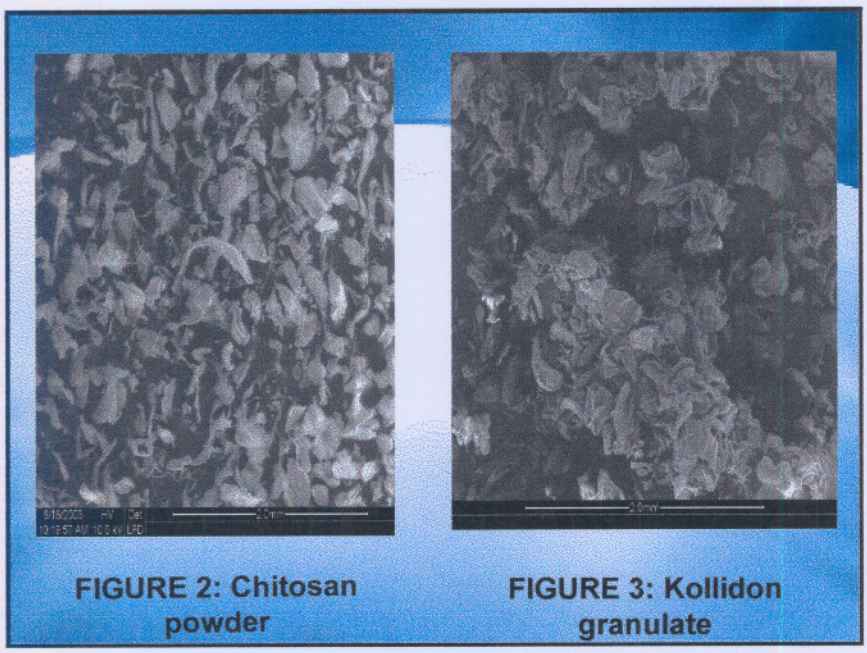


FIGURE 2: Chitosan powder

FIGURE 3: Kollidon granulate

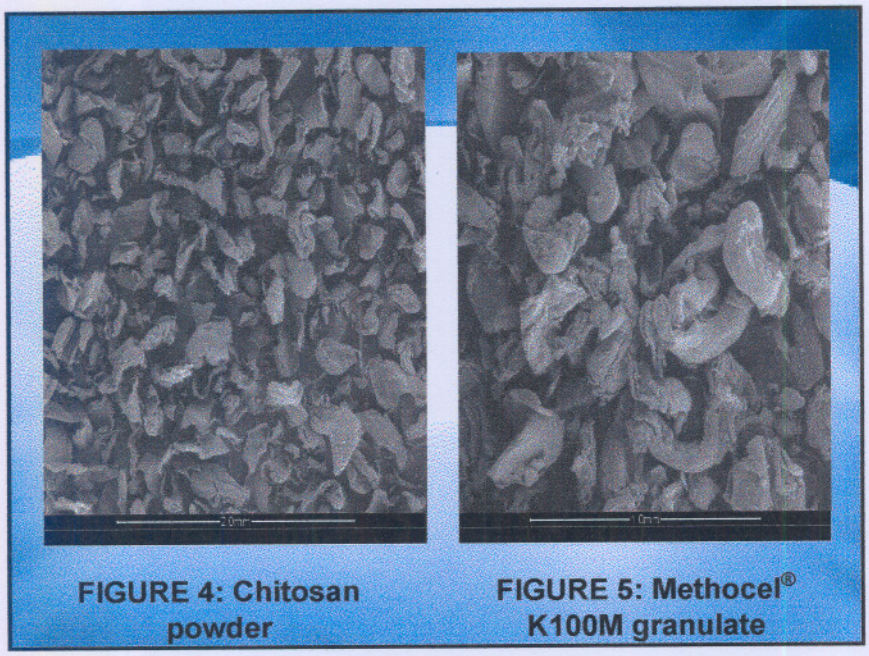
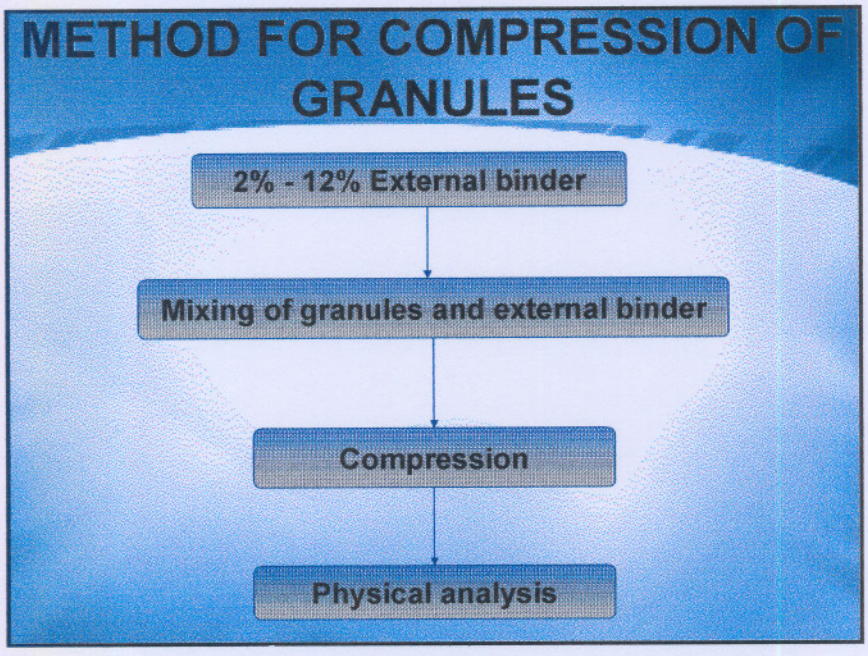


FIGURE 4: Chitosan powder

FIGURE 5: Methocel® K100M granulate



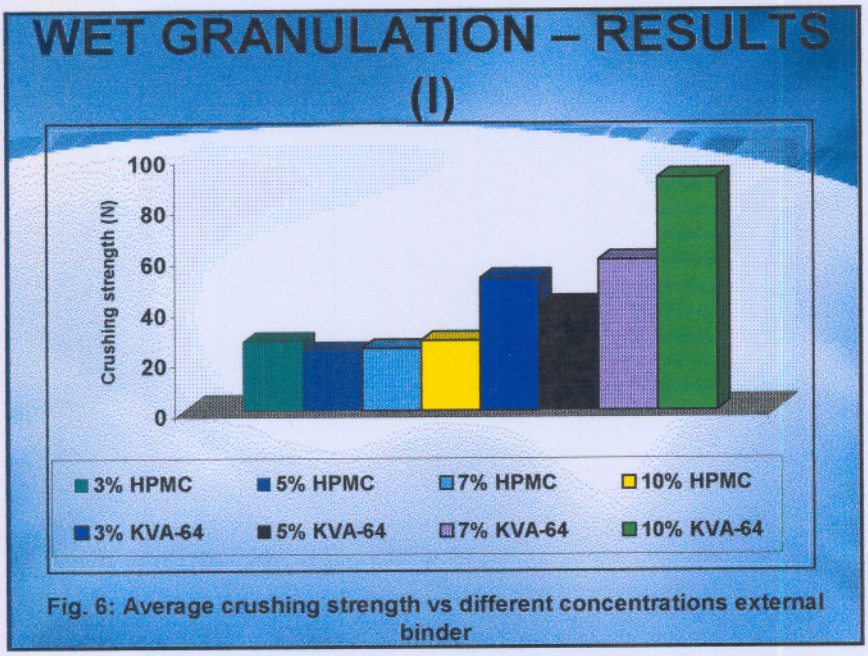


Fig. 6: Average crushing strength vs different concentrations external binder

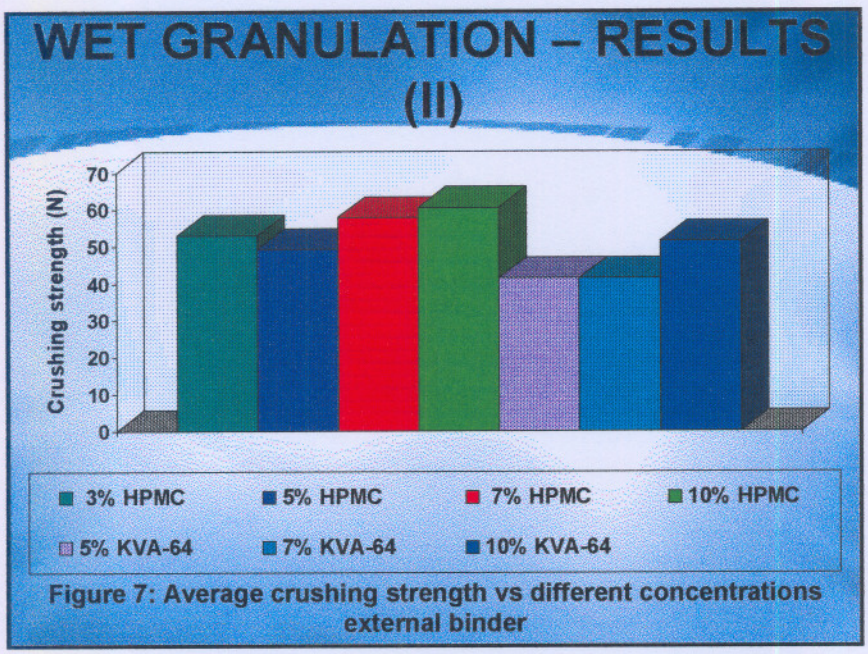


Figure 7: Average crushing strength vs different concentrations external binder

DISSOLUTION STUDIES

- Wet granulation formulations that delivered best results were used.
- Furosemide – tracer drug (20mg).
- Dissolution medium – 0.1 M HCl with pH value of ± 1 (900cm^3).
- Temperature – 37 ± 0.5 ˚C.
- Baskets to facilitate tablet sinking.
- Dissolution apparatus protected from light to avoid photolytic degradation of furosemide.

DISSOLUTION

- Sampling took place at t = 1, 3, 5, 10, 15, 30, 40, 60, 120, 240, 360, 720, 1440 minutes.
- 5 cm^3 - 0.3 µm prefilter.
- Spectrophotometrically analysed at 277nm.

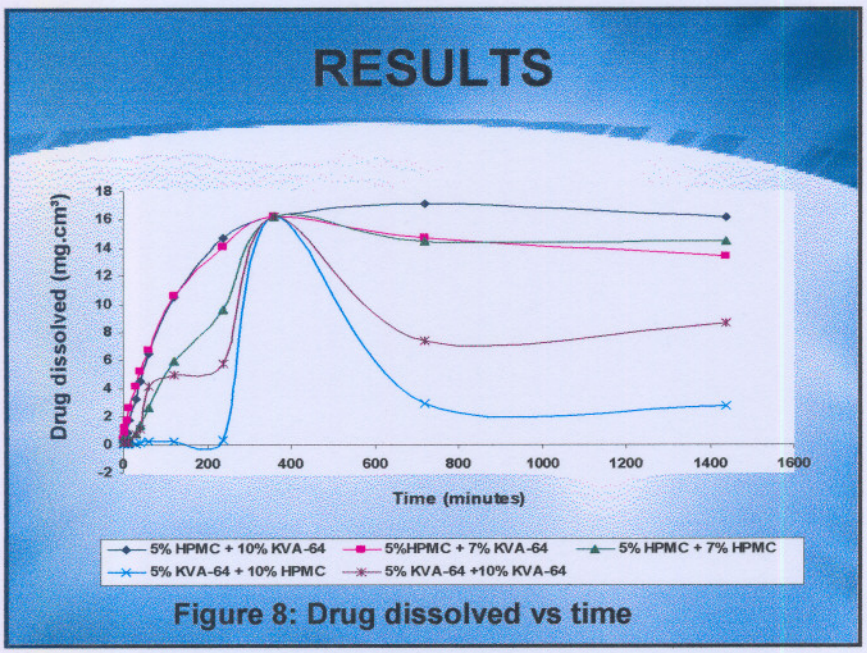


Figure 8: Drug dissolved vs time

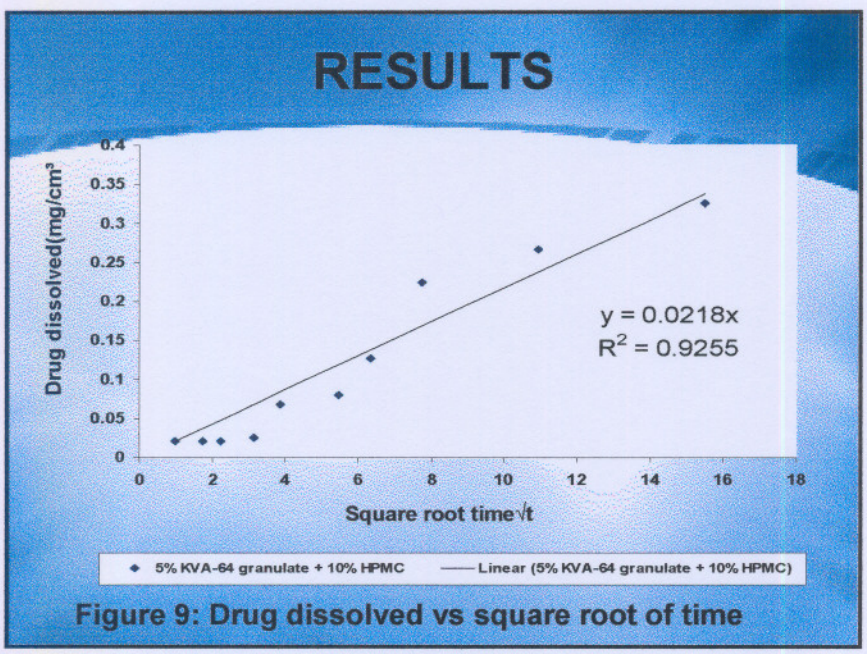


Figure 9: Drug dissolved vs square root of time

DISCUSSION AND CONCLUSION

- Filler required for direct compression.
- Granulation – improve poor flowability and compressibility.
- External binder
- Sustained drug release (matrices).

ACKNOWLEDGEMENTS

- Dr. A.F. Marais – Department Pharmaceutics (North West University).
- Prof. W. Liebenberg – Institute for Industrial Pharmacy (North West University).
- Dr. L. Tiedt - Electronmicroscopy (North West University).

ANNEXURES

ANNEXURE A: THE CHARACTERISATION OF CHITOSAN POWDER

Table A.1.1: *The flow properties.*

	Mass (g)	Diameter (cm)	Height (cm)	Angle of repose (°)
	99.33	15.5	6.1	36.2
	100.07	15.5	5.7	36.3
	100.24	15.7	6.8	41.2
Average	**99.88**	**15.6**	**6.2**	**37.9**
STDEV	**0.4838388**	**0.12**	**0.56**	**2.86**
% RSD	**0.4844201**	**0.742**	**8.98**	**7.54**

Table A.1.2: *Densities of chitosan powder.*

Repitition	Mass (g)	Vp (cm^3)	Vt (cm^3)	ρ_b ($g.cm^{-3}$)	ρ_t ($g.cm^{-3}$)
1	100	527	370	0.190	0.270
2	100	510	369	0.196	0.271
3	100	520	370	0.192	0.270
Average	**100**	**519**	**369.7**	**0.193 (1.6)**	**0.271 (0.2)**

Where V_p = Poured volume, V_t = Tapped volume, ρ_b = bulk density and ρ_t = tapped density.

Table A.1.3: Compressibility of chitosan powder

Repitition	Porosity	Carr's Index	Hausner ratio
1	0.3	29.8	1.4
2	0.3	27.6	1.4
3	0.3	28.8	1.4
Average	**0.3 (3.7)**	**28.8 (3.7)**	**1.4 (1.5)**

Particle size analysis

MALVERN INSTRUMENTS **MASTERSIZER X**

Version 1.2a

Tue, Sep 16, 2003 9:29AM

Chitosan :Run Number 1

Batch nr.: 021010 Drum: 115
Dispersant: 15 ml Ethanol in MSX1

Sample 1
Sample File Name: JOE_01 , Record: 1
Measured on: Fri, Jan 04, 1980 6:51PM Last saved on: Fri, Jan 04, 1980 6:51PM

Source: Analysed

Presentation: 2THD
Very Polydisperse model

Volume Result

Focus = 300 mm.

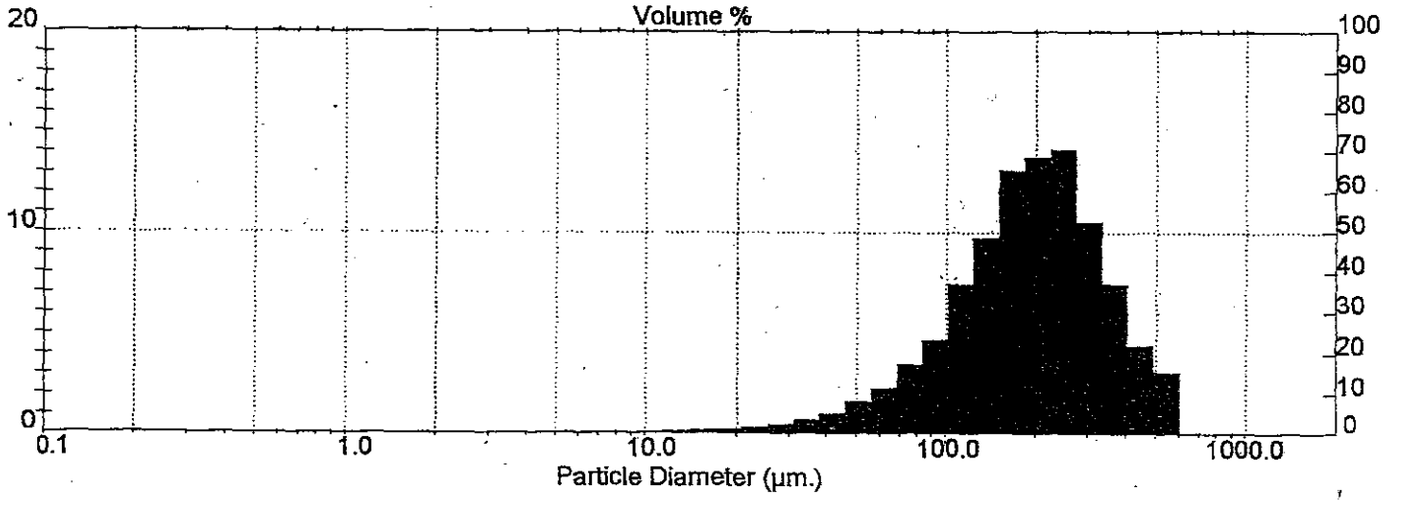
Residual = 2.162 %
d (0.5) = 193.31 µm
D [4, 3] = 212.56 µm
Sauter Mean (D[3,2]) = 124.48 µm
Specific Surface Area = 0.0482 sq. m. / gm

Concentration = 0.075 %
d (0.1) = 77.21 µm
Span = 1.54

Obscuration = 23.18 %
d (0.9) = 375.78 µm

Mode = 208.64 µm
Density = 1.00 gm. / c.c.

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.50	0.00	1.32	0.00
1.32	0.00	1.60	0.00
1.60	0.00	1.95	0.00
1.95	0.00	2.38	0.01
2.38	0.01	2.90	0.02
2.90	0.02	3.53	0.04
3.53	0.04	4.30	0.08
4.30	0.07	5.24	0.15
5.24	0.09	6.39	0.24
6.39	0.11	7.78	0.36
7.78	0.12	9.48	0.48
9.48	0.14	11.55	0.61
11.55	0.17	14.08	0.78
14.08	0.21	17.15	0.99
17.15	0.27	20.90	1.26
20.90	0.36	25.46	1.62
25.46	0.53	31.01	2.14
31.01	0.74	37.79	2.88
37.79	1.13	46.03	4.01
46.03	1.61	56.09	5.62
56.09	2.34	68.33	7.96
68.33	3.47	83.26	11.43
83.26	4.73	101.44	16.17
101.44	7.41	123.59	23.57
123.59	9.92	150.57	33.49
150.57	12.77	183.44	46.26
183.44	14.24	223.51	60.50
223.51	13.74	272.31	74.23
272.31	10.68	331.77	84.91
331.77	7.46	404.21	92.37
404.21	4.49	492.47	96.86
492.47	3.14	600.00	100.00



MALVERN INSTRUMENTS **MASTERSIZER X**

Version 1.2a

Tue, Sep 16, 2003 9:29AM

Chitosan :Run Number 3

Batch nr.: 021010 Drum: 115
Dispersant: 15 ml Ethanol in MSX1

Sample 2
Sample File Name: JOE_01 , Record: 3 Source: Analysed
Measured on: Fri, Jan 04, 1980 6:56PM Last saved on: Fri, Jan 04, 1980 6:57PM

Presentation: 2THD
Very Polydisperse model

Volume Result

Focus = 300 mm.

Residual = 0.818 %
d (0.5) = 193.99 µm
D [4, 3] = 208.86 µm
Sauter Mean (D[3,2]) = 123.69 µm
Specific Surface Area = 0.0485 sq. m. / gm

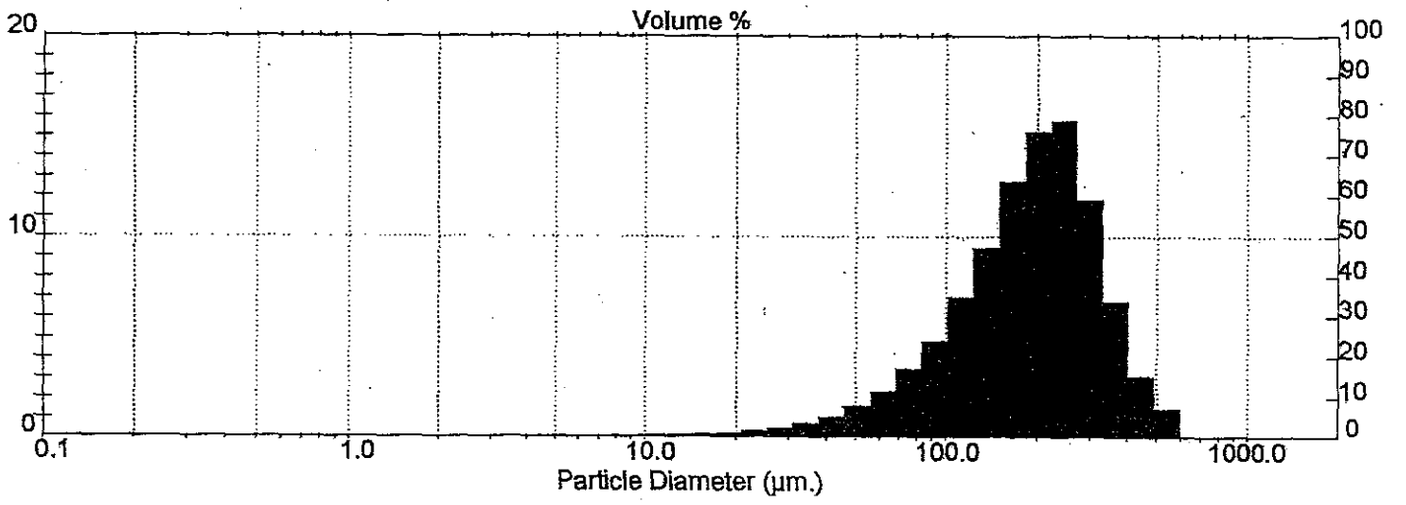
Concentration = 0.062 %
d (0.1) = 77.22 µm
Span = 1.46

Obscuration = 19.72 %
d (0.9) = 359.54 µm

Mode = 229.54 µm
Density = 1.00 gm. / c.c.

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.50	0.00	1.32	0.00
1.32	0.00	1.60	0.00
1.60	0.00	1.95	0.00
1.95	0.00	2.38	0.01
2.38	0.01	2.90	0.02
2.90	0.02	3.53	0.04
3.53	0.05	4.30	0.09
4.30	0.08	5.24	0.17
5.24	0.09	6.39	0.26
6.39	0.10	7.78	0.36
7.78	0.12	9.48	0.48
9.48	0.14	11.55	0.61
11.55	0.17	14.08	0.78
14.08	0.21	17.15	0.99
17.15	0.27	20.90	1.26
20.90	0.37	25.46	1.63

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
25.46	0.52	31.01	2.15
31.01	0.74	37.79	2.89
37.79	1.11	46.03	4.00
46.03	1.61	56.09	5.61
56.09	2.36	68.33	7.97
68.33	3.47	83.26	11.45
83.26	4.80	101.44	16.25
101.44	7.22	123.59	23.47
123.59	9.72	150.57	33.19
150.57	12.74	183.44	45.93
183.44	14.76	223.51	60.70
223.51	14.85	272.31	75.54
272.31	11.08	331.77	86.63
331.77	7.23	404.21	93.86
404.21	3.83	492.47	97.69
492.47	2.31	600.00	100.00



Malvern Instruments Ltd.
Malvern, U.K.

MasterSizer X Ver. 1.2a
Serial No.

16 Sep 03 0

ANNEXURE B: WET GRANULATION OF CHITOSAN

Key to abbreviations:

WV = Average weightvariation (mg)

CS = Average crushing strength (N)

T = Average tablet thickness (mm)

D = Average tablet diameter (mm)

F = Percentage friability (%)

DisT = Average disintegration time (sec)

Table B.1.1: *Results obtained from the physical analyses of tablets containing 3% Kollidon® VA-64 – granulate (low speed granulation).*

Concentration external binder (%w/w)	WV	CS	T	D	F	DisT
3	206.69 (1.09)	34.69 (4.69)	2.85 (0.95)	9.01 (0.04)	0.31	3.81 (0.005)
5	208.58 (0.63)	34.16 (6.76)	2.95 (0.66)	9.02 (0.07)	0.61	1.43 (0.003)
7	209.96 (0.79)	37.62 (7.48)	2.97 (0.95)	9.00 (0.10)	0.61	3.32 (0.004)
10	205.05 (4.33)	36.09 (19.76)	3.01 (0.73)	9.01 (0.16)	0.42	*N/D

*No disintegration

Table B.1.2: *Results obtained from the physical analyses of tablets containing 5% Kollidon® VA-64 – granulate (low speed granulation).*

Concentration external binder (%w/w)	WV	CS	T	D	F	DisT
3	205.4 (1.2)	34.8 (6.8)	2.9 (0.7)	9.0 (0.1)	0.39	1.3 (0.00)
5	208.4 (0.9)	41.4 (5.3)	2.9 (0.4)	9.0 (0.1)	0.34	5.5 (0.00)
7	203.5 (1.0)	40.9 (5.7)	2.9 (0.7)	9.0 (0.1)	0.09	6.6 (0.00)
10	207.7 (1.0)	51.5 (3.7)	2.9 (0.5)	9.0 (0.1)	0.34	*N/D

*No disintegration

Table B.1.3: *Results obtained from the physical analyses of tablets containing 3% Methocel® K100M – granulate (low speed granulation).*

Concentration external binder (%w/w)	WV	CS	T	D	F	DisT
3	183.6 (4.5)	10.4 (19.6)	3.3 (1.2)	9.0 (0.1)	2.01	*N/D
5	183.6 (4.5)	22.9 (17.3)	2.9 (0.8)	9.0 (0.1)	0.67	0.5 (0.00)
7	203.8 (6.3)	31.5 (30.8)	2.9 (0.9)	9.0 (0.2)	0.77	1.1 (0.00)
10	190.0 (5.4)	37.8 (26.7)	5.9 (0.5)	9.5 (0.1)	0.1	6.2 (0.01)

Table B.1.4: *Results obtained from the physical analyses of tablets containing 5% Methocel® K100M – granulate (low speed granulation).*

Concentration external binder (%w/w)	WV	CS	T	D	F	DisT
3	175.4 (2.0)	12.8 (10.0)	2.9 (0.9)	9.0 (0.1)	1.5	0.5 (12.3)
5	165.2 (2.6)	9.1 (16.9)	2.9 (1.6)	9.0 (0.1)	1.9	0.9 (0.0)
7	168.2 (2.0)	6.9 (11.3)	3.3 (0.5)	9.1 (0.2)	4.7	1.1 (0.0)
10	176.7 (3.3)	8.9 (32.9)	3.2 (1.5)	9.1 (0.2)	2.8	4.5 (0.0)

Table B.2.1: *Results obtained from the physical analyses of tablets containing 3% Kollidon® VA-64 granulate (high speed granulation) and varying concentrations of Kollidon® VA-64 external binder.*

Concentration external binder (%w/w)	WV	CS	T	D	F	DisT
3	208.0 (1.1)	35.6 (6.9)	2.9 (1.4)	9.0 (0.1)	0.3	4.1 (0.0)
5	208.9 (0.7)	35.3 (6.1)	2.9 (0.7)	9.0 (0.1)	0.34	1.9 (0.0)
7	210.6 (0.8)	38.8 (7.6)	2.9 (1.1)	9.0 (0.1)	0.4	3.2 (0.0)
10	207.0 (4.1)	44.0 (2.8)	3.0 (1.3)	9.0 (0.3)	0.4	*N/D

*No disintegration

Table B.2.2: *Results obtained from the physical analyses of tablets containing 3% Kollidon® VA-64 granulate (high speed granulation) and varying concentrations of Methocel® K100M external binder.*

Concentration external binder (%w/w)	WV	CS	T	D	F	DisT
3	208.9 (1.1)	30.2 (13.8)	3.3 (0.6)	9.1 (0.1)	1.0	0.1 (0.001)
5	202.8 (0.7)	22.9 (6.5)	3.3 (1.0)	9.1 (0.1)	1.6	0.1 (0.003)
7	201.7 (0.9)	22.8 (16.8)	3.3 (1.5)	9.1 (0.2)	1.6	0.2 (0.003)
10	194.3 (0.8)	17.5 (13.3)	3.4 (1.0)	9.1 (0.2)	6.8	0.2 (0.003)

Table B.2.3: *Results obtained from the physical analyses of tablets containing 5% Kollidon® VA-64 granulate (high speed granulation) and varying concentrations of Kollidon® VA-64 external binder.*

Concentration external binder (%w/w)	WV	CS	T	D	F	DisT
3	205.9 (1.2)	36.1 (2.5)	2.9 (0.5)	9.0 (0.1)	0.2	1.2 (0.0)
5	207.6 (0.6)	41.5 (2.5)	2.9 (0.4)	9.0 (0.1)	0.3	4.7 (0.4)
7	204.4 (0.8)	41.8 (3.4)	2.9 (0.6)	9.0 (0.1)	0.2	7.1 (0.1)
10	207.8 (1.0)	52.2 (2.5)	2.9 (0.4)	9.0 (0.3)	0.1	*N/D

*No disintegration

Table B.2.4: *Results obtained from the physical analyses of tablets containing 5% Kollidon® VA-64 granulate (high speed granulation) and varying concentrations of Methocel® K100M external binder.*

Concentration external binder (%w/w)	WV	CS	T	D	F	DisT
3	206.6 (1.6)	57.9 (5.2)	3.1 (0.8)	9.1 (0.2)	0.16	0.3 (0.001)
5	202.2 (0.9)	49.4 (5.4)	3.1 (0.6)	9.0 (0.0)	0.37	0.3 (0.004)
7	207.7 (0.8)	53.0 (7.7)	3.1 (0.7)	9.0 (0.1)	0.20	0.2 (0.003)
10	212.8 (0.6)	60.6 (9.1)	3.1 (0.8)	9.0 (0.1)	0.07	1.1 (0.002)

Table B.2.5: *Results obtained from the physical analyses of tablets containing 3% Methocel® K100M granulate (high speed granulation) and varying concentrations of Kollidon® VA-64 external binder.*

Concentration external binder (%w/w)	WV	CS	T	D	F	DisT
3	163.8 (3.7)	12.6 (22.5)	3.6 (1.2)	9.1 (0.02)	5.0	1.4 (0.0)
5	165.3 (1.6)	14.9 (3.9)	3.5 (1.4)	9.1 (0.2)	3.4	1.4 (0.0)
7	163.5 (2.5)	22.5 (11.5)	3.3 (1.3)	9.1 (0.1)	1.9	1.7 (0.0)
10	165.7 (1.7)	31.2 (7.1)	3.1 (1.1)	9.1 (0.2)	0.8	2.4 (0.0)

Table B.2.6: *Results obtained from the physical analyses of tablets containing 3% Methocel® K100M granulate (high speed granulation) and varying concentrations of Methocel® K100M external binder.*

Concentration external binder (%w/w)	WV	CS	T	D	F	DisT
3	178.0 (2.3)	9.5 (12.1)	3.3 (0.6)	9.1 (0.1)	2.1	0.3 (0.001)
5	183.6 (4.5)	17.3 (22.9)	2.9 (0.8)	9.1 (0.1)	0.7	0.5 (0.001)
7	194.3 (21.8)	40.9 (1.8)	2.9 (0.9)	9.0 (0.2)	0.7	1.1 (0.005)
10	180.0 (1.9)	12.6 (9.9)	3.3 (1.3)	9.1 (0.5)	1.4	1.9 (0.003)

Table B.2.7: *Results obtained from the physical analyses of tablets containing 5% Methocel® K100M granulate (high speed granulation) and varying concentrations of Kollidon® VA-64 external binder.*

Concentration external binder (%w/w)	WV	CS	T	D	F	DisT
3	185.8 (2.3)	54.2 (3.8)	3.0 (1.3)	9.1 (0.1)	0.4	0.9 (0.002)
5	172.7 (1.9)	48.8 (4.2)	3.0 (0.9)	9.1 (0.1)	0.6	1.4 (0.001)
7	178.8 (2.8)	59.7 (3.9)	2.9 (0.6)	9.1 (0.1)	0.1	1.8 (0.001)
10	189.9 (2.0)	90.2 (0.7)	2.9 (0.4)	9.0 (0.1)	0.2	3.5 (0.000)

Table B.2.8: *Results obtained from the physical analyses of tablets containing 5% Methocel® K100M granulate (high speed granulation) and varying concentrations of Methocel® K100M external binder.*

Concentration external binder (%w/w)	WV	CS	T	D	F	DisT
3	213.0 (0.4)	27.5 (7.8)	3.1 (0.5)	9.1 (0.1)	0.4	1.4 (0.0)
5	202.1 (4.1)	27.1 (3.9)	3.1 (0.6)	9.1 (0.1)	0.5	1.9 (0.0)
7	203.8 (2.4)	28.1 (3.1)	3.1 (0.6)	9.1 (0.1)	0.5	2.7 (0.0)
10	204.2 (1.8)	28.3 (6.5)	3.1 (0.5)	9.1 (0.1)	0.1	*N/D

ANNEXURE C: DISSOLUTION STUDIES OF CHITOSAN TABLETS

ANNEXURE C.1: Physical properties of tablets utilised in dissolution studies.

Table C.1.1: *Obtained data from physical analyses of chitosan tablets containing furosemide as tracer drug (%RSD values indicated in parenthesis).*

Granulate type	**Kollidon® VA-64**		**Methocel® K100M**	
External binder	**Kollidon®**	**Methocel®**	**Kollidon®**	**Methocel®**
Average tablet weight (mg)	198.2 (0.5)	200.4 (0.7)	215.0 (0.9)	217.0 (0.5)
Crushing strength (N)	49.2 (14.0)	36.9 (16.2)	63.9 (13.3)	81.0 (12.2)
Thickness (mm)	3.2 (0.6)	3.2 (0.6)	3.2 (0.5)	3.1 (0.7)
Diameter (mm)	9.1 (0.2)	9.1 (0.1)	9.1 (0.1)	9.1 (0.1)
Friability (%)	0.8	1.1	1.0	0.6
Disintegration time (minutes)	2.9 (0.001)	*N/D	0.2 (0.002)	2.6 (0.002)

* No disintegration

Table C.1.2: *Obtained data from physical analyses of chitosan tablets without the inclusion of furosemide (%RSD values indicated in parenthesis).*

Granulate type	Kollidon® VA-64		Methocel® K100M	
External binder	**Kollidon®**	**Methocel®**	**Kollidon®**	**Methocel®**
Average tablet weight (mg)	207.6 (1.0)	212.8 (0.6)	189.9 (2.0)	204.2 (1.8)
Crushing strength (N)	51.5 (3.7)	60.6 (9.1)	90.2 (0.7)	82.3 (6.5)
Thickness (mm)	2.8 (0.5)	3.1 (0.8)	2.9 (0.4)	3.1 (0.5)
Diameter (mm)	9.0 (0.3)	9.0 (0.1)	9.0 (0.1)	9.1 (0.1)
Friability (%)	0.3	0.01	0.2	0.1
Disintegration time (minutes)	*N/D	1.1 (0.002)	3.5 (0.001)	N/D

* No disintegration

ANNEXURE C.2: Dissolution profiles of furosemide and chitosan from suspension.

Table C.2.1: *Dissolution data of furosemide suspension.*

Sample time (minutes)	Drug concentration (µg.cm^{-3})
0	0.0000
1	0.0031
3	0.0065
5	0.0083
15	0.0115
20	0.0128
30	0.0129
40	0.0138
60	0.0140
120	0.0130
240	0.0140
360	0.0140
720	0.0130
1440	0.0140

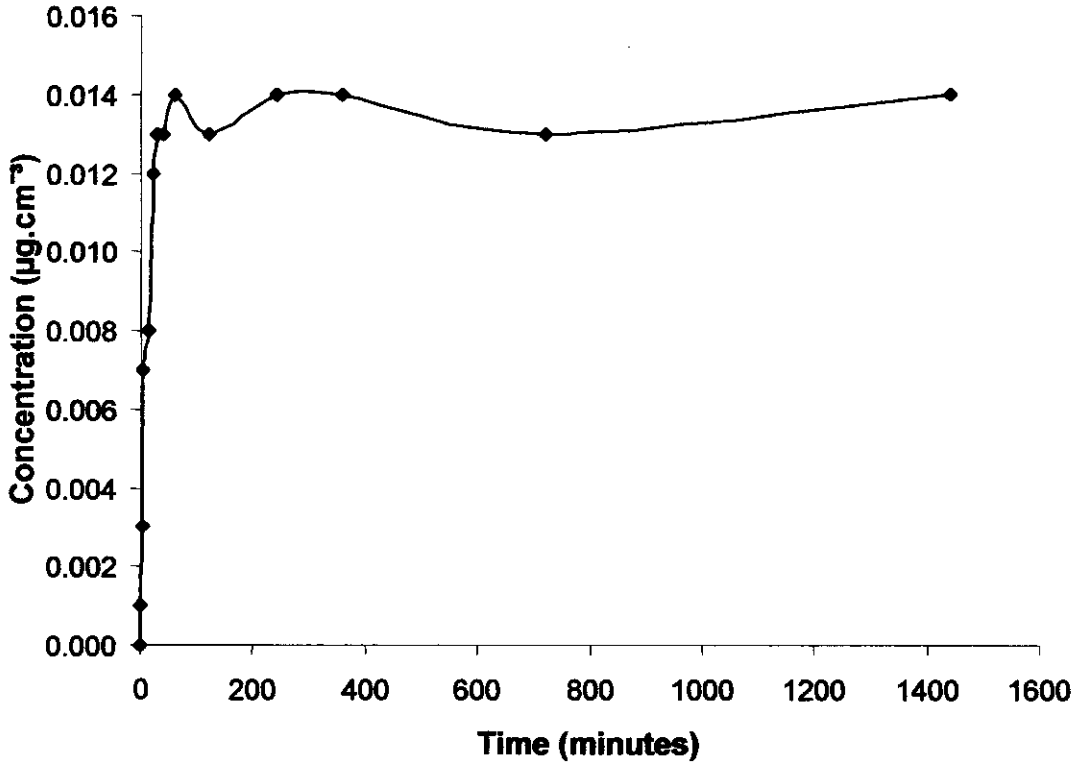


Figure C.2.1: *Dissolution profile of furosemide suspension (Table C.2.1).*

Table C.2.2: *Dissolution data of chitosan suspension.*

Sample time (minutes)	Drug concentration ($\mu g.cm^{-3}$)
0	0.000
1	0.000
3	0.001
5	0.002
15	0.005
20	0.010
30	0.011
40	0.012
60	0.013
120	0.014
240	0.014
360	0.015
720	0.015
1440	0.015

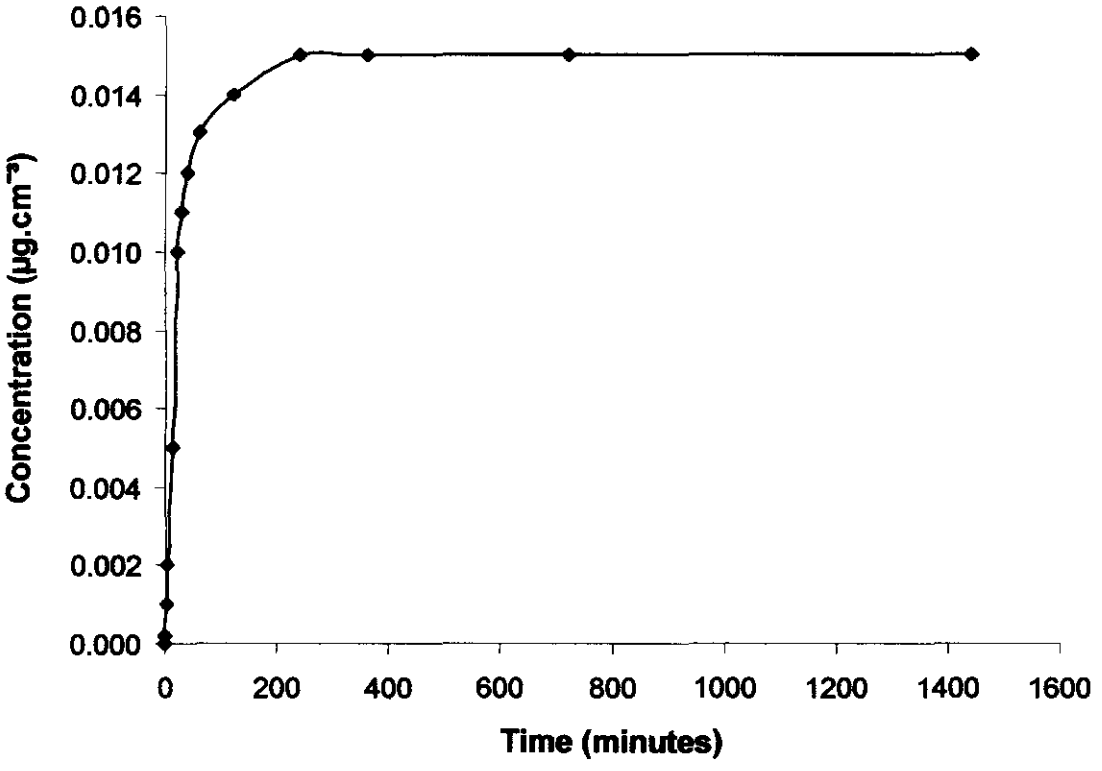


Figure C.2.2: *Dissolution profile of chitosan suspension (Table C.2.2).*

ANNEXURE C.3: Dissolution data of furosemide from chitosan tablets.

Formulation: *Kollidon® VA-64 granulate, Kollidon® VA-64 as external binder (10 % w/w), furosemide.*

Table C.3.1: *Dissolution data of three repetitions.*

Time (min)	*C1	C2	C3	Average	s	% RSD
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.01	0.01	0.02	0.01	0.01	0.45
3	0.01	0.02	0.02	0.01	0.01	0.36
5	0.02	0.02	0.03	0.02	0.01	0.44
10	0.02	0.02	0.03	0.02	0.01	0.44
15	0.02	0.03	0.06	0.04	0.02	0.66
30	0.03	0.08	0.11	0.07	0.04	0.54
40	0.03	0.08	0.13	0.08	0.05	0.60
60	0.08	0.08	0.13	0.09	0.03	0.29
120	0.08	0.11	0.16	0.12	0.04	0.34
240	0.08	0.11	0.19	0.13	0.09	0.45
360	0.11	0.18	0.21	0.17	0.05	0.30
720	0.13	0.21	0.21	0.18	0.05	0.26
1440	0.11	0.21	0.22	0.18	0.06	0.33

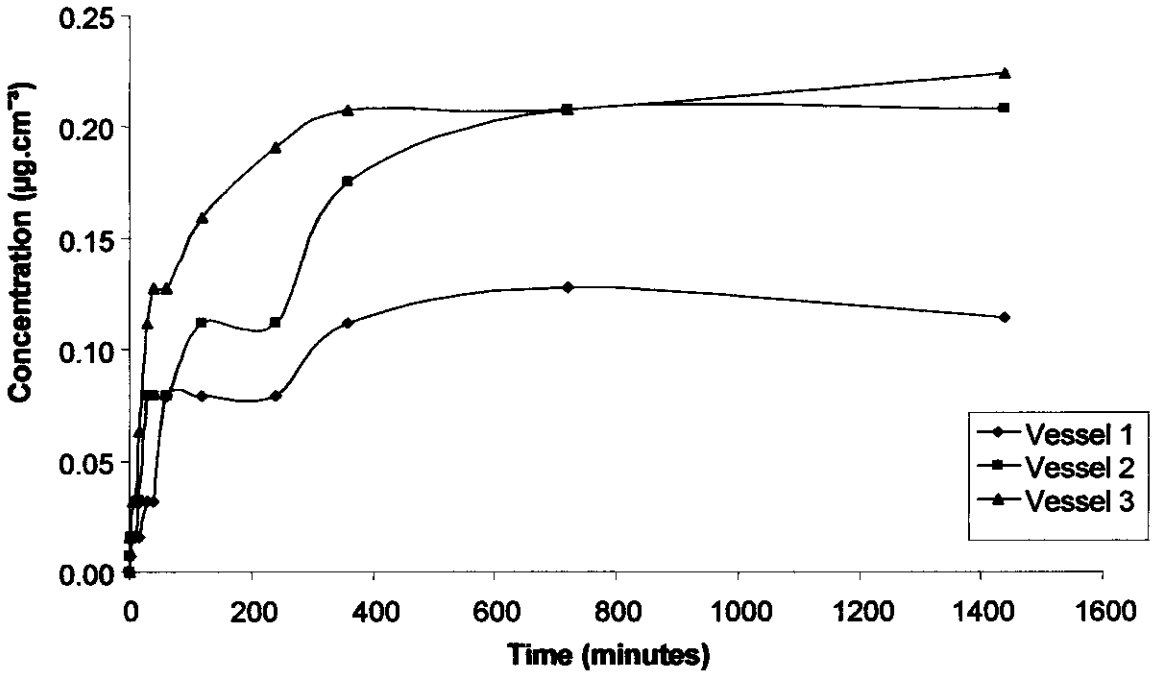


Figure C.3.1: *Dissolution profiles of individual stations (Table C.3.1).*

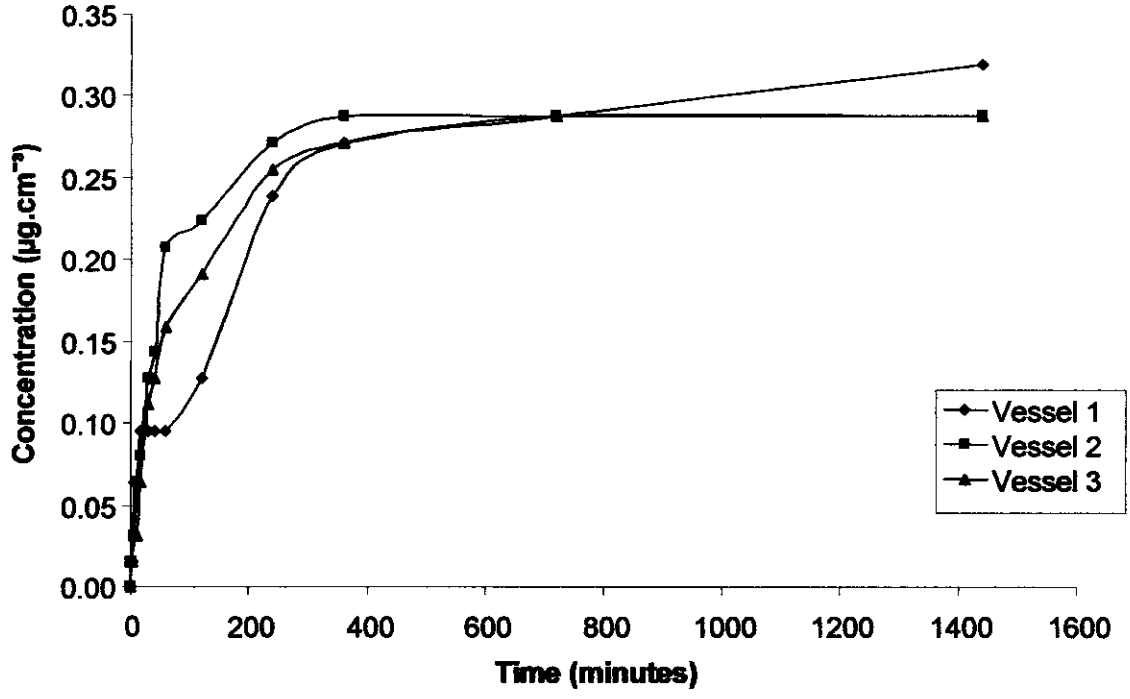


Figure C.3.2: *Dissolution profiles of individual stations (Table C.3.2).*

Formulation: *Kollidon® VA-64 granulate, Methocel® K100M as external binder (10 % w/w), furosemide.*

Table C.3.2: *Dissolution data of three repetitions.*

Time (min)	*C1	C2	C3	Average	s	% RSD
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.02	0.02	0.02	0.02	0.00	0.00
3	0.02	0.02	0.02	0.02	0.00	0.00
5	0.06	0.03	0.03	0.04	0.02	0.44
10	0.06	0.06	0.03	0.05	0.02	0.35
15	0.09	0.08	0.06	0.08	0.02	0.20
30	0.09	0.13	0.11	0.11	0.02	0.14
40	0.09	0.14	0.13	0.12	0.02	0.20
60	0.09	0.21	0.16	0.15	0.06	0.36
120	0.13	0.22	0.19	0.18	0.05	0.27
240	0.24	0.27	0.25	0.26	0.02	0.06
360	0.27	0.29	0.27	0.28	0.01	0.03
720	0.29	0.29	0.28	0.28	0.00	0.00
1440	0.32	0.29	0.28	0.29	0.02	0.06

*Corrected sample concentration ($\mu g.cm^{-3}$)

Formulation: *Kollidon® VA-64 granulate, Kollidon® VA-64 as external binder (10 % w/w).*

Table C.3.3: *Dissolution data of three repetitions.*

Time (min)	*C1	C2	C3	Average	s	% RSD
0	0.00	0.00	0.00	0.00	0.000	0.00
1	0.02	0.03	0.00	0.02	0.02	1.40
3	0.03	0.18	0.00	0.07	0.09	1.00
5	0.03	0.02	0.00	0.02	0.02	1.30
10	0.08	0.02	0.00	0.03	0.04	0.90
15	0.08	0.08	0.00	0.05	0.05	0.90
30	0.13	0.11	0.00	0.08	0.07	0.90
40	0.37	0.32	0.00	0.23	0.19	0.90
60	0.75	0.73	0.01	0.49	0.43	0.90
120	0.93	0.81	0.01	0.58	0.51	0.90
240	2.04	1.82	0.02	1.29	1.12	0.90
360	3.02	2.51	0.03	1.84	1.61	0.90
720	3.70	6.58	0.07	3.43	3.29	1.00
1440	3.80	3.80	0.01	2.53	2.19	0.90

Corrected sample concentration ($\mu g.cm^{-3}$)

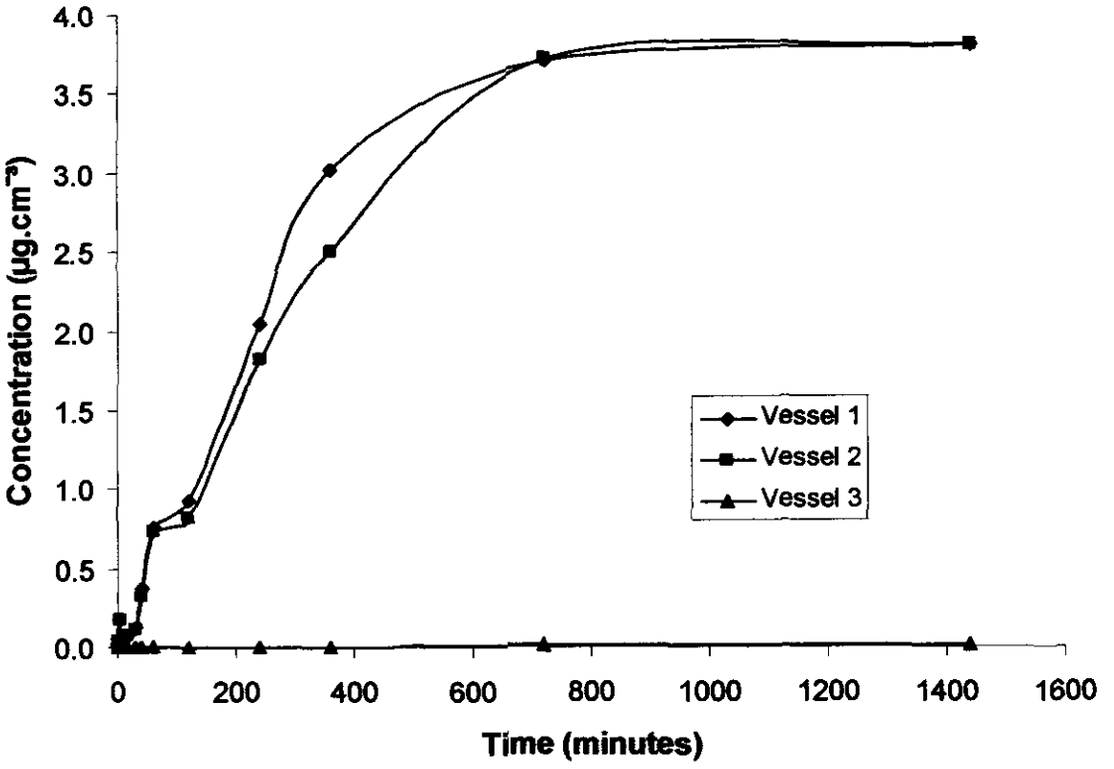


Figure C.3.3: *Dissolution profiles of individual stations (Table C.3.3).*

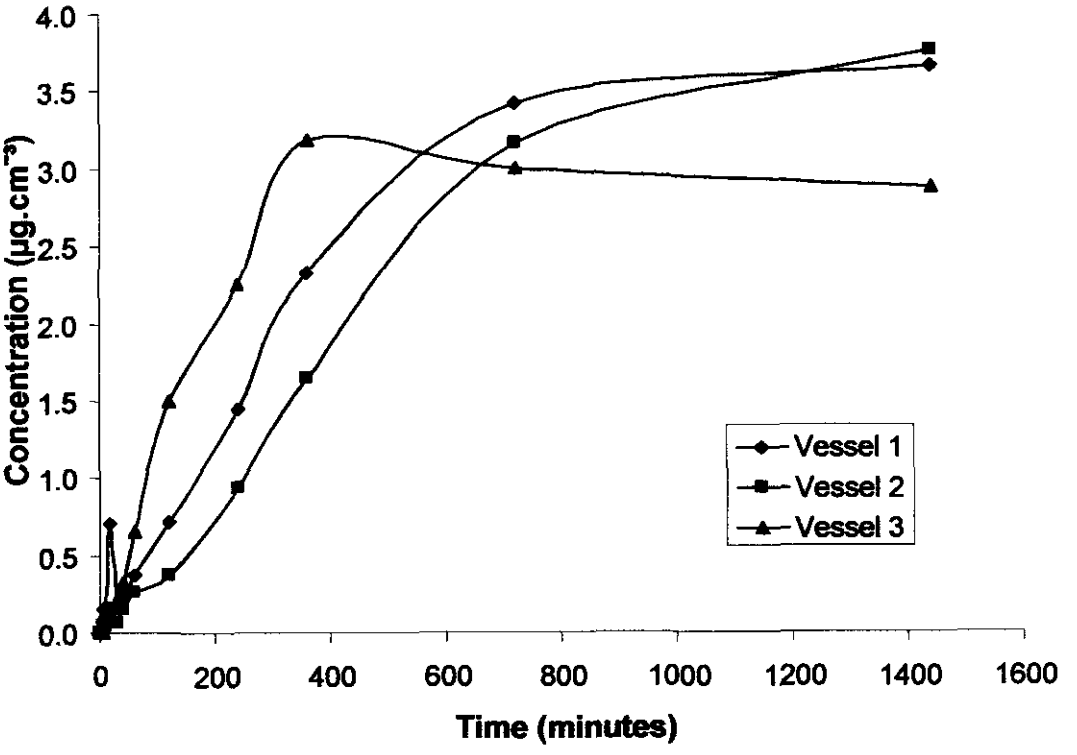


Figure C.3.4: *Dissolution profiles of individual stations (Table C.3.4).*

Formulation: *Kollidon® VA-64 granulate, Methocel® K100M as external binder (10 % w/w).*

Table C.3.4: *Dissolution data of three repetitions.*

Time (min)	*C1	C2	C3	Average	s	% RSD
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00
3	0.00	0.00	0.00	0.00	0.00	0.00
5	0.14	0.06	0.00	0.06	0.07	1.15
10	0.09	0.03	0.11	0.08	0.04	0.53
15	0.70	0.14	0.16	0.34	0.32	0.95
30	0.18	0.06	0.21	0.15	0.08	0.51
40	0.24	0.14	0.32	0.23	0.09	0.38
60	0.36	0.26	0.65	0.43	0.21	0.48
120	0.72	0.36	1.50	0.86	0.58	0.67
240	1.45	0.94	2.25	1.55	0.66	0.43
360	2.33	1.64	3.17	2.38	0.77	0.32
720	3.42	3.16	3.00	3.19	0.21	0.07
1440	3.66	3.75	2.87	3.43	0.48	0.14

Corrected sample concentration ($\mu g.cm^{-3}$)

Formulation: *Methocel® K100M granulate, Kollidon® VA-64 as external binder (10 % w/w), furosemide.*

Table C.3.5: *Dissolution data of three repetitions.*

Time (min)	*C1	C2	C3	Average	s	% RSD
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.24	0.03	0.30	0.19	0.14	0.74
3	0.30	0.22	0.40	0.31	0.09	0.29
5	0.46	0.24	0.54	0.41	0.16	0.38
10	0.96	0.32	1.18	0.82	0.45	0.55
15	1.82	0.56	2.19	1.52	0.85	0.56
30	3.54	0.57	3.99	2.70	1.86	0.69
40	4.84	0.65	5.41	3.64	2.60	0.71
60	6.91	1.68	7.73	5.44	3.28	0.60
120	11.4	1.82	12.1	8.44	5.75	0.68
240	15.0	2.04	15.3	10.8	7.56	0.70
360	16.2	3.03	16.2	11.8	7.59	0.64
720	15.7	3.16	15.7	11.5	7.24	0.63
1440	14.4	3.13	14.4	10.7	6.53	0.61

Corrected sample concentration ($\mu g.cm^{-3}$)

Formulation: *Methocel® K100M granulate, Methocel® K100M as external binder (10 % w/w), furosemide.*

Table C.3.6: *Dissolution data of three repetitions.*

Time (min)	*C1	C2	C3	Average	s	% RSD
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00
3	0.00	0.00	0.00	0.00	0.00	0.00
5	0.11	0.00	0.00	0.02	0.07	3.29
10	0.05	0.00	0.07	0.03	0.05	1.37
15	0.73	0.11	0.12	0.32	0.36	1.11
30	0.14	0.02	0.18	0.11	0.08	0.75
40	0.36	0.23	0.30	0.30	0.06	0.21
60	0.75	0.36	0.68	0.59	0.21	0.35
120	1.57	1.00	1.62	1.40	0.35	0.25
240	2.55	1.78	2.46	2.27	0.42	0.19
360	3.77	3.48	3.50	3.58	0.16	0.04
720	4.03	4.14	3.50	3.82	0.46	0.12
1440	4.05	4.05	3.53	3.88	0.30	0.08

**Corrected sample concentration ($\mu g.cm^{-3}$)*

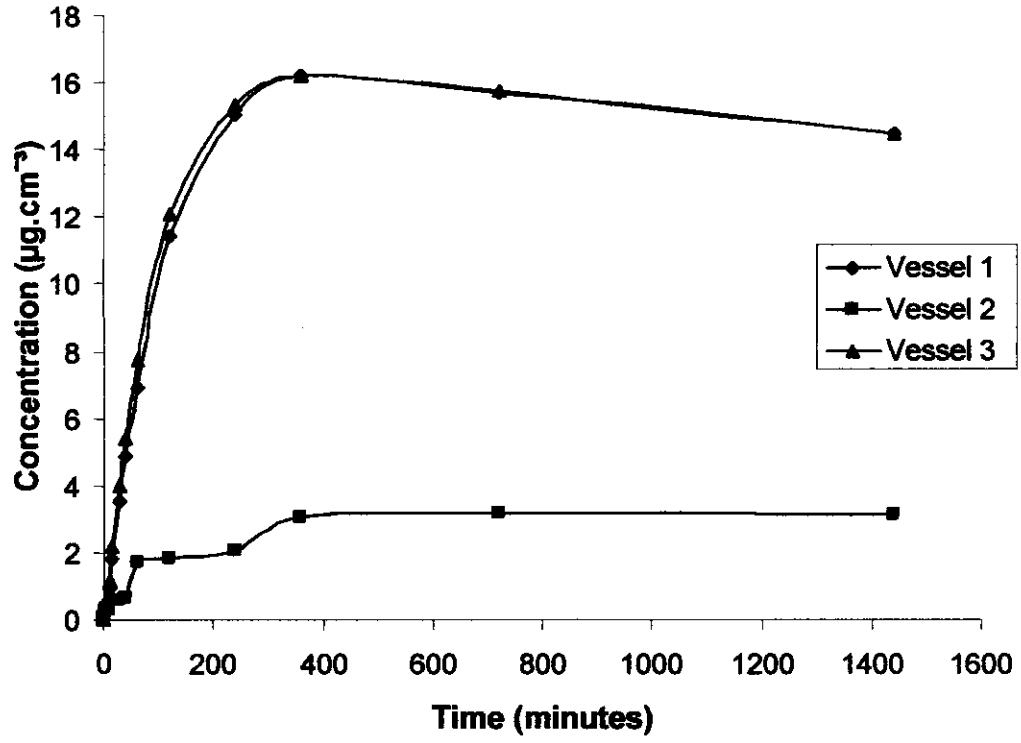


Figure C.3.5: *Dissolution profiles of individual stations (Table C.3.5).*

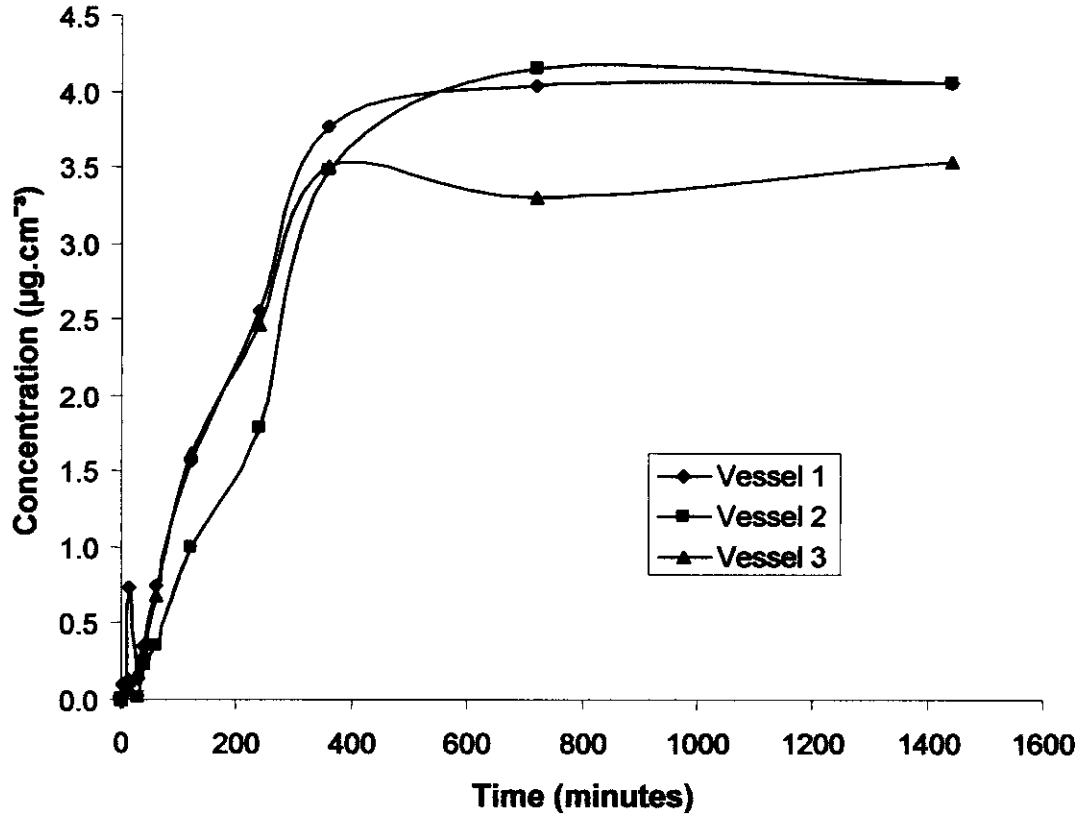


Figure C.3.6: *Dissolution profiles of individual stations (Table C.3.6).*

Formulation: *Methocel® K100M granulate, Kollidon® K100M as external binder (10 % w/w).*

Table C.3.7: *Dissolution data of three repetitions.*

Time (min)	*C1	C2	C3	Average	s	% RSD
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.06	0.00	0.03	0.03	0.03	1.01
3	0.06	0.05	0.03	0.05	0.02	0.34
5	0.13	0.05	0.22	0.13	0.10	0.75
10	0.22	0.03	0.57	0.48	0.23	0.47
15	0.61	0.65	0.59	0.64	0.07	0.11
30	0.86	0.72	1.01	1.20	0.47	0.39
40	1.04	1.74	1.82	1.53	0.43	0.28
60	3.18	1.74	2.04	2.68	0.58	0.22
120	3.18	2.83	3.08	3.12	0.05	0.02
240	3.58	3.10	3.03	3.24	0.30	0.09
360	3.70	3.32	3.16	3.40	0.28	0.08
720	4.10	3.26	3.13	3.50	0.53	0.15
1440	3.54	3.19	3.13	3.29	0.22	0.07

**Corrected sample concentration ($\mu g.cm^{-3}$)*

Formulation: *Methocel® K100M granulate, Methocel® K100M as external binder (10 % w/w).*

Table C.3.8: *Dissolution data of three repetitions.*

Time (min)	*C1	C2	C3	Average	s	% RSD
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.08	0.06	0.01	0.05	0.04	0.75
3	0.01	0.01	0.02	0.01	0.00	0.45
5	0.18	0.05	0.18	0.13	0.07	0.56
10	0.24	0.10	0.14	0.16	0.07	0.46
15	0.39	0.32	0.29	0.33	0.06	0.17
30	0.43	0.67	0.48	0.53	0.13	0.24
40	0.48	0.83	1.76	1.02	0.66	0.65
60	0.62	1.19	1.93	1.25	0.66	0.53
120	0.69	1.52	2.89	1.70	1.11	0.66
240	0.83	1.64	3.69	2.05	1.47	0.72
360	3.86	3.67	3.66	3.73	0.12	0.03
720	3.96	3.61	3.59	3.72	0.21	0.06
1440	3.99	3.69	3.18	3.62	0.41	0.11

Corrected sample concentration ($\mu g.cm^{-3}$)

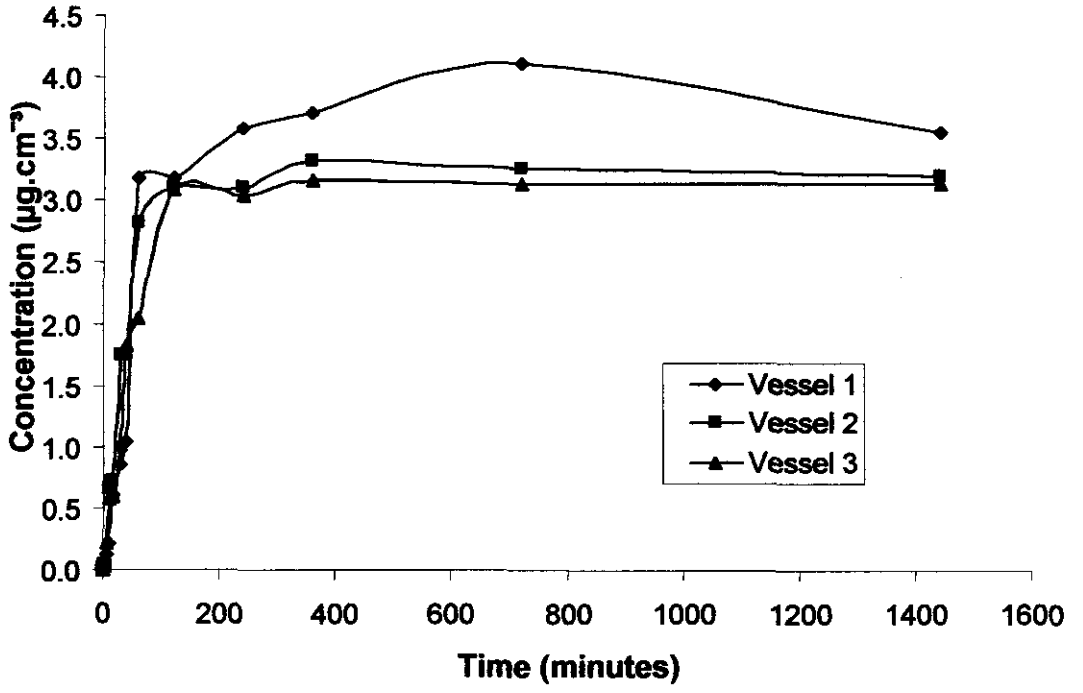


Figure C.3.7: *Dissolution profiles of individual stations (Table C.3.7).*

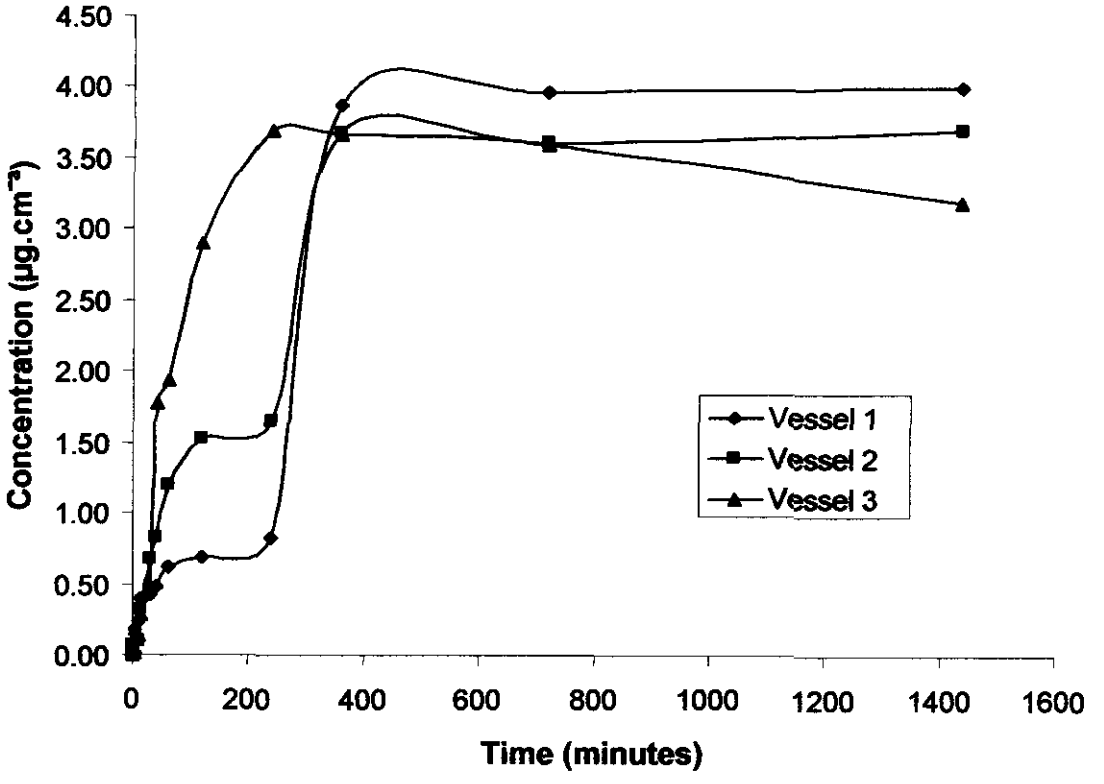


Figure C.3.8: *Dissolution profiles of individual stations (Table C.3.8).*

Formulation: *Kollidon® VA-64 (20 % w/w), furosemide.*

Table C.3.9: *Dissolution data of three repetitions.*

Time (min)	*C1	C2	C3	Average	s	% RSD
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.45	0.38	0.45	0.43	0.04	0.09
3	1.02	0.56	0.93	0.84	0.24	0.29
5	1.55	0.85	1.23	1.21	0.35	0.29
10	2.21	1.31	1.67	1.73	0.45	0.26
15	3.31	2.24	2.40	2.65	0.58	0.22
30	4.89	3.73	3.89	4.17	0.63	0.15
40	5.84	4.84	4.91	5.20	0.56	0.11
60	7.33	6.48	6.38	6.73	0.67	0.08
120	10.80	6.48	11.07	10.56	0.51	0.06
240	14.34	9.80	14.34	14.04	0.00	0.00
360	16.26	13.45	16.26	16.25	0.26	0.02
720	14.96	16.25	14.59	14.67	0.29	0.02
1440	14.97	14.49	14.59	13.32	0.30	0.02

**Corrected sample concentration ($\mu g.cm^{-3}$)*

Formulation: *Kollidon® VA-64 (20 % w/w).*

Table C.3.10: *Dissolution data of three repetitions.*

Time (min)	C1	C2	C3	Average	s	% RSD
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.37	0.56	0.21	0.38	0.18	0.47
3	0.30	0.22	0.14	0.22	0.08	0.34
5	0.27	0.26	0.19	0.24	0.04	0.18
10	0.34	0.41	0.22	0.32	0.09	0.29
15	0.43	0.58	0.32	0.44	0.13	0.29
30	0.74	0.90	0.62	0.75	0.14	0.18
40	1.31	1.60	1.36	1.43	0.15	0.11
60	2.45	2.78	2.82	2.68	0.20	0.08
120	5.56	5.68	6.73	5.99	0.64	0.11
240	8.89	9.36	10.54	9.60	0.85	0.09
360	16.23	16.23	16.23	16.23	0.00	0.00
720	12.85	15.38	15.12	15.12	1.39	0.09
1440	13.64	15.38	15.10	14.41	0.67	0.05

Corrected sample concentration ($\mu g.cm^{-3}$)

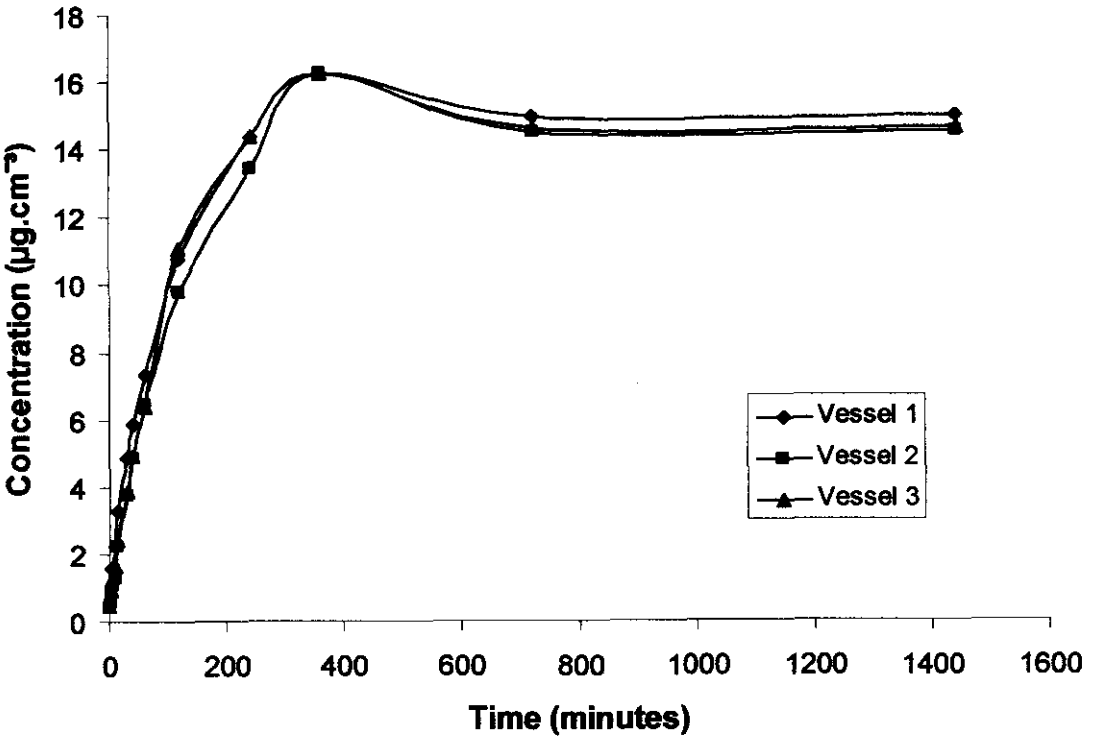


Figure C.3.9: *Dissolution profiles of individual stations (Table C.3.9).*

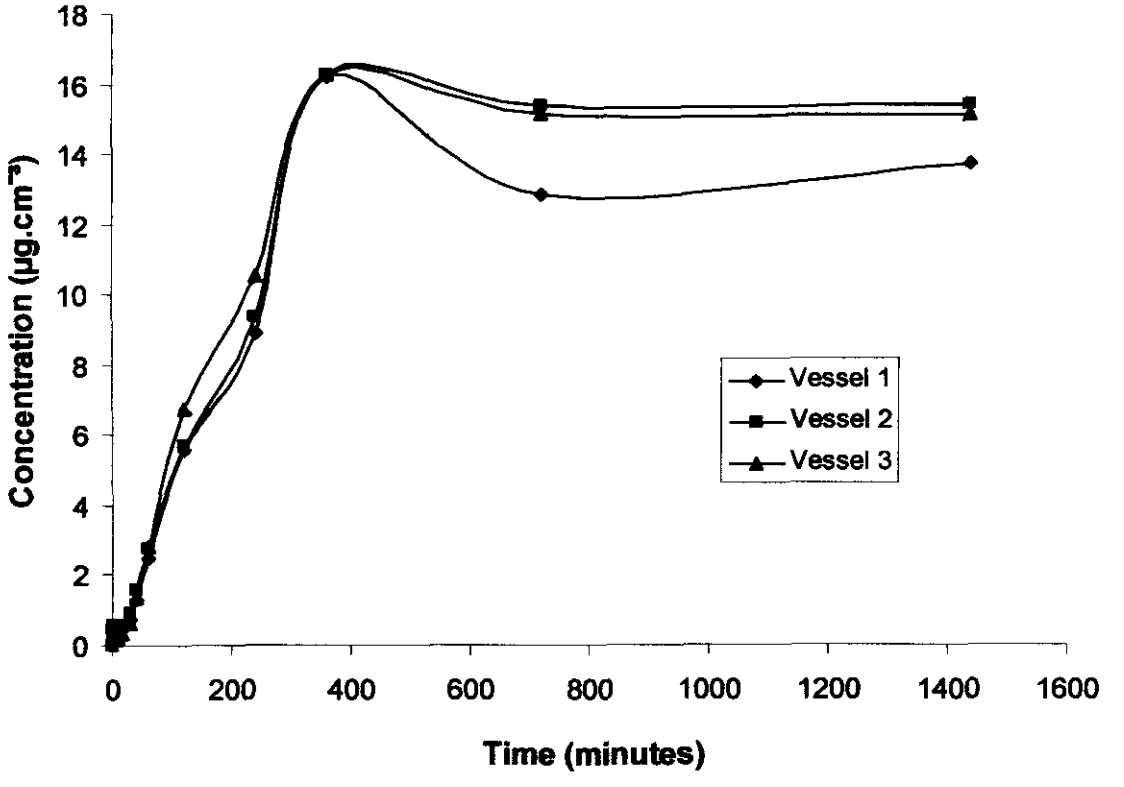


Figure C.3.10: *Dissolution profiles of individual stations (Table C.3.10).*

ANNEXURE D: STABILITY EVALUATION OF CHITOSAN

Table D.1.1: *Physical properties of chitosan tablets compressed from raw material exposed to elevated temperatures.*

Temperature (°C)	Physical properties	Time (hours)			
		1	2	4	8
30 °C	Moisture content (%)	4.9	5.1	5.1	5.2
	Crushing strength (N)	80.7	84.0	81.7	79.4
	Friability (%)	0.03	0.01	0.00	0.41
	Hardness-friability ratio ($N.\%^{-1}$)	2690.0	8400.0	0.0	47.3
40 °C	Moisture content (%)	4.5	4.0	4.6	4.0
	Crushing strength (N)	78.5	66.4	83.3	80.9
	Friability (%)	0.00	0.00	0.01	0.03
	Hardness-friability ratio ($N.\%^{-1}$)	0.0	0.0	83330.0	2696.7
50 °C	Moisture content (%)	3.5	3.3	2.9	2.6
	Crushing strength (N)	64.4	65.9	51.9	30.6
	Friability (%)	1.00	0.30	0.05	1.41
	Hardness-friability ratio ($N.\%^{-1}$)	64.4	219.7	1038.0	21.7
60 °C	Moisture content (%)	2.7	3.6	3.2	2.8
	Crushing strength (N)	95.6	49.6	51.9	38.5
	Friability (%)	0.43	1.70	0.24	0.32
	Hardness-friability ratio ($N.\%^{-1}$)	222.3	29.2	216.3	120.3

Annexure D.2: Long-term stability evaluation of chitosan raw material and tablets.

Table D.2.1: *Physical properties of chitosan tablets (30% w/w Avicel® PH200) stored at 25 °C / 60 RH. % RSD include in parenthesis.*

Physical property	Time (months)					
	0	1	2	3	4	5
Average weight (mg)	205.6 (1.2)	205.9 (3.3)	211.2 (1.2)	212.1 (1.6)	213.3 (1.5)	209.6 (1.2)
Crushing strength (N)	86.2 (8.9)	65.9 (18.3)	73.7 (7.3)	68.1 (13.5)	69.1 (9.8)	56.2 (12.3)
Friability (%)	0.2	0.2	0.4	0.3	0.3	2.2
Disintegration time (minutes)	*N/D	N/D	N/D	N/D	N/D	N/D

** No disintegration*

Table D.2.2: *Physical properties of chitosan tablets (30% w/w Avicel® PH200) stored at 40 °C / 75% RH. %RSD include in parenthesis.*

Physical property	Time (months)					
	0	1	2	3	4	5
Average weight (mg)	205.6 (1.2)	210.6 (2.5)	211.0 (1.5)	214.0 (1.5)	214.0 (1.7)	208.3 (1.9)
Crushing strength (N)	86.2 (8.9)	70.4 (11.9)	67.9 (15.5)	63.5 (11.2)	63.1 (13.8)	50.3 (16.9)
Friability (%)	0.2	0.6	0.5	0.4	0.4	2.3
Disintegration time (minutes)	*N/D	N/D	N/D	N/D	N/D	N/D

**No disintegration*

Table D.2.3: *Physical properties of chitosan tablets (30% w/w Avicel® PH200) compressed from raw material stored at 25 °C / 60% RH. %RSD include in parenthesis.*

Physical property	Time (months)					
	0	1	2	3	4	5
Average weight (mg)	205.6 (1.2)	218.7 (2.0)	214.4 (0.9)	203.8 (0.9)	209.7 (1.0)	208.3 (1.0)
Crushing strength (N)	86.2 (8.9)	98.1 (12.6)	78.5 (5.3)	72.1 (8.8)	63.3 (10.9)	52.9 (15.3)
Friability (%)	0.2	0.0	0.4	0.1	0.5	1.3
Disintegration time (minutes)	*N/D	N/D	N/D	N/D	N/D	N/D

** No disintegration*

Table D.2.4: *Physical properties of chitosan tablets (30% w/w Avicel® PH200) compressed from raw material stored at 40 °C / 75% RH. %RSD include in parenthesis.*

Physical property	Time (months)					
	0	1	2	3	4	5
Average weight (mg)	205.6 (1.2)	214.3 (1.3)	217.2 (1.3)	213.5 (1.6)	214.5 (1.0)	209.3 (1.9)
Crushing strength (N)	86.2 (8.9)	76.4 (10.2)	66.8 (13.1)	61.5 (8.1)	57.3 (13.3)	49.6 (12.9)
Friability (%)	0.2	0.1	0.4	0.1	0.5	2.9
Disintegration time (minutes)	*N/D	N/D	N/D	N/D	N/D	N/D

** No disintegration*

Annexure D.3: Long-term stability evaluation of tablets containing chitosan granules.

Table D.3.1: *Physical properties of chitosan tablets containing 3% w/w Kollidon® granulate (25 °C / 60% RH). % RSD include in parenthesis.*

Physical property	Time (months)					
	0	1	2	3	4	5
Average weight (mg)	193.4 (0.8)	249.4 (1.8)	216.7 (1.0)	207.1 (1.6)	207.9 (1.1)	180.1 (2.3)
Crushing strength (N)	44.0 (5.3)	127.3 (18.3)	65.3 (3.7)	50.5 (14.0)	21.0 (16.8)	20.5 (17.6)
Friability (%)	6.7	0.1	1.2	0.7	2.8	3.5
Disintegration time (minutes)	0.2	3.4	1.4	0.3	0.2	0.1

Table D.3.2: *Physical properties of chitosan tablets containing 3% w/w Kollidon® granulate (40 °C / 75% RH). %RSD include in parenthesis.*

Physical property	Time (months)					
	0	1	2	3	4	5
Average weight (mg)	193.4 (0.8)	218.4 (0.9)	213.7 (1.3)	209.1 (0.9)	208.6 (0.8)	195.6 (1.3)
Crushing strength (N)	44.0 (5.3)	25.6 (6.9)	29.1 (9.1)	23.8 (3.8)	19.8 (4.0)	18.4 (6.9)
Friability (%)	6.7	2.2	1.7	0.7	6.2	8.3
Disintegration time (minutes)	0.2	0.2	0.2	5.4	N/D	N/D

Table D.3.3: *Physical properties of chitosan tablets containing 5% w/w Kollidon® granulate (25 °C / 60% RH). %RSD include in parenthesis.*

Physical property	Time (months)					
	0	1	2	3	4	5
Average weight (mg)	212.8 (0.6)	216.1 (1.1)	213.7 (1.3)	203.7 (2.0)	203.7 (1.0)	200.7 (1.0)
Crushing strength (N)	60.6 (9.1)	25.5 (15.5)	29.1 (13.7)	23.1 (11.7)	15.6 (11.8)	14.9 (16.3)
Friability (%)	0.0	1.8	1.7	1.2	5.5	6.3
Disintegration time (minutes)	1.1	0.1	0.2	0.2	0.1	0.1

Table D.3.4: *Physical properties of chitosan tablets containing 5% w/w Kollidon® granulate (40 °C / 75% RH). %RSD include in parenthesis.*

Physical property	Time (months)					
	0	1	2	3	4	5
Average weight (mg)	212.8 (0.6)	209.1 (1.4)	213.5 (0.6)	203.7 (2.0)	201.6 (1.5)	200.3 (1.8)
Crushing strength (N)	60.6 (9.1)	25.1 (19.3)	28.1 (15.3)	23.1 (11.7)	20.6 (6.3)	20.3 (13.5)
Friability (%)	0.0	1.6	1.8	1.2	4.3	5.6
Disintegration time (minutes)	1.1	0.1	0.6	0.2	1.1	1.0

Table D.3.5: *Physical properties of chitosan tablets containing 3% w/w Methocel® granulate (25 °C / 60% RH). %RSD include in parenthesis.*

Physical property	Time (months)					
	0	1	2	3	4	5
Average weight (mg)	215.7 (1.6)	199.9 (3.9)	204.5 (1.1)	188.2 (5.5)	147.9 (5.9)	N/D*
Crushing strength (N)	61.2 (9.1)	84.1 (26.4)	69.6 (16.9)	69.3 (4.9)	43.9 (27.5)	N/D
Friability (%)	0.8	0.6	3.4	0.5	6.3	N/D
Disintegration time (minutes)	1.1	1.3	0.1	1.9	0.1	N/D

** No data*

Table D.3.6: *Physical properties of chitosan tablets containing 3% w/w Methocel® granulate (40 °C / 75% RH). %RSD include in parenthesis.*

Physical property	Time (months)					
	0	1	2	3	4	5
Average weight (mg)	215.7 (1.6)	208.9 (2.5)	211.7 (4.5)	189.4 (4.6)	N/D*	N/D
Crushing strength (N)	61.2 (9.1)	100.7 (6.3)	82.7 (3.6)	61.3 (10.5)	N/D	N/D
Friability (%)	0.8	0.4	0.5	0.5	N/D	N/D
Disintegration time (minutes)	1.1	1.4	2.3	1.6	N/D	N/D

Table D.3.7: *Physical properties of chitosan tablets containing 5% w/w Methocel® granulate (25 °C / 60% RH). %RSD include in parenthesis.*

Physical property	Time (months)					
	0	1	2	3	4	5
Average weight (mg)	189.9 (2.0)	178.8 (3.5)	196.3 (3.4)	172.4 (1.6)	147.9 (5.9)	N/D*
Crushing strength (N)	70.2 (5.6)	23.8 (13.8)	32.9 (26.4)	30.4 (14.0)	30.9 (27.5)	N/D
Friability (%)	0.2	2.1	1.5	0.5	5.5	N/D
Disintegration time (minutes)	2.4	2.4	2.4	2.3	0.1	N/D

** No data*

Table D.3.8: *Physical properties of chitosan tablets containing 5% w/w Methocel® granulate (40 °C / 75% RH). %RSD include in parenthesis.*

Physical property	Time (months)					
	0	1	2	3	4	5
Average weight (mg)	189.9 (2.0)	185.7 (5.9)	197.1 (3.2)	194.7 (5.5)	N/D*	N/D
Crushing strength (N)	90.2 (5.6)	65.0 (3.5)	48.3 (13.6)	40.3 (13.1)	N/D	N/D
Friability (%)	0.2	1.0	0.9	0.5	N/D	N/D
Disintegration time (minutes)	3.5	2.4	2.5	2.5	*N/D	N/D

* No data