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Evaluation of the matrix-forming ability of chitosan through direct compression using a freely water-soluble drug

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Dedicated to my loving parents,

Irene & Cornelius Koopman

"Be still and know that I am God"

(Psalm 46:10)

Acknowledgements

"Be still and know that I am God" (Psalm 46:10). For all those times You said those words to me, I want to thank you Abba. I give You all the glory and honour for what You have helped me achieve. Through You, oh Lord, all things are possible and it is by your grace that we are blessed and without You I can do nothing and I am nothing. Our wisdom comes from You and I want to thank You for the person You have helped me to become. I love You, Abba.

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BACKGROUND AND OBJECTIVES

Chitosan was first studied in 1859. For the past 20 years, a substantial amount of work has been published on this polymer and its potential use in various applications. The interest shown by the pharmaceutical industry in recent years was due to the discovery of the absorption-enhancing, controlled-release and bio-adhesive properties. Chitosan forms part of a group of highly molecular cationic polysacchrides derived from the chitin found in crustacean shell. Chitosan's role in sustained-release dosage forms, for example matrix tablets, has been well documented. However, the ability to incorporate chitosan in a directly compressed formulation proved to be a challenging task. Furthermore, for the formulation of a hydrophilic matrix system for the purpose of drug release through diffusion of the gel layer, a poorly-soluble drug is often used. In this study, a freely soluble drug, propranolol hydrochloride, was chosen to determine if chitosan could fascilitate sustained-release through a matrix system using a freely soluble drug.

The physical powder properties of chitosan indicated the potential problems that may arise when the direct compression method is applied. Chitosan is a powder with a rigid particle structure presenting intermediary flow properties. This organic powder mixture, with a degree of deacytelation of 91.49 %, could not be directly compressed as a single component mixture.

For the purpose of this study chitosan was utilised to achieve the following objectives:

- To employ the direct compression method with chitosan as primary excipient;
- To incorporate a freely water-soluble drug for the purpose of obtaining sustained-release; and
- To evaluate the ability of chitosan to be utilized as a matrix carrier and produce a pharmaceutically acceptable matrix system.

ABSTRACT

Evaluation of the matrix-forming ability of chitosan through direct compression using a freely water-soluble drug

To utilise the direct compression method in this study was a very challenging task due to the physical powder properties of chitosan. The compressibility of chitosan was evaluated in the initial phase and the results revealed that chitosan could not be compressed as a single component mixture. The following step was to improve the compressibility of the powder and this was done by the inclusion of Emcompress®, a filler with high compressibility properties. Various ratios of the two powders were evaluated and the results revealed that only a small quantity of Emcompress® was necessary to fascilitate direct compression. However, increasing quantities of chitosan in this powder mixture caused a decrease in tablet crushing strength.

The following step in the formulation process was to determine whether chitosan could form a matrix tablet. At this stage, a placebo tablet was formulated. In order to enhance tablet properties as well as the binding capability of chitosan, an additional hydrophilic polymer binder, Methocel®, was included in the formulation and evaluated at varying concentrations of 20, 25 and 30%. These formulations caused an increase in crushing strength and no disintegration, a property that is favourable for matrix tablets. Chitosan was the primary excipient at this stage and the tablet properties revealed the potential matrix-forming ability of chitosan. The rank order for the binders were found to be Methocel® K15M>K4M>K100M with regards to the improvement of the tablet properties of the initial powder mixture.

Propranolol hydrochloride, a freely water-soluble drug, was chosen for this study. This drug is characterised as having very weak flow properties and due to the high concentration included in the final phase of the formulation, the powder mixture was

adversely affected. Various measures were taken to improve the flow of the powder mixture and thus also the tablet properties, such as, the incorporation of a lubricant and glidant, changing the binder concentration and binder type and changing the chitosan:Emcompress® ratio. The additional binder that was introduced was Kollidon® SR. The measures taken proved successful because tablets with excellent properties were produced.

In order to determine if a matrix system was in fact achieved, a dissolution study was conducted. During the disintegration test, a gel layer was formed and swelling took place. This presentation is indicative of a matrix system. However, the fact that a freely water-soluble drug was used, the extent of drug release may not be as desired. Two tests were conducted, one in which a single medium was used and one in which two mediums were used. The results revealed sustained release during all of the tests conducted. The dissolution testing extended to 24 hours. The two-medium dissolution in which and initial 2 hours in a HCl buffer of pH 1.2 followed by a 22-hour test in a phosphate buffer of pH 6.8 revealed 24-hour drug release with the drug still in tact after 24 hours. Literature indicates that chitosan cannot fascilitate sustained-release at a high pH. The rank order for the different formulations with regards to drug release was K15M>K4M>K100M>Kollidon® SR. Chitosan still consumed the highest concentration in the formulation (38.36% w/w) and thus acted as a filler, binder and matrix carrier and the objective was thus achieved.

During this study an additional experiment was conducted to evaluate the stability of the final formulation containing the active ingredient. For all Methocel® formulations a slight increase in tablet weight and a decrease in tablet hardness were observed over the 3 months at both storage conditions. The magnitude of these changes was more significant during the first month of storage compared to the following 2 months. The changes could be attributed to moisture absorption by tablet compounds, especially chitosan and the binders. Stabilization after 1 month could probably be attributed to the fact that the compounds responsible for moisture absorption reached their equilibrium moisture content within the first month and further absorption was negligible.

The results of this study revealed:

- ❖ Chitosan can be used in a directly compressed formulation with the aid of small quantities of additional excipients;
- ❖ Chitosan can be used in a directly compressed formulation where a large quantity of a very weakly flowing active ingredient is used;
- ❖ Chitosan can be incorporated in the largest quantity of a directly compressed formulation; and
- ❖ Chitosan can be utilized in a directly compressed matrix tablet and produce sustained release of up to 24 hours.

OPSOMMING

Evaluering van kitosan se vermoë om 'n matriks te vorm deur die direkte samepersings metode en met die gebruik van 'n hoogs water oplosbare geneesmiddel

Die grootste uitdaging in hierdie studie was die toepassing van direkte samepersing tydens die formulering van kitosan tablette, gesien in die lig van die fisiese eienskappe van laasgenoemde en die swak saampersbaarheidseienskappe van die grondstof. In die eerste fase van die studie is die poeier- en saampersbaarheideienskappe van chitosan geëvalueer. Die slotsom van die ondersoek was dat skoon kitosan nie direk saamgepers kon word nie, waarskynlik as gevolg van swak bindingseienskappe en swak vloei-eienskappe.

Vervolgens is die kombinasie van kitosan met 'n nie-disintegrerende, onoplosbare direksaampersbare vulstof, naamlik Emcompress® ondersoek ten einde die verhouding te vind wat hierdie mengsel direksaampersbaar sou maak. Verskillende verhoudings van die twee stowwe is vermeng, getabletteer en die tablette geëvalueer. Die resultate van die studie het getoon dat 'n minimum van 10% Emcompress® nodig was om kitosan direk te kon saampers.

Vervolgens is gepoog om 'n matrikstabletsisteem met kitosan te formuleer. Vir die doel is verskillende konsentrasies (20, 25 of 30%) van verskillende grade van Methocel® (K4M, K15M en K100M) as bindmiddel getoets. Kombinasie van hierdie stowwe met chitosan het tabletsterkte bevorder, sonder om disintegrasie te induseer. Hierdie afwesigheid van disintegrasie is 'n vereiste vir matrikssisteme. Gemete tableteienskappe het die potensiaal van kitosan as matriksvormende komponent aangetoon. Met betrekking tot die doeltreffendheid van die verskillende bindmiddels om tablet-eienskappe te verbeter is die volgende rangorde bepaal: Methocel® K15M > K4M > K100M.

Ten einde die vermoë van chitosan as matriksvormende stof te evalueer, is propranololhidrochloried (160 mg), 'n wateroplosbare geneesmiddel, in die kitosan formules geïnkorporeer. Byvoeging van die geneesmiddel het 'n negatiewe effek op die tableteienskappe gehad en enkele aanpassings moes gemaak word, insluitend 'n verlaging van die bindmiddelkonsentrasie (na 15%), 'n verandering van die chitosan/Emcompress®-verhouding (van 90/10 na 80/20), verhoging in tabletmassa (van 300 na 400 mg), byvoeging van 'n gly- en smeermiddel (silika en magnesiumstearaat onderskeidelik) en verandering van stempelvorm (van plat na bikonkaaf). Tydens hierdie fase is 'n polivinielpirrolidoon bindmiddel, naamlik Kollidon® SR ook getoets en die invloed daarvan met die van die ander drie Methocel®-grade vergelyk in terme van effek op geneesmiddelvrystelling. In al die finale formules het chitosan steeds die grootste bydrae tot die totale tabletmassa uitgemaak (ongeveer 38%)

Die sukses, al dan nie, om chitosan as matriksvormer te evalueer, is gedoen aan die hand van bestudering van die disitntegrasiegedrag en dissolusiestudies van die finale formules. Tydens disintegrasie is gelvorming en swelling by al die formules waargeneem, wat 'n aanduiding was dat matriksvorming wel voorgekom het. Aangesien 'n goed wateroplosbare geneesmiddel gebruik is, moes die mate van vertraging van geneesmiddelvrystelling egter met behulp van dissolusietoetsing bepaal word. Dissolusiestudies is uitgevoer in 0,1M HCl by pH 1,2 (vir eerste 2 ure) gevolg deur 'n 22-uur dissolusie in 'n fosfaatbuffer by pH 6,8. Die resultate het 24-uur geneesmiddelvrystelling getoon met intakte tabletstrukture na 24 uur. Die rangorde van die verskillende bindmiddels in die formules met betrekking tot verlengde geneesmiddelvrystelling was as volg: Methocel® K15M > K4M > K100M > Kollidon® SR. Die resultate het dus bevestig dat chitosan kon optree as vulstof, bindmiddel en matriksvormer en sodoende as 'n meerdoelige tablethulpstof geklassifiseer kan word.

As 'n finale fase van die studie is die invloed van bewaringskondisies op die fisiese stabiliteit van die formules bepaal. Tablette van die finale formuleringsfase (waarin die geneesmiddel teenwoordig was) is vir drie maande by 25 °C/60% RH (relatiewe humiditeit) en 40 °C/75% RH bewaar en maandeliks getoets met betrekking tot tabletmassa, hardheid, disintegrasie en verbrokkeling. Die resultate het getoon dat

tabletmassa deurgans toegeneem het, terwyl breeksterkte diensooreenkomstig afgeneem het. Die grootste veranderinge in fisiese eienskappe het egter tydens die eerste maand van bewaring voorgekom, waarna die verandering grootliks gestabiliseer het. Enige van die waargenome verandering kon toegeskryf word aan die absorpsie van vog deur veral die kitosan en bindmiddels, terwyl die stabilisering verklaar kon word aan die hand van die bereiking van die ewewigsvoginhoud van die betrokke bestanddele wat verdere waterabsorpsie voorkom het.

Die resultate van die studie het die volgende getoon:

- Dat kitosan wel direksaamgepers kan word in teenwoordigheid van minimale hoeveelheide direksaampersbare vulstowwe (en dus as die hoofkomponent m.b.t. bydrae tot tabletmassa gebruik kan word);
- Dat kitosan wel groot hoveelhede (hoë massa persentasie) geneesmiddel met swak vloei- en saamperbaarheideienskappe kan akkommodeer;
- Dat kitosan wel oor die vermoë beskik om 'n matrikssisteem te lewer waaruit geneesmiddelvrystelling vir ten minste 24-uur gehandhaaf kan word.

CHAPTER 1
THE USE OF CHITOSAN AS A FILLER IN MATRIX FORMULATIONS VIA DIRECT COMPRESSION: EFFICACY OF HYDROPHILIC MATRICES

1.1 Introduction

The enhancement of dosage forms, particularly solid dosage forms, for the efficient delivery of drugs has been and still is the focus point in the pharmaceutical industry. For the past few years the use of controlled-release technology in pharmaceutical products has become increasingly important. Hydrophilic matrices were, in view of their biopharmaceutical and pharmacokinetic properties, clearly an interest that was completely justified (Longer, 1990:1675). The matrix system is most often used for a drug controlled-release from a pharmaceutical dosage form. Among the countless methods used in controlled-release of drugs from pharmaceutical dosage forms, the matrix system is the most frequently applied; it is a release system for delay and control of the release of a drug that is dissolved or dispersed in a resistant support to disintegration. Although developing a hydrophilic matrix tablet offers a simple and effective approach to formulate a drug for extended-release, it requires a careful consideration of the physicochemical properties of the drug, polymer and excipients (Longer, 1990:1676).

The principal goal of controlled-release dosage forms or any dosage form for that matter, is the improvement of drug therapy as assessed by the relationship between advantages and the disadvantages of the use of controlled-release systems (Malinowski, 1983:1255). Among the advantages, the most important will be mentioned:

- Minimisation of the patient compliance problems;
- Reduction of both local and systemic side effects;
- Less potentiation or reduction in drug activity with chronic use;

- Minimisation of drug accumulation in body tissues with chronic dosing; and
- Minimisation or annihilation of "peaks" and "valleys" in the drug blood level, improving efficiency in treatment.

Although there are many positive aspects, some disadvantages have been identified:

- Difficulty in controlling the effects of a drug when serious poisoning or intolerance occurs;
- Reproducibility of action affected by the rate of gastric emptying;
- Release rate dependant on pharmaceutical dosage form integrity;
- Large size of pharmaceutical dosage form;
- Greater cost than conventional dosage forms.

The formulation of the drugs in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in the field of controlled release. In fact, a matrix is defined as a well-mixed composite of one or more drugs with a gelling agent (hydrophilic polymer) (Buri, 1980:189). These systems are called swellable controlled systems. Figure 1.1 shows the two different hydrophilic matrices.

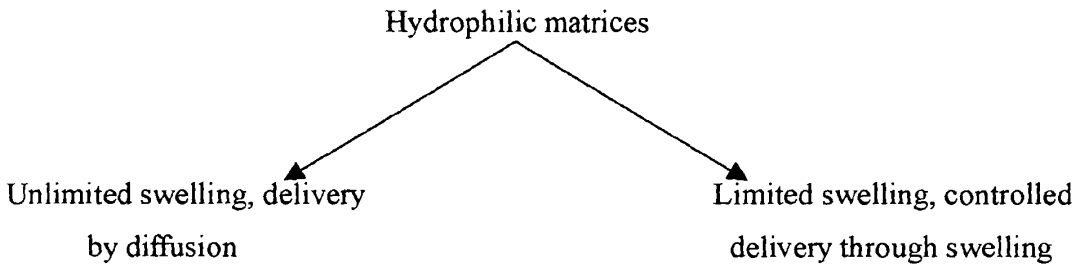


Figure 1.1: Two types of hydrophilic matrices.

With conventional dosage forms made of drug dispersed through soluble excipients the drug is very rapidly liberated from its dosage form and quickly builds up to a high concentration, which then falls exponentially until the next dose. As a result, concentration patterns of the drug in the plasma and tissues displays the movement or appearance of a wave, high concentrations alternating low concentrations, causing the optimal therapeutic level to be present for only a brief period of time. The following

drawbacks appear: the fluctuating drug levels in blood and tissues lead to an insufficient influence on the mechanism of the disease and are related to an excessive use of the drug and/or initial overdosing produces a high frequency of damaging side effects. Because of the brief duration of therapeutic drug level, the frequency of the regimen is very high leading to bad treatment because of the limited reliability of the patient or even its non-compliance: omission, wrong dosage or wrong frequency (Ainaoui & Vergnaud 2000:383). For the reasons mentioned above, a sustained-release dosage form holds many advantages above conventional dosage forms

1.2 Tableting through direct compression

In 1960 direct compression was introduced to the pharmaceutical industry. As its distinct advantages became increasingly evident, it only received increased attention over recent years. The term direct compression was long used to identify the compression of a single crystalline compound (usually an inorganic salt such as sodium chloride, sodium bromide or potassium bromide) into a compact without the addition of any other substances. Few chemicals possessed the flow, cohesion, and lubricating properties under pressure to make such compacts possible. If and when compacts were formed, prolonged disintegration occurred, thus delaying drug release, and possibly causing physiological problems. Furthermore, the effective doses for most drugs were so small that this type of direct compression was not practical (Sheth *et al.*, 1980:147).

The term direct compression is currently used to define the process by which tablets are compressed directly from powder blends of the active ingredient and suitable excipients, including fillers, disintegrants and lubricants, which will flow uniformly into a die cavity and form into a firm compact. For this purpose, a series of directly compressible excipients were developed which possess both fluidity and compressibility. The first such vehicle was spray-dried lactose, which, although it was subsequently shown to have shortcomings in terms of compressibility and colour stability, initiated the "direct compression revolution" (Sheth *et al.*, 1980:148). Other excipients that were developed shortly after and are still in use today were microcrystalline cellulose (Avicel®), the first

effective dry binder and filler; (Sta-Rx 1500® starch), a compressible starch which maintains its disintegrant properties; (Emcompress®), a free-flowing dicalcium phosphate and a number of direct compression sugars.

Many problems have been encountered with this method of formulating, such as, problems with uniform distribution of drug content, the incorporation of poorly compressible, poorly flowing drugs with a high therapeutic dosage, interparticular friction and segregation of particles and the attaining of a uniform colour distribution.
The following list indicates the excipients intended for tableting should adhere to:

- Good flow properties;
- Good compressing properties;
- Physiologically inert;
- Compatible with a large variety of drugs;
- Physically and chemically stable- especially against moisture, air, light and heat;
- Be able to accommodate a large amount of active ingredient;
- Colourless and tasteless;
- A particle distribution that coincides with a series of drugs;
- Does not influence the bioavailability of the drug;
- Be able to accommodate colourants;
- Cause a pleasant sensation in the mouth, especially in the case of sublingual tablets (Sheth *et al.*, 1980:152).

In practice, no one single material fulfills all these criteria and it may be necessary to blend two or more materials to achieve the desired compression properties.

1.3 Properties of powders intended for tableting

In order to produce a pharmaceutically viable tablet, there are three primary requirements that all powders intended for tableting should adhere to namely, fluidity, anti-adherence and compressibility. When considering the two primary methods used for tablet

manufacture, i.e. wet granulation and direct compression, it is important to bare in mind that not all powders meet the prescribed requirements. For instance, during wet granulation particle size enlargement and uniformity takes place, thus improving compressibility and fluidity during compression. The granulate is also able to withstand high compression forces, thus no deformation will occur. In the case of direct compression, blending time and speed of the mixture plays an important role. The physicochemical properties of the drug will eventually be the deciding factor. Nevertheless, all factors should be considered (Armstrong, 1998:649; Rubinstein, 1988:306).

1.3.1 Fluidity

The necessity for good flow properties in a mixture could not be stressed enough. Not only does it enhance the flow rate of the mixture into the die, but it also decreases the necessity for a glidant. Insufficient flow of the mixture into the die will produce variable tablet weight distribution and thus also variation in drug content. There are many ways to improve fluidity of a powder intended for tableting, for instance, the incorporation of a glidant which increases powder flow by decreasing adhesion and cohesion forces, change in particle size and particle size distribution (Staniforth, 1988:614), spray-drying or by means of granulation (Rubinstein, 1988:306).

Martin *et al.* (1983:516) stated that a bulk powder is somewhat analogous to a non-Newtonian liquid, which exhibits plastic flow and sometimes dilatancy, the particles being influenced by attractive forces to varying degrees. Pharmaceutical powders are either free-flowing or cohesive, with free-flowing powders producing tablets with more favourable tablet properties. During processing and formulation changes in particle size, density, shape and electrostatic charge may occur which will significantly affect flow properties. It is the aim of manufacturers to standardize flow properties of powders so as to optimise formulations, because poorly flowing powders or granulations present many difficulties to the pharmaceutical industry.

Particles with high density and a low internal porosity tend to possess free-flowing properties, while elongated or flat particles tend to pack to give powders with a high porosity. Surface roughness leads to poor flow characteristics due to friction and cohesiveness. Occasionally, poor flow may result from the presence of moisture, in which case drying of the particles will reduce cohesiveness (Martin, 1983:517).

1.3.2 Compressibility

Good compressibility of a powder intended for tableting is essential for tablet manufacture. On application of pressure by the tablet press during manufacture, an intact mass is expected to be produced (Rubinstein, 2000:306). The ideal is to produce tablets, which are hard, of uniform mass, resistant to mechanical stress, and disintegrates within the required time.

The physics of compaction may be simply stated as: "The compression and consolidation of a two-phase (particulate solid-gas) system due to the applied force". Compression is regarded as a reduction in the bulk volume of the material as a result of displacement of the gaseous phase, whereas consolidation is an increase in the mechanical strength of the material resulting from particle-particle interactions (Marshall, 1986:66).

As mentioned above, compression involves the compaction of a bulk volume powder mass. The external mechanical forces applied to this powder mass cause a deformation of the mass depending on the physical properties of the powder mixture. Two types of deformation exist, namely plastic and elastic deformation. In the case of plastic deformation, particles resemble the behaviour of modelling clay. In this case the shear strength is less than the tensile strength. In the case of elastic deformation, it is said to display rubber-like behaviour in which case the deformation is reversible.

1.3.3 Anti-adherence

Some materials are found to have strong adhesive properties toward the metal of the

punches and dies, which results in the unwanted effect of the material adhering to the punch surfaces. Anti-adherents, lubricants and glidants all fall in the same class due to their overlapping functions. Lubricants reduce friction between the walls of the tablet and the walls of the die cavity during tablet ejection, while anti-adherents reduces adhering of powder or granulation to the surface of the punch or walls of the die cavity (Banker & Anderson, 1986:328; Bandelin, 1989:177).

1.4 Excipients in hydrophilic matrix formulations

1.4.1 Hydroxypropyl methylcellulose

Hydroxypropyl methylcellulose (HPMC now also referred to as hypromellose) is the most common and predominantly used hydrophilic polymer carrier used in the formulation of oral controlled-release drug delivery systems (Colombo, 1993:37-57). Drug-release from hypromellose has been given great attention over the past 20 years. Various mathematical models have been designed to describe and predict the drug release from theses vehicles and to elucidate the water and drug transport processes (Gao, 1995:965; Ju, 1995:1464). However, there are many physical properties to be taken into account, thus making the mathematical description of the entire drug release process rather difficult. Among these physical properties are:

- Diffusion of water into the hypromellose matrix;
- Hypromellose swelling; drug diffusion out of the device;
- Polymer dissolution
- Axial and radial transport in a three-dimensional system;
- Changing matrix dimensions;
- Porosity and composition

There are certain assumptions made by each model: restriction of the transport phenomena to one dimension, neglect of polymer swelling (Katzhendler *et al.*,

1997:110), or neglect of polymer dissolution (Gao *et al.*, 1995:967). As a result of these assumptions, the respective models can only be applied to certain drug-polymer systems.

Hypromellose is a very versatile excipient. It is available in a wide range of molecular weights and thus control of gel viscosity is provided. The grade of viscosity for the various types of hypromellose determines the rate of hydration in the formulation. A commonly used hypromellose, Methocel® (Dow Chemical Company) has four premium grade namely, K, E, F and A. The recommended guidelines to formulate a robust modified release matrix is to use at least 20% and preferably 30% Methocel®, keeping the formula and process as simple as possible. The actual method of production, i.e. direct compression or wet granulation, has little or no effect on the release rate.

The actual mechanism of release from hypromellose matrices is modified by drug solubility. For water-soluble drugs, release is affected by both diffusion of the drug through the hypromellose and by slow dissolution of the matrix itself following hydration, a process known as attrition (Ford *et al.*, 1985:340).

Ford *et al.* (1985:341) found that the release rate of propranolol hydrochloride decreased with increasing concentrations of hypromellose in the tablet. Thus, primary control of the release rate should be achieved by the hypromellose content, varying the ratio of drug to polymer. This mechanism holds true for all types of drug and should be used as the primary means of controlling the release rate.

1.4.2 Effect of particle size

Extreme variation in particle size of the active ingredient and excipients will have an impact on the release rate by affecting the dissolution of the drug as well as the efficiency of gel formation. It is thus important to standardize the particle size so that they may be as similar in size as possible.

As mentioned above, various grades of hypromellose exist and Methocel® K was highly recommended as first to be evaluated when preparing a matrix formulation. The reason being that this product hydrates quickly to form the gel layer with excipients as well as being able to provide acceptable flow and binding properties (Colorcon, 2000)

1.4.3 Effect of polymer viscosity

Increasing viscosity yields slower release rates because a stronger more viscous gel is formed, providing a greater barrier to diffusion and slower attrition of the tablet with insoluble drugs. The fining of modified release systems may be achieved by blending different viscosity grades where the desired dissolution rate is not obtained with a single viscosity grade. The uniform distribution of hypromellose throughout the matrix is the most important manufacturing factor, but the dosage size does affect drug release since larger dosage forms give slower dissolution and extra excipient can slow drug release (Colorcon, 2000).

1.5 Factors affecting drug release

When formulating a hydrophilic matrix, a thorough knowledge of the properties of the polymer chosen as a binder is essential so as to be aware of any interactions.

1.5.1 Hydration ability of the polymer

It is important that the hydration/swelling process of various polymer and polymeric combination be known. There are various steps in polymer dissolution and of these the most important are, absorption/adsorption of water in more accessible places, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling and finally, dispersion of polymeric chain in dissolution medium. Methocel K hydrates quickly because of its low content of methoxyl groups and its popular use matrix systems is justified. The first minutes of

hydration are generally considered the most important, because they correspond to the time when the protective gel coat is formed around matrices containing hypromellose (Salsa *et al.*, 1997:934).

1.5.2 Composition of the polymer

The most commonly used polymers are composed of rather complex cellulose ethers. Specifically hydroxyl groups which covalently bond with a variety of species. The influence of alteration in methoxyl/hydroxyl ratio on drug release rate was evaluated and it was found that in matrices obtained by granulation the drug dissolution rate was directly proportional to hydroxypropyl content, and favourable results were obtained when hypromellose had content greater than 7.5%.

1.5.3 Polymer viscosity

With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular weight or viscosity of the polymer in a matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater the viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution

1.5.4 Suitable proportions of polymer to drug

The proportion of polymer is generally used as a control variable in drug rate delivery. In the case of water-soluble drugs, this proportion is calculated from Higuchi's equation (Higuchi, 1963:1145).

1.5.5 Gelling tendency

A gel is defined as a viscous cross-linked system (Florence, 1988:289). A gel is a polymer-solvent system containing a three dimensional network of quite stable bonds unaffected by thermal motion. Figure 1.2 depicts the mechanism of action of polymer in a matrix system. As soon as the polymer comes into contact with a solvent it partially hydrates and a gel layer is formed and there is an initial burst of the drug. Permeation of water into the tablet then increase the viscous gel layer and at this point the drug begins to diffuse through the layer thus causing sustained release. Alderman *et al.* (1985:7) described the prolonged release from hypromellose matrices and concluded that a gelatinous layer, formed when the polymer hydrated on contact with water, controlled the release of drugs by two mechanisms. Water-soluble drugs were released by diffusion out of the gelatinous layer and by erosion of the gel, whereas poorly soluble drugs were released slowly by erosion.

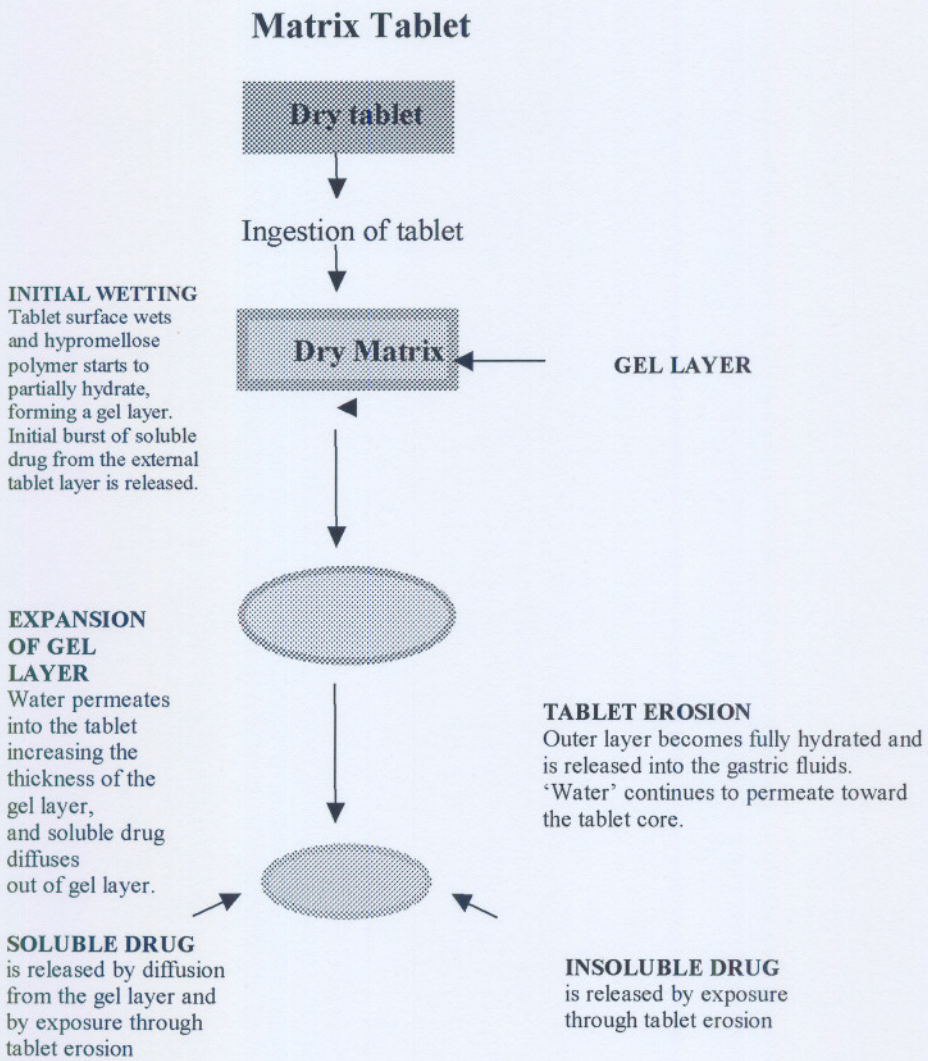


Figure 1.2: *Mechanism of action of a hydrophilic polymer in matrix tablets.*

1.6 Controlled-release formulations

The oral administration of single dose medicinals is considered the safest and simplest since the damage at the site of administration is minimal. Thus, of all the possible routes for administering controlled release medication to patients, single dose medicinals is preferred. When oral controlled release formulations enter the body, they are subjected to fluctuating pH levels as they are transported through the strongly acidic gastrointestinal tract to a weakly alkaline medium in the lower part of the small intestine. Not only is the fluctuating pH levels an important factor to consider when developing these formulations, but also the variable absorbing surfaces over the length of the GI tract. Variation in gastric emptying in different individuals can produce variable efficacy of oral controlled delivery systems.

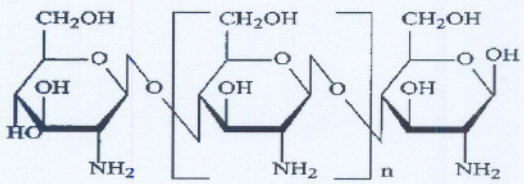
The polymeric controlled delivery systems are being used as part of a wide range of reagents in various environments. The most popular application is the drug delivery, in which the main objective is to achieve an effective therapeutic administration for an extended period of time. The technique is also termed as sustained release. These techniques have been used in the agricultural area for creating a continued environment of soil nutrients, insecticides, herbicides and other agro-expedient agents using other polymers.

Chitosan is non-toxic and easily bioabsorbable with gel forming ability at low pH. Moreover, chitosan has antacid and anti-ulcer activities that prevent or weakens drug irritation in stomach. Also, chitosan matrix formulations appear to float and gradually swell in acid medium. All these interesting properties of chitosan made this natural polymer an ideal material for controlled drug release formulations (Kumar, 2000).

1.6.1 Chitosan

The history of chitosan dates back to the last century, when Rouget discussed the deacetylated form of chitosan in 1859. During the past 20 years, a substantial amount of work has been published on this polymer and its potential use in various applications. Chitosan has recently been introduced to the pharmaceutical industry in drug delivery application due to its absorption-enhancing, controlled-release and bioadhesive properties.

Chitosan is a term given to a family of high molecular weight cationic polysaccharides derived from chitin that naturally occurs in crustacean shells. The repeating units in chitosan are a 2-deoxy-2-(acetyl-amino) glucose and a 2-deoxy-2amino glucose linked with glucosidic bonds into a linear polymer. Chitosans differ in their degree of polymerization and their degree of deacetylation, which also plays an important role in formulations. The chemical structure of chitosan is depicted in figure 1.3.



Chitosan

Figure 1.3: *Chemical structure of chitosan.*

Chitosan is a weak base and this characteristic gives it distinctive solubility properties. At acidic pH values the amino groups become protonated, causing the chitosan to uncoil and become more soluble. As pH values increase above its pK_a of approximately 6.5 (Schipper *et al.*, 1996:1687) chitosan loses this charge, coils up and is likely to precipitate from solution.

Chitosan has considerable potential for many pharmaceutical applications (Illum, 1998:1326). Many studies have investigated the use of chitosan in the design of

sustained release dosage forms, such as matrix tablets, and have shown that, in general, chitosan provides excellent sustained release properties in vitro especially at low pH values where a gel matrix is formed (Kawashima *et al.*, 1985:2472). Upadrashta *et al.* (1992:1707) claimed that an increase in chitosan concentration would produce stronger tablets with a higher degree of sustained release. However, in this respect, the degree of polymerization and deacetylation should be taken into account.

1.6.2 Chitosan and its gelling tendency

Kumar (2000) did various studies on the gelling behaviour of chitosan. Hydrogels are highly swollen, hydrophilic polymer networks that can absorb large amounts of water and drastically increase in volume. It is well known that the physicochemical properties of the hydrogel depend not only on the molecular structure, the gel structure, and the degree of crosslinking but also on the content and state of water in the hydrogel. Hydrogels have been widely used in controlled release systems. Recently, hydrogels, which swell and contract in response to external pH, are being explored. The pH sensitive hydrogels have a potential use in site-specific delivery of drugs to specific regions of GI tract and have been prepared for low molecular weight and protein drug delivery. It is known that the release of drugs from the hydrogels depends on their structure or their chemical properties in response to environmental pH. These polymers, in certain cases, are expected to reside in the body for a longer period and respond local environmental stimuli to modulate drug release. On the other hand, it is some times expected that the polymers are biodegradable to obtain a desirable device to control drug release. Thus, to be able to design hydrogels for a particular application, it is important to know the nature of systems in their environmental conditions to design them in proper situation. Some recent advances in controlled release formulations using gels of chitin and chitosan are presented here (Kumar, 2000). Peppas *et al.* (2000:9) shows a diagram of all tissue locations for hydrogel-based drug delivery systems (figure 1.4).

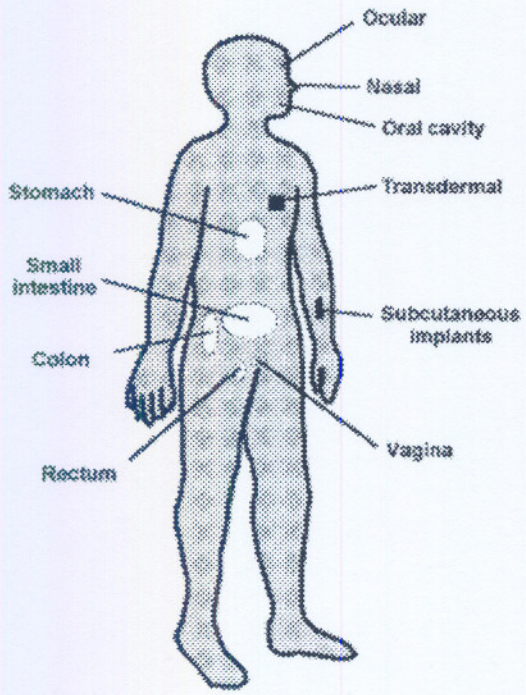


Figure 1.4: Tissue locations applicable for hydrogel-based drug delivery (Peppas *et al.* 2000:9).

It is well known that physiochemical properties of the hydrogel depend not only on the molecular structure, the gel structure and the degree of crosslinking but also on the content and state of water in the hydrogel. Since the inclusion of water significantly affects the performance of hydrogels, a study on the physical state of water in the hydrogels is of great importance because it offers useful suggestion on their microstructure and enables to understand the nature of interactions between absorbed water and polymers. The effect of ionic strength on the rate of hydrolysis of a gel has been studied and it was observed that there was rapid hydrolysis of the gel with a decrease in ionic strength, i.e., a higher degree of swelling was observed in a lower ionic strength solution (Kumar:2000).

1.6.3 Chitosan: A sustained-release excipient

Chitosan tablets can be formulated by either direct compression or conventional granulation methods. Employment of chitosan in sustained-release formulations is by incorporating it as a gel-forming excipient in matrix formulations. Numerous tests were done on chitosan when its retardant effects were first noticed. Kawashima *et al.* (1985:2473), found that chitosan decreased dissolution rates at acidic and slightly acidic pH levels while Akbŭga (1993:259) found that at pH levels of 7.4, chitosan displayed no slow-release properties. The conclusion was made that the effects of chitosan depended on the pH levels.

The cationic nature of chitosan has been assumed to be the reason for its effects in different pH media. Mi *et al.* (1997:2502) did an extensive study on the mechanism of action of chitosan. His results showed that hydration of and gel-forming effect of chitosan took place more readily at pH values of 1.2 than at a pH of 7.2. Thus, it can he concluded that the retardant effect of chitosan is more pronounced in an acidic environment.

Factors affecting release from chitosan matrix systems:

- Amount of chitosan: increasing the amount of chitosan in a formulation decreases the releases rate;
- Nature of the drug: slow-release is easily achieved with poorly-soluble or slightly-soluble drugs, whereas additional slow-release excipients is required with readily soluble drugs (Kawashima *et al.*, 1985:2473); and
- Grade of chitosan: Kristl *et al.*, (1993:18) found that drug release was most successfully retarded by chitosan of a higher molecular weight and Sabnis *et al.* (1997:253) suggested that drug release decreased as degree of deacetylation increased.

1.6.4 Chitosan as permeation enhancer

It has been reported that chitosan, due to its cationic nature is capable of opening tight junctions in a cell membrane. This property has led to a number of studies to investigate the use of chitosan as a permeation enhancer for hydrophilic drugs that may otherwise have poor oral bioavailability, such as peptides. Because the absorption enhancement is caused by interactions between the cell membrane and positive charges on the polymer, the phenomenon is pH and concentration dependant. Furthermore increasing the charge density on the polymer would lead to higher permeability. This has been studied by quaternising the amine functionality on chitosan.

1.6.5 Chitosan as mucoadhesive excipient

A drug with low oral bioavailability or where sustained-release is required, a bioadhesive excipient is added to the formulation to increase the residence time of the drug in the GI tract. A comparative study between chitosan and other commonly used polymeric excipients indicated chitosan possessed higher bioadhesivity compared to other natural polymers, such as cellulose, Xantham gum, and starch (Kotze & Luessen, 1999).

1.7 Additional excipients

1.7.1 Lubricant

When selecting a lubricant, the specifications of the final tablet should be taken into consideration so as to ensure efficiency of compression. The reason for this is that many studies have shown that there is no universal lubricant. Two factors play a role in the efficacy of a lubricant in a formulation, i.e. particle size and the extent of mixing.

Variation in particle size between different lots of the same lubricant will have an effect on the properties of the tablet formulation, as is the case with most excipients (Sheth *et al.*, 1988:129-131). As already been mentioned, lubricants facilitate the ease of ejection of the tablets, thus, it is generally added during the final phase of blending. Excessive mixing of the lubricant can cause coating of other excipients in the formulation and cause impairment of their function. This problem is overcome by mixing the lubricant at a latter stage of blending. A uniform distribution of magnesium stearate is important and although short mixing times can cause poor distribution, the lubricating effects remained unaffected compared to longer mixing times (Ragnarrson *et al.*, 1979:130).

The hydrophobic fatty lubricants are the most effective, but excessive use of this type of lubricant will render the tablet hydrophobic thus retarding disintegration of the tablet and drug dissolution. Used in appropriate proportions and possibly the addition of a surfactant in the formulation, hydrophobic lubricants generally do not pose problems with their use (Sheth, *et al.*, 1988:130).

As mentioned earlier lubrication of solid mixtures improves both fluidity and particle characteristics of the materials intended for tableting. (Shah & Mlodozeniec, 1977:1378) proposed three mechanisms of lubrication that affect to some degree the coverage of particles.

These mechanisms are summarized as follows.

- Adsorption or surface contact adhesion;
- Diffusion or solids penetration;
- Delamination or deagglomeration of the lubricant agent to coat particles with a film, which is usually discontinuous.

Magnesium stearate, the most widely used lubricant in the pharmaceutical industry was described by (Rajala & Laine, 1995:178) to exhibit particles of a plate-like structure. It exhibits its lubricating properties by forming a film of low shear strength between the die wall and the compact, thus reducing friction. It also has anti-adhesive properties that prevent tablets from sticking to the die wall and punch faces. Both mixing intensity and

particle surface-areas of magnesium stearate and powder particles influence the coverage of particles by the lubricant. A short mixing time provides a sufficient lubricant distribution and action (Kikuta & Kitamori, 1994:350).

Although magnesium stearate holds so many advantageous properties, its hydrophobic character holds some disadvantages as well. The lubricant forms a hydrophobic film around the granules that can negatively affect the tablet properties such as crushing strength, disintegration time, friability and dissolution (Johansson, 1984:307). This film shields the particles from water as well as hinders the interaction of dispersion forces (Marshall & Rudnic, 1991:370).

The shielding effect of magnesium stearate films on dispersion forces between particles decrease adhesive and cohesive interactions at material and metal surfaces. Thus, as a result, the flow of particles is hindered to a smaller extent due to the decrease in particle-particle contact (Podczeck & Miah, 1996:188). Additional studies indicated that the enhancement of fluidity is limited to an optimum level of magnesium stearate. Above this optimum, magnesium stearate can affect fluidity negatively. Increases in lubricant film thickness and fine lubricant particles are probable explanations for the detrimental effect on fluidity. The lubricant improved fluidity when it was added at the latter stage of blending, but the compressibility was still low and brittle tablets were produced.

1.7.2 Kollidon® SR

Kollidon® SR is a spray-dried physical mixture of the polymers polyvinyl acetate and povidone in the ratio 8:2. It is used as a matrix sustained-release excipient. Kollidon® SR is insoluble in water. It offers outstanding flow properties having a repose angle well below 30°. It can therefore enhance the fluidity of other components added for a tablet formulation of direct compression. The high compressibility is an expression of its excellent dry binding properties, which is another important parameter for direct compression technology of tablets (Buhler, 2003:245-249).

Due to the combination of the very plastic polyvinyl acetate and the strongly binding povidone, high tablet hardness levels are obtained with soluble drugs (Buhler, 2003:249). Kollidon® SR can be used for the production of the following sustained release matrix dosage forms: tablets, pellets and granules. The required content of Kollidon® SR in the tablet depends mainly on the particle size and solubility of the active ingredient. The finer the particles, the faster the dissolution. Table 1.1 gives the required concentrations of Kollidon® SR to obtained sustained release during a period of 12-24 hours.

Table 1.1: *Required concentrations of Kollidon® SR in tablets (Buhler, 2003:256-257).*

Solubility of active ingredient	**Kollidon® SR concentration in tablet**
Very slightly soluble to practically insoluble	15-25%
Sparingly soluble to slightly soluble	25-40%
Soluble to freely soluble	40-55%

Outstanding and important properties that makes Kollidon® SR an ideal excipient

- The drug release is independent of pH;
- The drug release is independent of the ionic strength of the dissolution medium;
- The drug release is independent of the usual compression force and tablet hardness.
- For the production of sustained release tablets with Kollidon® SR as matrix, the direct compression technology is recommended.

The uniform particle size and shape of Kollidon® SR, which explains its excellent fluidity, is shown in figure 1.5.

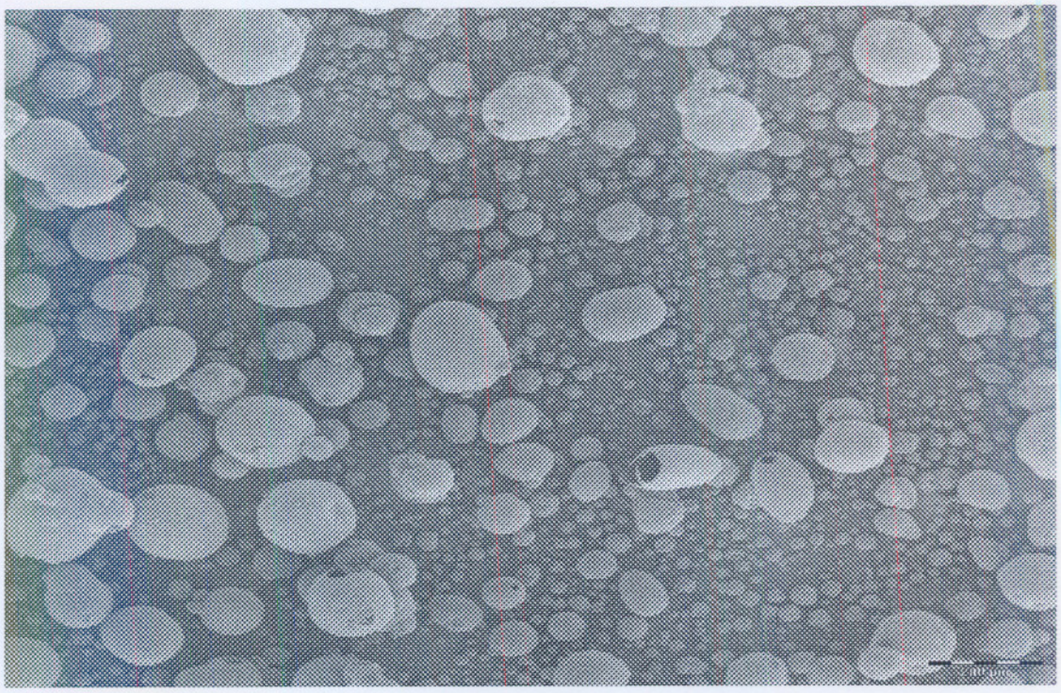


Figure 1.5: *SEM micrograph of Kollidon® SR.*

1.8 Conclusion

Various dosage forms have been developed over the past few decades and yet oral solid dosage forms still remain the most popular and widely used dosage forms in the pharmaceutical industry. One of the many reasons why consumers prefer this dosage form is because of its ease of use and excellent organoleptic properties.

There are two primary methods of tablet manufacture and they are tableting by direct compression and tableting by wet granulation. Direct compression was introduced to the pharmaceutical industry more than four decades ago and there is still extensive research being done to optimize this method of manufacture. This method is easy, not time-consuming and relatively inexpensive. For this reason, pharmaceutical companies aim to optimize and develop commercially available directly compressible excipients.

Over recent years, a method was developed to even further assist patient compliance, i.e. a sustained-release dosage form. This allows for high daily doses to be taken once daily and controlled to achieve a constant sustained-release within the body. Thus, non-toxic drug levels are reached and maintained and the risk of a patient missing a dose is avoided. The most common form of sustained-release is formulated in the form of a hydrophilic polymer matrix. The drug is embedded within this polymer matrix and as soon as the polymer comes into contact with a solvent it partially hydrates forming a gel layer and there is an initial burst of the drug. As the solvent then permeates further into the tablet the gel layer thickens and the drug then slowly diffuses through the gel layer and sustained or controlled-release is achieved.

Chitosan is non-toxic and easily bioabsorbable with gel forming ability at low pH. Moreover, chitosan has antacid and anti-ulcer activities that prevent or weakens drug irritation in stomach. Also, chitosan matrix formulations appear to float and gradually swell in acid medium. All these interesting properties of chitosan made this natural polymer an ideal material for controlled drug release formulations. Chitosan has been used for many years, in nutrition, i.e. a weight loss medicament, in dyes and various other applications exist. It was only recently introduced to the pharmaceutical industry as an excipient when its pharmaceutical potential came under the attention of researchers. When chitosans absorption-enhancing, controlled-release and bioadhesive properties was noticed, further research into this polymer was only logical.

Hydroxypropylmethylcellulose (now known as hypromellose) is the most predominantly used hydrophilic polymer carrier used in the formulation of oral controlled-release drug delivery systems. At high concentrations it is able to produce tablets with excellent properties that produce favourable decreased dissolution rates. This polymer has excellent gelling properties and shares a similar mechanism to chitosan. The ability of hypromellose to produce sustained-release is well documented and is currently still the number one choice when formulating a hydrophilic matrix.

In order to optimise chitosan as a matrix-forming excipient, it is necessary to include various other excipients such as a dry binder like hypromellose, a filler which in this case will be Emcompress® and depending on the choice of drug and how its properties would effect the formulation, a lubricant.

In the following chapter, the experimental methods are discussed as well as the motivation for the choice of drug used.

CHAPTER 2
EXPERIMENTAL PROCEDURES

2.1 Introduction

When designing a direct compression tablet it is of utmost importance to assess the physical properties of the powder such as particle size, fluidity, compressibility, etc. in order to predict through thorough evaluation methods if acceptable properties will be produced. This chapter discusses why a specific drug was chosen in these formulations and the excipients most suited for the study. It also describes the experimental procedures used to evaluate the effect of the chosen excipients on the dissolution rate of a water-soluble drug in a matrix formulation.

2.2 Model drug: Propranolol hydrochloride

Propranolol hydrochloride is one of many biopharmaceutical class 1 agents that are freely soluble in water. Its permeability appears to be high because it is rapidly and almost completely absorbed following oral administration. The solubility of propranolol hydrochloride has made it a choice drug for pharmaceutical investigations. It has low and dose-dependant bioavailability, the result of extensive first metabolism in the liver. It is said that effective oral doses of propranolol are greater than effective intravenous doses, owing to first-pass hepatic inactivation. It has a half-life of 3-6 hours, but can be absorbed for up to 24 hours. This freely soluble drug will ensure a challenging and yet rewarding task when formulated for a sustained-release or long acting dosage form using a chitosan tablet matrix.

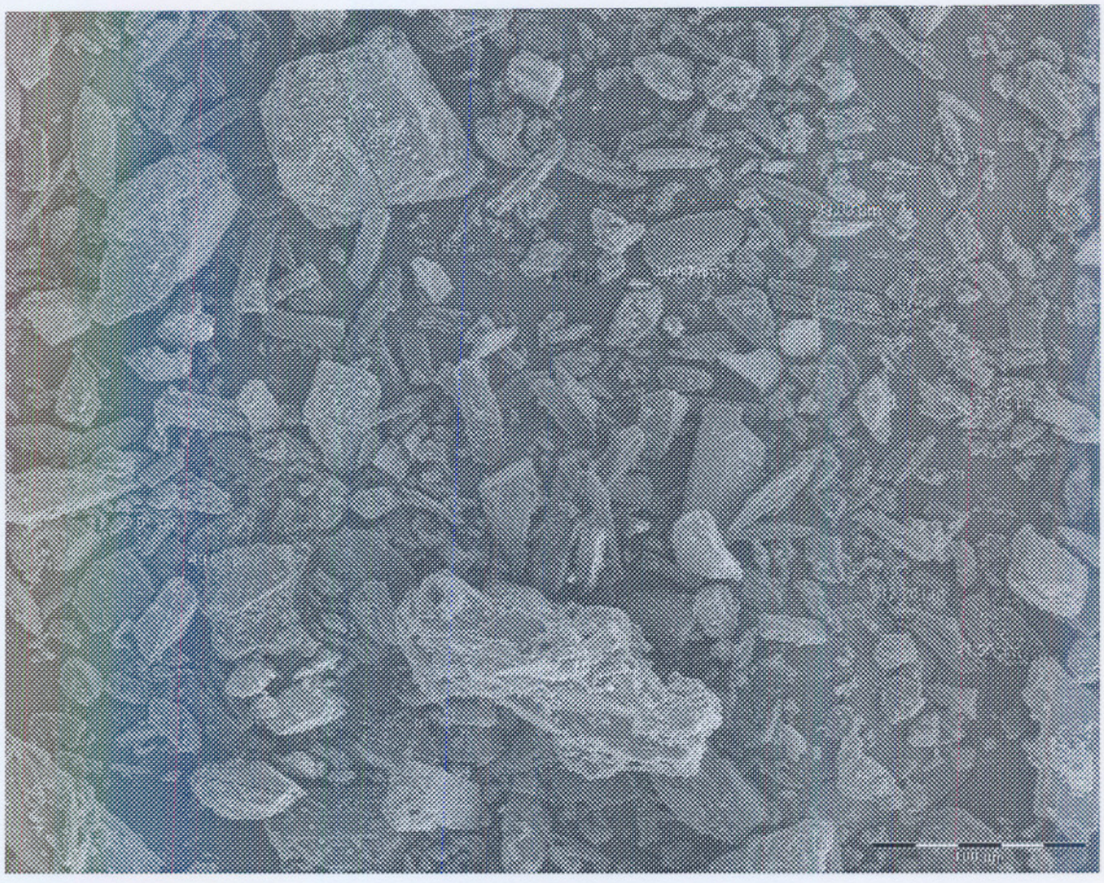


Figure 2.1: *SEM micrograph of propranolol hydrochloride.*

The above micrograph illustrates an irregular crystal like structure with variable particle size.

2.3 Materials

The materials were chosen based on the physical properties and use as controlled-release and directly compressible excipients. Materials used in this study are presented in Table 2.1.

Table 2.1: *Materials, lot numbers and the names of the manufacturers used in this study.*

Compound	Lot number	Manufacturers
Propranolol hydrochloride	PHC 030827	Kothari Phytochemicals International
Magnesium stearate	ART 5876	Merck, Darmstadt, Germany
Chitosan	021010	Warren Chem, England
Kollidon® SR	31-9011	BASF Aktiengesellschaft, Ludwigshafen, Germany
Methocel® K4M	QC17012N32	Colorcon
Methocel® K15M	QB24012N01	Colorcon
Methocel® K100M	QD	Colorcon

2.4 Physical characterization of excipients

2.4.1 Morphology of powder particles

Scanning electron microscopy (SEM) served to visualize the morphology and surface aspects of particles at 100x and 1000x magnifications. Each sample was gold/ palladium (4:1) – coated with an Elko IB ion coater (Elko Engineering, Japan) and observed with a Phillips® XL 30 DX4i scanning electron microscope.

2.4.2 Flow properties

When examining the flow properties of different single component powders, a calculated assessment can be made about various tablet properties.

2.4.2.1 Angle of repose

A pre-determined amount of powder (100 g) was poured into a cylindrical Perspex container fitted with a shutter containing an orifice of 18.84 mm in diameter. The shutter was opened and the powder was discharged through the orifice onto a horizontal glass surface from a height of 15 cm. The height (h) and diameter (d) of the resulting cone was measured and, using equation 2.1., the angle of repose was calculated.

$$\mathbf{Tan}\,\theta = \frac{h}{r} \qquad [2.1]$$

Where h is the height of the powder cone and r is the radius of the diameter of the base line. The time it took for the powder to discharge was also noted as the flow rate of the powder.

2.4.2.2 Hopper flow rate

The simplest method of determining powder flow properties directly is to measure the rate at which powder discharge from hopper. A hopper, fitted with a shutter at the bottom, was filled with a predetermined amount of powder (approximately 100 g). The shutter was opened and at the same time a stopwatch was started and the time was recorded for the powder to discharge completely. By dividing discharge powder weight by time, a flow rate was obtained and used to evaluate the variability, if any, of the excipients. This experiment was conducted in triplicate, using different samples of about 100 g of each powder.

2.4.2.3 Powder density

Density is described as the weight divided by the volume of a substance or a tablet expressed in $g.cm^{-3}$. True, bulk and tapped density is often used to describe a powder and its constituent particles.

2.4.2.3.1 True density (ρt)

Only the solid portion of the powder particles is taken into consideration when the true density is measured. The true densities of the materials were determined using a Quanta chrome® stereopycnometer, by degassing an accurately weighed sample powder (20 cm^3) in a container of known volume.

2.4.2.3.2 Bulk (poured) density (ρb)

The bulk density is defined as the ration of the weight of a powder to the volume it occupies. This density term accounts for the volume of the solid portion of the particles, the voids within the particle and the voids between particles. Poured density is essentially the same as bulk density. The bulk density of each filler was determined by pouring a predetermined weight of powder (100 g) into a graduate cylinder and measuring the volume it occupied. The density was calculated with the following equation:

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

Where ρ_b in $g.cm^{-3}$, w is the weight (g) and V_b is the volume (cm^{-3}) of the powder.

2.4.2.3.3 Tapped density

The tapped density of each filler was determined by pouring a predetermined weight (100 g) into a graduated cylinder. The cylinder was placed on a vibrating surface and vibrated for 5-minute intervals at amplitude of 5 ampere. After each time interval the powder volume was noted. This was repeated until the powder volume remained constant. The average tapped density was calculated using equation 2.2.

2.4.2.4 Porosity

A set of monosized apherical particles can be arranged in many different geometric configurations. At one extreme, when the spheres form a cubic arrangement, the particles are most loosely packed and have a porosity of 48%. At the other extreme, when the spheres form a rhombohedral arrangement, they are most densely packed and a porosity of only 26%. Porosity (ε) is thus defined as the spaces between particles. The porosity is determined as the ratio of the void volume to the bulk volume according to equation 2.3.

$$\frac{V_b - V_t}{V_b} = 1 - \frac{V_t}{V_b} \qquad [2.3]$$

Where V_b is the bulk volume (cm^{-3}) and V_t the true volume (cm^{-3}), obtained individually from the bulk density and the true density. Porosity is expressed as a percentage, ε x 100.

2.5 Composition and preparation of the mixture

2.5.1 Mixtures containing chitosan and Emcompress

Since chitosan could not be compressed directly, mixtures were prepared containing various ratios of chitosan and a directly compressible filler/binder, namely Emcompress®. The mixture compositions are presented in table 2.2.

Table 2.2: *Composition of chitosan:Emcompress® mixtures.*

Composition	% w/w
Chitosan	50, 60, 70, 80 or 90
Emcompress®	Qs to 100 %

Twelve gram mixtures were prepared in 900 cm^3 honey jars, covered with Parafilm® and mixed for 5,10 and 20 minutes respectively in a Turbula® mixer as 69 rpm. Various mixing times were used to determine its effect on tablet properties due to differences in component distribution.

Tableting was done on an eccentric Cadmach® tablet press using 9 mm flat-faced punches to produce tablets with an average weight of 300 mg. For all the formulations the fill volume was kept constant and a compression setting of 50 (maximum) was employed. The first 15 tablets were disposed of. The tablets were collected in glass jars, covered with Parafilm® and stored in a dark, cool environment for 24 hours prior to evaluation.

2.5.2 Mixtures containing chitosan, Emcompress® and various dry binders

In order to produce a matrix tablet structure, various dry binders in different concentrations were evaluated. Mixtures containing chitosan and Emcompress® (90:10 ratio) combined with the different binders were prepared at a mixing time of 10 mintues in a Turbula® mixer at 69 rpm. The compositions of the formulations are presented in table 2.3.

Table 2.3: *Composition of chitosan:Emcompress formulations containing different dry binders.*

Composition	% w/w
Chitosan	50, 60, 70, 80 or 90
Emcompress®	Qs to 100 %
Binders (Methocel® K100M, K4M or K15M)	20 25 or 30

Tableting was done as previously described using te same punch and die set and compression setting.

2.5.3 Mixtures containing an active ingredient

During the initial phase of the evaluation of drug release from the matrix tablets produced in the previous phase, tablet mixtures were prepared containing 160 mg of propranolol hydrochloride (53.33% w/w), chitosan and Emcompress® (90:10 ratio) and various dry binders. The mixture compositions are presented in table 2.4.

Table 2.4: *Composition of propranolol hydrochloride formulations for initial evaluation of drug release.*

Composition	% w/w
Propranolol hydrochloride	160 mg
Binder	20 or 25 % w/w
Chitosan: Emcompress®	24 or 19.5 % w/w* 2.6 or 2.16 % w/w

**The ratio of chitosan:Emcompress® was 90:10.*

Mixing conditions and tableting was done as previously described and tablet averaging 300 mg was produced.

Due to poor physical properties (brittle tablets with the occurrence of picking and sticking during tableting) of all the tablet formulations, the formulation needed to be altered. The formulation clearly needed a lubricant and glidant, and the tablet weight needed to be adjusted. The composition of the final formulations is presented in table 2.5.

Table 2.5: *Composition of altered propranolol hydrochloride formulations.*

COMPOUND	FUNCTION	% w/w
Propranolol hydrochloride	Active ingredient	35.55
Chitosan	Filler/binder	Qs to 100
Emcompress®	Filler	9.583
Methocel®K4M, Methocel® K100M, Methocel® K15M or Kollidon® SR	Binders	15.0
Magnesium stearate	Lubricant	0.5
Silica	Glidant	1.0

Mixtures of 36 grams were prepared. In order to protect the active ingredient from light all mixing jars containing were covered with aluminium foil. Mixing was kept constant at 10 minutes and 69 rpm in a Turbula® mixer. Due to the necessity of the addition of a lubricant, mixing was divided into two stages. Initial blending of all components (except the lubricant) was done for 8 minutes after which the lubricant was added to the mixture and mixed for another 2 minutes. The mixtures were tableted immediately after preparation.

2.6 Tablet evaluation

The most important physical properties of the tablets for each formulation were determined. These were:

- crushing strength;
- weight variation;
- friability, and
- disintegration time

2.6.1 Tablet crushing strength

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

2.6.2 Weight variation

Twenty tablets from each formulation were randomly selected, dusted with an art brush and weighed on a Precisa® analytical balance. The average weight, standard deviation and the percentage relative deviation were calculated and assessed.

2.6.3 Friability

Ten tablets were randomly selected from each batch and dusted with an art brush and accurately weighed. The sample was placed in the drum of a Roche® friabilator, which was then operated for 4 minutes at 25 rpm. The tablets were dusted and weighed again. The percentage friability was determined using the following equation:

$$\% \text{ friability} = \frac{weight(before) - weight(after)}{weight(before)} \times 100 \qquad [2.4]$$

2.6.4 Disintegration time

The disintegration times of six tablets were determined in distilled water at 37°C ± 0.5°C using the Erweka® tablet disintegration 3-station test unit (Erweka®, Heustenstamm, Germany), fitted with internal self-regulating thermostat.

2.7 Dissolution studies

Dissolution studies were done in a six-station dissolution apparatus at 37°C (model DT6R, Erweka®, Heustenstamm, Germany) using the standard USP baskets, fitted with a thermostat and variable speed synchronous motor.

2.7.1 Release studies

Dissolution tests were conducted on tablets according to the USP XXII monograph for propranolol hydrochloride tablets. The dissolution conditions were USP Apparatus I, 50 rpm, 900 mL, 0.1M HCl, for a 24 hour dissolution. A second dissolution study was conducted on all 4 formulas to assess the effect of a change in pH. The samples were placed in 0.1M HCl for the first two hours after which it was removed from the medium and placed in a phosphate buffer pH 6.8 from 3 to 24 hours (900 mL), maintained at 37°C ± 0.5°C. Dissolution samples were collected at 5, 10, 15, 30, 60, and every proceding hour and analyzed spectrophotometrically at wavelengths of 289 nm. It was made clear that none of the ingredients used in the matrix formulations interfered with the assay. The release studies were conducted in triplicate (6 tablets in each set), and the mean values were plotted versus time with a standard deviation of 1 less than 3, indicating the reproducibility of the results.

2.8 Standard curve

Standard curve was prepared prior to each dissolution study. Standard solutions with concentrations of 20 to 100 $\mu g.cm^{-3}$ were prepared from a mother solution containing 200mg of propranolol hydrochloride. The propranolol hydrochloride was dissolved in approximately 10 ml of absolute ethanol and sonicated for 5 minutes. It was then diluted to 200 ml with 0.1M HCl in a volumetric flask. The UV-absorbencies were analyzed spectrophotometrically at a wavelength of 289 nm with 0.1M HCl as control.

The absorbencies were plotted against concentration and the best straight line through the data points was fitted using linear regression. The concentration range obeyed Beer's law with correlation coefficients of $(r^2) \geq 0.9997$. The slope (m) and y-intercept (c) calculated the propranolol concentration at each sample time.

2.9 Calculations

Microsoft® Excel 2000 for Windows was employed in al calculations (Microsoft® Corporation, Seattle, Washington, USA).

2.9.1 Dissolution data

The quantity of drug dissolved ($\mu.cm^{-3}$) at each sampling time was calculated using equation 2.5. The quantity of drug lost through sampling was calculated using equation 2.6.

$$X = \frac{y^* - c}{1000m} \qquad [2.5]$$

Where y* is the corrected absorbency; x is the drug concentration ($\mu.cm^{-3}$); m is the slope and c is the y-intercept which was obtained from the standard curve.

$$y_n^* = y_n + \frac{V_s}{V_m} \cdot \sum^{n-1} y^* \qquad [2.6]$$

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

Four runs of each formulation was done and the dissolution profiles presented are propranolol hydrochloride ($\mu g.cm^{-3}$) as a function of time (hours).

2.9.2.1 DR_i and AUC, calculated dissolution parameters

The initial slope of the dissolution curve between t_o and t_6 is proposed to be a justified estimate of the initial dissolution rate of propranolol (DR_i) from the various tablet formulations. The area under the dissolution profile (AUC) was calculated from to up to the completion of the dissolution test at 24 hours (t_{24}) and would be an indication of the extent of drug dissolution at the end of the dissolution test. The AUC is described by the trapezoidal rule shown by equation 2.

$$AUC=0.5\sum_{t=n}^{t=0}(t_n - t_{n-1})(C_n + C_{n-1}) \qquad [2.7]$$

Where t_n-t_{n-1} is the time difference between two consecutive sampling times and c_n-c_{n-1} is the drug concentration ($\mu g.cm^{-3}$) in samples at sample times corresponding to t_n and t_{n-1}.

2.10 Stability testing of chitosan tablet formulations

An additional experiment was conduct to analyze and assess the stability of chitosan under controlled condition. The results produced from this experiment should provide insight into the optimum storage conditions of the tablets.

2.10.1 Procedures and testing

2.10.1.1 Tableting

The final formulations containing the active ingredient were once again prepared as previously discussed. The same parameters were used. Batches of 150 tablets for the four formulas were prepared. Tablets were stored in glass containers, labelled and sealed with Parafilm®.

2.10.1.2 Storage conditions

Tablets were stored in stability chambers under controlled conditions of humidity and temperature. The stability tests were conducted at 25 °C and 60% relative humidity and 40 °C and 60% relative humidity. These conditions should provide an indication on the degree of exposure the tablets can withstand.

2.10.1.3 Sampling and evaluation

The various batch was analysed on the same day of production, i.e. day 0. The following day, the tablets were stored under specified conditions and extractions were made on a monthly basis for analysis. For this study only physical properties (crushing strength, weight variation, friability and disintegration) were analysed.

CHAPTER 3
PHYSICAL ANALYSIS OF THE TABLETABILITY OF CHITOSAN WITH REGARDS TO CHARACTERIZATION AND PROPERTIES

3.1 Introduction

Chitosan has been well documented for its use as a directly compressible excipient in the pharmaceutical industry. It has been used as a tablet disintegrant, for the production of controlled-release dosage forms and as a tablet binder. This chapter will be focusing on chitosan's ability to be directly compressed in tablet formulations with regards to its compressibility, fluidity, particle size etc. Because a filler/binder makes up the largest quantity of the final tablet mass, an evaluation of its powder characteristics should allow for an accurate prediction of the tablet properties.

3.2 Powder characterization

Powders exhibit characteristic properties that influence their behaviour during formulation. As mentioned previously, compressibility, density and porosity are all important factors to take into consideration. Fluidity, which is evaluated by calculating the angle of repose and the measure of the flow rate of a powder are also important because it is one of the factors that determine how tablet mass will vary from one dosage unit to the next. Table 3.1 shows the above characteristics for chitosan (determined as described in section 2.4.2).

Table 3.1: *Summarized values of the powder characterization of chitosan.*

Property	Chitosan
Mean particle size (μm)	115.63
Angle of repose (°)	36.821
Flow rate ($g.sec^{-1}$)	12.803
Porosity	0.9634
Uniformity of flow (%RSD)*	33.662
Bulk density ($g.cm^{-3}$)	0.1835
Tapped density ($g.cm^{-3}$)	0.2593
Compressibility	No data available

**Percentage relative standard deviation (STD/average x 100).*

Although particle size is not the only factor to be taken into consideration with regards to the fluidity of a powder, it is, to a large degree, the determining factor. Chitosan has a particle size of less than 200 μm and thus interparticulate forces and friction becomes more important. However, the results obtained from the analysis of chitosan powder tends to be misleading when considering the experimental results obtained for chitosan by the direct compression method. Alderborn (1982:390) stressed the importance of being aware of the relationship between particle size and tablet strength when designing a direct compression formulation. The angle of repose is relatively high and would place chitosan in a class of those having intermediary flow properties. Attempts to directly compress pure chitosan raw materials failed, and no tablets could be produced at various compression settings. During the tableting process it was quite obvious that pure chitosan did not possess flow properties to uniformly fill the tablet die and inherent binding properties to form a compact with enough strength to produce pharmaceutically acceptable tablets.

Chitosan has a very irregular particle structure (Refer to figure 3.2). Thus, the interparticulate bonding capability of such a single-component powder comes into

question. Eriksson and Alderborn (1995:1031) investigated the effect of interparticulate bond formation on powder compaction and concluded that the interparticulate bond structure in a pharmaceutical compact can be described simply in terms of the number and the bonding force of interparticulate bonds. The product of these will theoretically govern the tensile strength of the compact. Thus, chitosan, as a single-component powder will not produce directly compressible tablets due to its poor flow (refer to section 2.4) and the addition of a filler and/or binder is justified.

3.3 Addition of filler and evaluation of tablet properties

The choice of an additional filler was based on whether its physical properties would compliment chitosan in such a way that the latter would still consume the largest quantity in the final tablet mass and still produce acceptable tablet properties. Emcompress®, which is an example of dibasic calcium phosphate dihydrate, was used as a binder/filler for the production of chitosan tablets by the direct compression process. Direct compression tablets that have been made with Emcompress® offer high quality, uniformity and economic advantages through substantial savings in time and labour. Its particles are of a size, shape and density that create those flow conditions demanded by modern high-speed tablet presses in which a maximum flow is essential for high-speed tablet production and reduced tablet weight variation. Emcompress® is insoluble and non-disintegrating which properties that are favourable for matrix systems are. Mixtures were prepared containing different ratios of chitosan and Emcompress® to determine the maximum amount of chitosan that can be incorporated and still produce tablets with acceptable properties.

Because Emcompress® cannot be manufactured as a single-component mixture without a lubricant, it can only be assumed that the exclusion of a lubricant in the formulation could be awarded to chitosan's physico-chemical properties. Tablets were evaluated in terms of tablet hardness, weight variation, friability and disintegration as discussed in section 2.6. The results obtained are shown in table 3.2.

Table 3.2: *Tablet properties containing various ratios of chitosan: Emcompress®. %RSD is indicated in parentheses.*

Ratio	Tablet Property	Mixing times		
		5	10	20
50:50	Hardness (N)	160.91(0.362)	160.13(0.406)	165.91(0.441)
	Average weight (mg)	320.0 (0.244)	313.9 (0.145)	317.8 (0.230)
	Friability (%)	0	0.067	0.065
	Disintegration (min:s)	NONE	NONE	NONE
60:40	Hardness (N)	123.52(0.379)	119.4(0.802)	121.45(0.808)
	Average weight (mg)	273.0 (0.074)	270.6 (0.195)	270.7 (0.101)
	Friability (%)	15	0	0.074
	Disintegration (min:s)	NONE	NONE	NONE
70:30	Hardness (N)	73.82 (1.290)	75.91 (1.207)	90.4 (1.198)
	Average weight (mg)	235.4 (0.218)	234.6 (0.211)	242.8 (0.094)
	Friability (%)	0.215	0.084	0
	Disintegration (min:s)	NONE	NONE	NONE
80:20	Hardness (N)	48.04 (0.300)	49.89 (0.323)	48.64 (0.834)
	Average weight (mg)	215.3 (0.093)	213.4 (0.094)	217.1 (0.128)
	Friability (%)	0.1	0.09	0.18
	Disintegration (min:s)	NONE	NONE	NONE
90:10	Hardness (N)	31.94 (1.09)	48.73 (0.6)	29.6 (0.960)
	Average weight (mg)	193.9 (0.101)	197.5 (0.149)	193.0 (0.055)
	Friability (%)	0.77	0.662	0.78
	Disintegration (min:s)	NONE	8.443 (5.935)	6.294 (7.032)

**The ratio can be read as chitosan: Emcompress®.*

3.3.1 Interpretation of data

The data correlates to a large extent with the properties of the powders. The variation in hardness for the different formulations can be awarded to the large molecular weight of

chitosan compared to Emcompress®. As shown in figure 3.1, an increasing proportion of chitosan resulted in a decrease in crushing strength (hardness) due to chitosan's poor ability to be direct compressed and the resulting decrease in fluidity of the mixture. The hardness for the 80:20 and 90:10 formulations were noticeably lower, which illustrates the low compactibility of an increasing quantity of chitosan. Although the hardness for the abovementioned formulations was lower, tablets were still produced and this indicated that only a small percentage of filler was needed to enhance the tabletting properties of chitosan. The friability proved favourable for all formulations, but the 90:10 ratio was almost 10 times higher than that of the 80:20 formulations, which supported the necessity of a binder if this ratio is used. The weight variation showed negligible variation as revealed by the low %RSD that confirmed the improved fluidity of the powder mixture due to the addition of a filler. Figure 3.1 shows the marked decrease in crushing strength with an increase of chitosan above 70%.

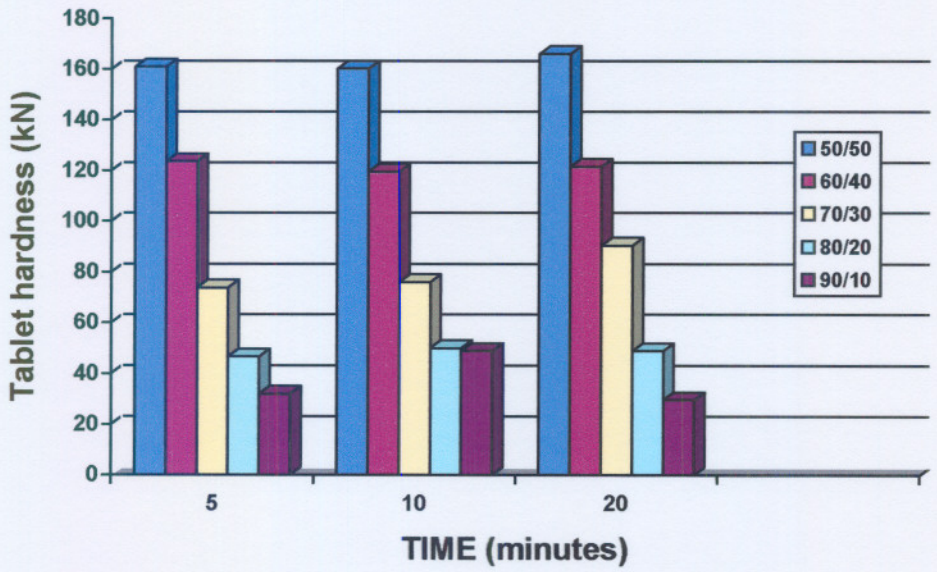


Figure 3.1: *Tablet hardness of various chitosan: Emcompress® ratios at different mixing times.*

3.3.2 Disintegration

The standard required time for tablets to break up into smaller particles or disintegrate in order to fascilitate drug dissolution is 15 minutes. In these formulations, the only formulation that disintegrated within the required time was the 90:10 formulations from the 10 and 20-minute batches. This was once again awarded to the low compactibility of these formulations. However, in this case, the inability of the other formulations to disintegrate was viewed as a positive result, because it confirmed chitosan's gelling tendency and it was also assumed that an accurate prediction of chitosan's matrix-forming ability could be made.

3.3.3 Effect of mixing time

Mixing time had no significant effect on the physical properties of the various formulation and all formulations showed the same tendency (as could be seen in figure 3.1 for the change in tablet hardness with mixing time).

Two formulations were chosen for the SEM studies to evaluate the effect, if any, of mixing times on the physical properties of the tablets. The formulations chosen were those of 70:30 and 90:10 as shown in figure 3.2.

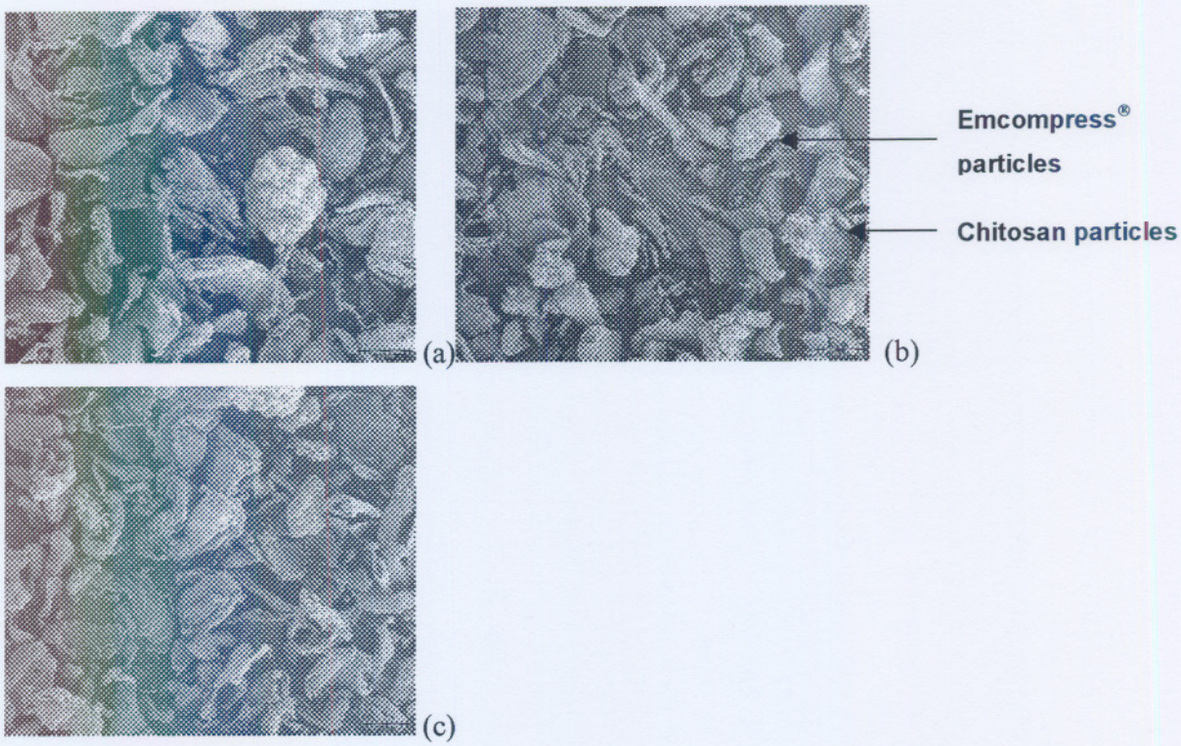


Figure 3.2: *SEM micrographs of chitosan: Emcompress® in a ratio of 70:30 with mixing time of (a) 5 minutes; (b) 10 minutes and (c) 20 minutes.*

A distinctive difference in particle shape could be seen. The mixing capacity could also be seen for the different mixing times. According to the blending theory, enough time should be allowed so that the probability of a specific particle being found at any given place within the mixture will be the same for all particles in the mixture and at any given area of the mixture. In fig. 3.2(a), the mixture does not seem as uniform after 5 minutes as it did after 10 minutes (b) where the Emcompress® particles could be seen throughout the mixture. In (c), fragmentation of the particles occurred and it could thus be deduced that, on this scale, 20 minutes was too long a mixing time.

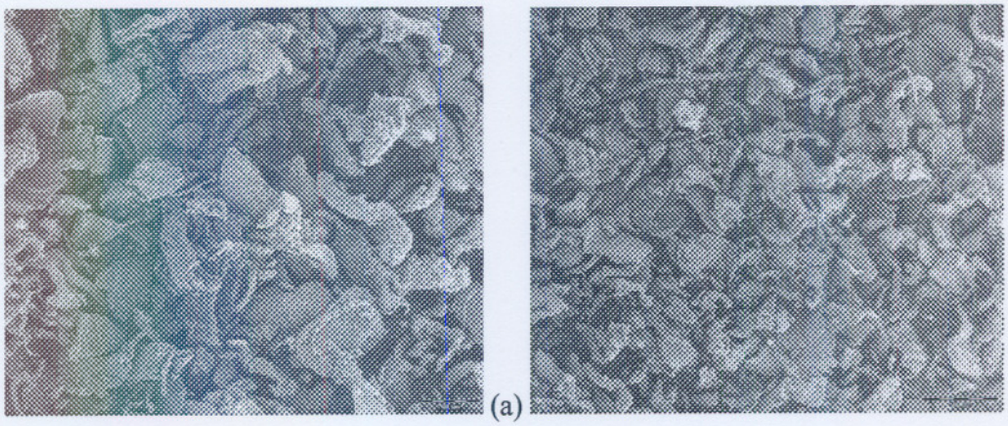


Figure 3.3: *SEM micrographs of chitosan: Emcompress® in a ratio of 90:10 with mixing time of fig. 3.2 (a) 10 minutes; and (b) 20 minutes.*

Chitosan has a very low bulk density and tapped density (table 3.1) and this appearance explains the less dense, more porous particle packing at this high ratio. In figure 3.3 (a) and (b) the unusual particle structure of chitosan could be seen. This highly porous tablet structure was seen in the low tablet weight and crushing strength when compared to the other formulations.

3.4 Conclusion

Chitosan has an irregular structure and thus produced a porous particle compact structure with unacceptable properties, yet the inclusion of an additional filler in a very minute quantity, in this case, Emcompress®, fascilitated direct compression. At a constant die filling volume and compression setting, these two filler blends showed very low weight variation and low variation in crushing strength. The crushing strength did, however, decrease with an increase in chitosan concentration. These results confirmed the weak flow properties of chitosan and its inability to be directly compressed without the aid of an additional excipient. Friability was extremely low for all formulation with values as low as 0%. It could thus be concluded that the addition of a small percentage of filler to a chitosan powder mixture enhances the binding capability and thus compressibility of these two powder blends. Disintegration occurred only in the 90:10 formulations

possibly due to the high concentration of chitosan and the consequent low compressibility. The absence of disintegration in the other formulas confirmed the gelling tendency of chitosan and its possible use in controlled-release dosage forms. The properties of chitosan allowed for a smooth ejection during the compression cycle and thus the exclusion of a lubricant.

It was concluded that chitosan is an excellent excipient for direct compression when used with an additional filler, even if only in a small proportion. It could be tableted without a lubricant, which sets it apart from other directly compressible excipients. However, the binding properties of chitosan when intended for sustained release, especially when a water-soluble drug is used, becomes challenging and thus supports the inclusion of a dry binder. The effect of this step in the formulation process will be further examined in the following section.

3.5 Incorporation of a dry binder

The previous section evaluated the tableting properties of chitosan with the aid of a single excipient. Chitosan showed low crushing strength with an increase in concentration especially above 70%. It was therefore necessary to evaluate the effect of a dry binder on the tableting properties of chitosan as well as its ability to form a matrix system. Chitosan is a cationic polyelectrolyte with excellent gelling properties in an acidic environment. This property has made it a widely used pharmaceutical excipient in controlled-release drug technology (see section 1.2). However, this is only true for poorly-soluble drugs. Therefore, the use of a freely soluble drug also supports the incorporation of an additional binder, preferably one that is commonly used in the formulation of hydrophilic matrices.

3.5.1 Hydrophilic polymer excipients

The use of hydrophilic polymer excipients has been extensively documented. One specific excipient that is especially common in controlled release dosage forms and the

choice for this study is hydroxypropylmethylcellulose, now known as hypromellose, which is a non-ionic polymer.

The Methocel® K premium grade was used, because it is the first choice in the formulation of sustained-release dosage forms due to its rapid relative rate of hydration. According to Colorcon the recommended guidelines to formulate a robust modified release matrix is to use at least 20% and preferably 30% Methocel® in a formulation producing a relatively simple process. Formulation composition, mixture preparation and tableting were described in section 2.5.2. The ratio of chitosan:Emcompress® was 90:10 for all formulations and the mixing times were kept constant at 10 minutes. This allowed the concentration of chitosan to vary between 60 and 70%, thus ensuring maximum concentration of chitosan within the mixtures. Once again, the mixture allowed smooth ejection of tablets during the tableting process and a lubricant was excluded. The tablets were evaluated in terms of tablet hardness, weight variation, friability and disintegration as discussed in section 2.6. Table 3.3 shows the physical properties of these formulations.

Table 3.3: *Physical properties of HPMC formulations. Disintegration is measured according to the degree of swelling. %RSD is shown in parentheses.*

Binders	Tablet Property	Methocel® Concentrations(%w/w)		
		20	25	30
K100M	Hardness (N)	87.9 (4.395)	96.19 (4.222)	119.92 (5.344)
	Average weight (mg)	208.2 (1.652)	212.1 (1.710)	216.6 (1.904)
	Friability (%)	0.164	0.066	0.323
	Disintegration (min:s)	Extensive	Relative	Negligible
K4M	Hardness (N)	87.98 (10.059)	104.23 (13.501)	153.76 (5.465)
	Average weight (mg)	212.0 (3.667)	218.9 (2.053)	226.7 (5.513)
	Friability (%)	0.16	0.036	0
	Disintegration (min:s)	Slight	Negligible	Negligible
K15M	Hardness (N)	101.04(14.87)	116.65 (5.7475)	137.83 (8.777)
	Average weight (mg)	214.3 (2.321)	218.1 (2.554)	224.5 (1.725)
	Friability (%)	0	0	0
	Disintegration (min:s)	Negligible	Negligible	Negligible

3.5.1.1 Crushing strength

The poor compressibility of chitosan and the improvement in crushing strength due to the addition of a dry binder is clearly demonstrated in figure 3.3. The percentage increase in crushing strength ranged from 100-600 % for the various binders and concentrations used. An increase in binder concentration resulted in a steady incline in crushing strength for all three binders with Methocel® K15M producing the strongest tablets at each concentration.

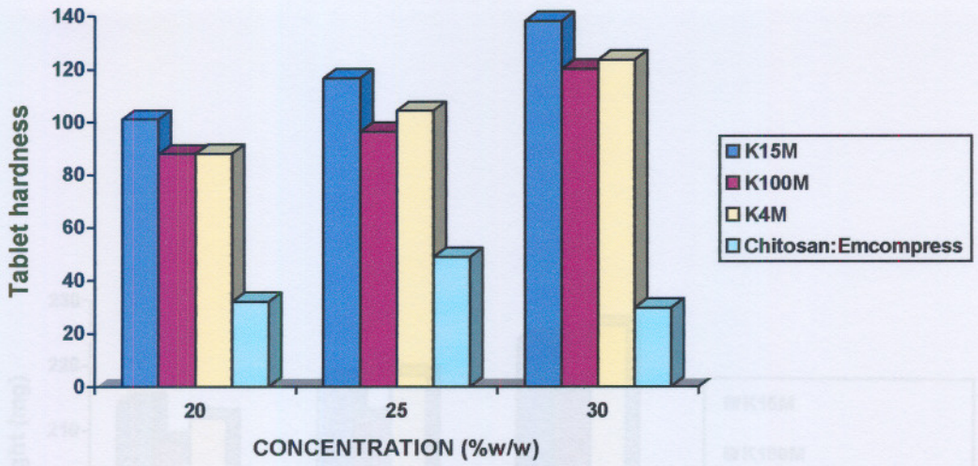


Figure 3.3: *Comparison between the tablet strength of chitosan placebo tablets and that of formulations containing a dry binder.*

It could therefore be concluded that if chitosan is to be used as the primary filler and sustained-release excipient in a directly compressed formulation, then an additional hydrophilic binder is necessary to facilitate this.

3.5.1.2 Weight variation

An improvement in weight variation was seen with the incorporation of the binder. This confirmed that the addition of the binder also improved the fluidity of the powder mixture. The % RSD was low for K15M and this grade was deemed more favourable than the other grades with regards to fluidity and compressibility. The average weight for the various batches increased with the presence of a binder in comparison with the average weight of the chitosan:Emcompress® formulation. Figure 3.4. showed the difference in average weight for the various formulations and how this differed from the intended tablet weight of 300 mg.

varied between extensive, relative, slight and negligible. The fact that swelling took

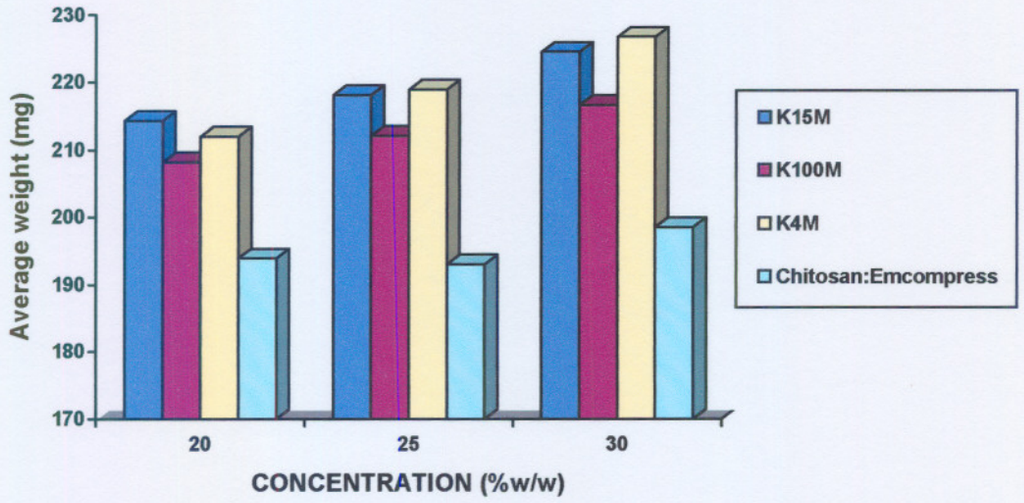


Figure 3.4: *Comparison between the average weight of binder formulations and chitosan placebo tablets.*

From the graph it was seen that not only was the average weight of the binder formulations higher than that of the chitosan placebo tablets, but it was also observed that the average weight of the binder formulations increased with increasing concentrations of each binder.

3.5.1.3 Friability

Friability was low for all formulations confirming the high resistance of the tablet to mechanical stress. The results found for the chitosan placebo tablets were between 10 and 80% when compared to the binder formulations. Therefore, the binding capability was improved and the binder formulations delivered friability values as low as 0% (see table 3.3).

3.5.1.4 Disintegration

Disintegration was measured according to the degree of swelling. The disintegration varied between extensive, relative, slight and negligible. The fact that swelling took

place is a positive result, because both polymers, i.e., chitosan and hypromellose have mechanisms of hydration and the formation of a gel matrix. The extent or degree of swelling, however, could have a favourable or adverse effect on drug dissolution. Bearing in mind that a freely soluble drug is being used, extensive swelling would in theory result in a quicker contact of drug with medium and this could increase the rate of drug dissolution and a negligible degree of swelling could result in inadequate or even no drug release with an unacceptable dissolution rate. Therefore, the acceptable degree of swelling for the matrix is yet to be determined.

These results shows that HPMC is widely used due to its rapid hydration, good compressibility and gelling characteristics, along with its ease of use, availability and very low toxicity (Khanvilkar *et al.*, 2002:602). Therefore, when used in conjunction with chitosan, the combined matrix-forming ability of these two polymers would quite possibly result in adequate drug dissolution.

3.5.2 Conclusion

Three viscosity grades of HPMC were incorporated in these formulations and all three proved to be acceptable binders for the intended matrix. Chitosan is still in the largest proportion and would thus have a greater influence on the eventual drug dissolution.
The intent is to include chitosan in the largest proportion and thus consider the lowest possible concentration of HPMC. Thus far, the various binders were ranked as K15M > K4M > K100M, because at a concentration of 20% w/w, K15M still produced the highest crushing strength, lowest weight variation and lowest friability. The favourable results produced by K15M were assumed to be because of its high viscosity. A greater comparison could be seen for the results obtained with K4M and K100M. These binders have been confirmed to have excellent sustained-release properties at high concentrations therefore, it can only be assumed that the rank order mentioned above also depicts the rate of drug dissolution for the different grades. Incorporation of a binder at this stage of the formulation process was the logical step.

The tablet properties discussed in this chapter may be affected or even completely altered with the addition of an active ingredient. The following chapter investigates the effects of the API (active pharmaceutical ingredient) on the results obtained thus far.

CHAPTER 4
CHITOSAN AS A DRUG DELIVERY SYSTEM: FORMULATION VARIABLES AND THE EFFECT THEREOF ON DRUG RELEASE.

4.1 Introduction

Chitosan's ability to fascilitate sustained-release and act as a matrix carrier has been well documented. Chitosan has been included in matrix formulations by means of coating and granulation (Koizumi *et al.*, 2001:277). The results found thus far illustrated a definite potential for chitosan to produce sustained-release by means of direct compression. The physical properties of the drug used in this study may alter the physical properties of the powder mixture. The particle size and therefore fluidity of the powder, as well as the quantity of drug in the mixture would be determining factors in this formulation. The drug:polymer ratio plays an important role in the rate of drug release, especially since the drug used is a freely water-soluble drug.

4.2 Incorporation of active ingredient

The motivation for the choice of propranolol hydrochloride as active ingredient was given in chapter 2 (section 2.2). Commercial slow-release formulations containing this drug contain either 80 or 160 mg per tablet. In this study it was decided to use a drug dose of 160 mg.

4.2.1 Effect on basic formulation

Mixtures containing chitosan and Emcompress® (90:10) and the various binders (20 or 25% w/w) were prepared and 9 mm flat-faced tablets with an avergage weight of 300 mg were produced as described in section 2.5.2. Tablet evaluation was done according to the procedures described in section 2.6.

All the formulations produced tablets that were extremely brittle after ejection. Since the basic formulation (chitosan, Emcompress® and binder) did not present this problem, the change in tablet properties could be attributed to the effect of the active ingredient and possibly due to the high drug content (53,33% w/w). The drug exhibits very poor flow properties and from the SEM study done (see figure 2.1) the variation in particle size provided a partial explanation for the tableting problems.

In an attempt to rectify the problem, the tablet was increased to 450 mg (thus reducing the drug content to 35.56% w/w), biconcave punches were used and the die diameter was increased to 10 mm. Although these changes produced harder tablets, tablet ejection was suddenly accompanied by a screeching sound and picking and sticking were observed. These problems clearly indicated die-wall friction.

4.2.2 Measures taken to improve tablet properties

4.2.2.1 Incorporation of a lubricant and glidant

Due to the observed die-wall friction, a lubricant was introduced into the formulation. Lubricants are an essential tableting auxillary and are incorporated into tablet formulations to ease tablet ejection (reducing die-wall friction), and to prevent excessive wear on dies and punches (refer to section 1.7.1). Magnesium stearate (0.5% w/w) was used.

Glidants are used to improve powder flow. It adheres to particle surfaces resulting in a reduction in the roughness of these surfaces. Silicone dioxide (silica) in a concentration of 1% w/w was included.

4.2.2.2 Changing the binder concentration and binder type

The next step was to reduce binder concentration to 15% w/w, and a different binder was also introduced, namely Kollidon® SR. The properties of this binder and its particular use in sustained-release formulations were discussed in section 1.7.2. Polyvinylpyrrolidone (PVP) is a popular binder, first developed as a plasma substitute in World War II, it is unreactive and is soluble in both water and alcohol (Seth *et al.*, 1980:126).

4.2.2.3 Changing the chitosan:Emcompress® ratio

Finally, in an attempt to prevent possible flow problems and to ensure sufficient binding properties the chitosan: Emcompress® ratio was changed to 80:20.

Despite all these changes, chitosan still remained the major component in the formulation (38.36% w/w) and could therefore be seen to act as a filler, binder and matrix carrier.

The composition of the final formulations is presented in table 2.5 (section 2.5.4). The results of the physical evaluation of the final formulations are presented in table 4.1.

Table 4.1: *Crushing strength, friability and disintegration of the various phases in the formulation process. The intermediary phases are represented where no data was found due to capping. %RSD is given in parentheses.*

Excipients concentration %w/w			Physical properties		
			Crushing strength (N)	**Friability (%)**	**Disintegration Time (min.)**
			Initial phase Chitosan:Emcompress (90:10)		
			No data	No data	No data
Binder	**Lubricant**	**Glidant**	**Final phase Chitosan:Emcompress (80:20)**		
K15M	**MgSt**	**SiO_2**			
15	0.5	1.0	146.49 (5.64)	0.083	Slight swelling
20	0.4	1.0	No data due to sticking and capping		
25	0.6	1.0			
K4M	**MgSt**	**SiO_2**			
15	0.5	1.0	142.6 (5.15)	0.073	Slight swelling
20	0.4	1.0	No data due to capping and sticking		
25	0.6	1.0			
K100M	**MgSt**	**SiO_2**			
15	0.5	1.0	141.21 (9.72)	0.083	Slight swelling
20	0.4	1.0	No data due to capping and sticking		
25	0.6	1.0			
KSR	**MgSt**	**SiO_2**			
15	0.5	1.0	194.86 (3.45)	0.075	Biconcave lost
20	0.4	1.0	No data due to capping and sticking		
25	0.6	1.0			

*K15M, K4M and K100M: Methocel® grades; *KSR: Kollidon®SR; *MgSt: magnesium stearate; *SiO_2: silica.

The tablet properties followed the same trend as was found with the tracer tablets. Tablets with high crushing strengths and very low friability were produced. Kollidon® SR

produced stronger tablets with a better disintegration compared to the Methocel® grades. The binders were included in a very low concentration for matrix formation and higher concentration failed in producing pharmaceutically acceptable tablets. Literature indicates that Methocel® should be present in a quantity of between 20 and 35%, whilst the Kollidon® SR concentration should be proportional to drug concentration to achieve sustained release when a water-soluble drug is used. The dissolution profiles discussed later in the chapter will illustrate whether the matrix-forming ability of chitosan compensates for the low binder concentration and perhaps produce a successful polymer blend.

4.2.2.4 Fluidity

From the initial to the final phase of formulation, the tablets improved from being pharmaceutically unacceptable to producing results that meet all the standard requirements of tableting (see table 4.1). The various batches showed a high consistency in average tablet weight, which confirmed the improvement in fluidity of the tablet mixture. Kollidon® SR produced tablets of a higher tablet weight, because this binder has excellent properties, high binding capability and compressibility (see section 1.7.2).

4.2.2.5 Crushing strength

As mentioned earlier, in the final phase the binder was decreased to 15% w/w and the chitosan content increased (due to an increase in tablet weight from 300-450 mg) and the mixture produced tablets with high crushing strength when compared to previous studies (refer to section 3). This confirmed the potential binding properties of chitosan that necessitate a small quantity of an additional binder. The Kollidon® SR formulation produced much higher crushing strengths (as discussed in section 1.7.2) which was expected when a soluble drug is used, due to the combination of the highly plastic polyvinyl acetate and a strongly binding povidone material providing a higher compressibility for this powder (Buhler, 2003:249).

4.2.2.6 Disintegration

The disintegration varied from batch to batch. The lowest viscosity grade, K100M, produced the highest degree of swelling compared to the other Methocel® grades although the swelling was still relatively low. K4M showed swelling that compared slightly to K100M, both forming a muffin-like shape when swelling. K15M had the lowest degree of swelling being the highest viscosity grade. Kollidon® SR showed no swelling, but rather disintegrated along the biconcave surfaces leaving a flat disc-like shape after 15 minutes. Kollidon® SR is insoluble in water, thus its ability to disintegrate even slightly in de-ionised water only shows that it does not have the same synergistic effect with chitosan when forming a matrix system as chitosan does with Methocel®.

4.2.2.7 Friability

The friability was as low as 0.074 % which showed the excellent resistance of the tablets to mechanical stress. The low friability values also confirmed the high compressibility of the tablet mixture.

4.3 Conclusion

The steps taken from the initial phase to the final phase improved the properties of the tablet mixture in such a way tablets with excellent tablet properties were produced. The fluidity was improved, high crushing strengths and compressibility was delivered and negligible weight variation when compared with the average weight was seen. At this stage, the formulation has definite potential for sustained release, confirmed by the absence of disintegration due to the gelling tendency of the hydrophilic polymers. The following discussion will illustrate the rate of drug release by means of dissolution profiles.

4.4 Dissolution studies

4.4.1 Introduction

Dissolution is the act of dissolving. The rate of dissolution or drug release is the rate of dissolving of a medicament from the solid state (Wagner, 1970:32). Under usual conditions the dissolution of the drug occurs from the fine particles as well as partial. In a matrix system, however, the tablet stays in tact and the dissolution occurs through diffusion of the gel layer that is formed when the matrix tablet comes into contact with fluid under suitable conditions (refer to figure 1.4). Lee and Robinson (1994:910) described a matrix device as one in which dissolved or dispersed drug is distributed uniformly in an inert polymeric matrix. A drug with a slow dissolution rate will yield an inherently sustained blood level. In principle, then, it would seem possible to prepare controlled-release products by controlling the dissolution rate of drugs that are highly water-soluble. This can be done by preparing an appropriate salt or derivative, by coating the drug with a slowly soluble material, or by incorporating it into a tablet with a slowly soluble carrier. Ideally, the surface area available for dissolution must remain constant to achieve a constant release rate. This is, however, difficult to achieve in practice (Lee & Robinson, 1994:911).

In this study, propranolol hydrochloride was used, a drug already prepared as a salt. The matrix carrier was chitosan, which is insoluble in water and was used in combination with a small percentage of a hydrophilic polymer binder. The drug was not coated, but incorporated along with other excipients and directly compressed. The dissolution profiles could be used to illustrate the extent of control of release of this freely soluble drug under above mentioned conditions and also chitosan's competency as a matrix carrier. From the dissolution data, two dissolution parameters were calculated, namely DR_i (indicating the initial drug dissolution) and the AUC (representing the extent of drug dissolution) (see section 2.9.2.1). These results are presented in table 4.2.

Table 4.2: *The AUC and DR_i of propranolol hydrochloride tablets with different hydrophilic binders in addition to chitosan in constant proportion. %RSD shown in parentheses.*

Binder type	Dissolution properties	
	DR_i ($\mu g.cm^{-3}.min^{-1}$)	AUC ($\mu g.min.cm^{-3}$)
Kollidon® SR	0.543 (4.44)	75610.60 (0.93)
Methocel® K100M	0.335 (1.07)	59831.07 (0.89)
Methocel® K4M	0.275 (3.44)	23640.49 (4.01)
Methocel® K15M	0.325 (9.48)	59507.44 (4.41)

4.4.2 Dissolution profiles

The first dissolution studies were done on the previously evaluated tablets using an acidic medium consisting of 0.1 M HCl at 50 rpm with a pH of 1.2. The dissolution profiles for the four formulations are illustrated in figure 4.1.

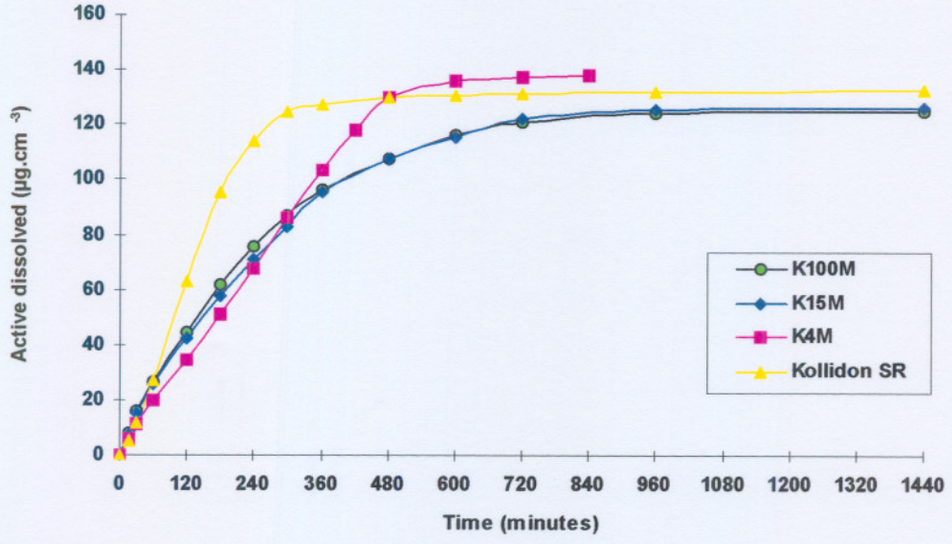
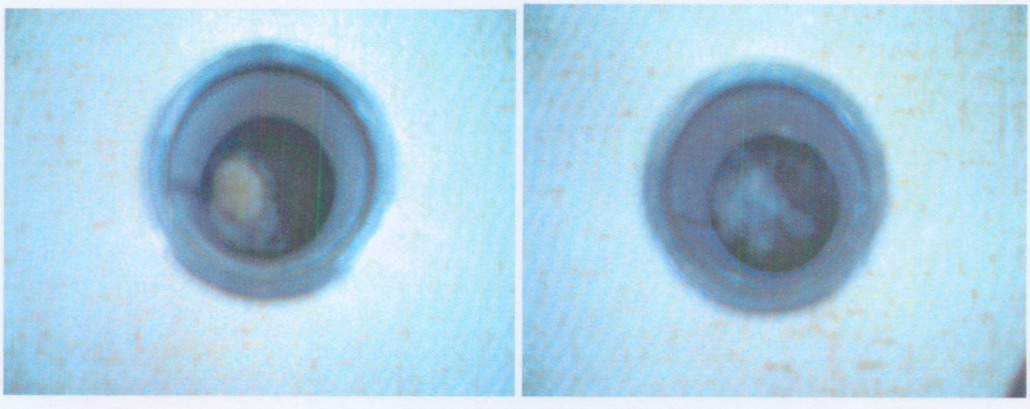


Figure 4.1: *Comparitive profiles of propranolol hydrochloride formulations containing various binders.*

As mentioned in section 1.5.1.2, in a chitosan formulation, slow-release is easily achieved with poorly soluble or slightly soluble drugs, whereas additional slow-release excipients are required with readily soluble drugs.

As seen in table 4.2., greater initial dissolution for Kollidon® SR than for the hypromellose binders with a consequent greater AUC or extent of dissolution. However, from the dissolution profile in figure 4.1 it was seen that the ability to retard or sustain drug release was a lot weaker for Kollidon® SR than for the hypromellose binders. After 5 hours the tablets containing Kollidon® SR had almost completely disintegrated. A stringed transparent network and a clearly visible white residue or precipitate could be seen. The integrity of the matrix was compromised by the combination of chitosan, because the binding forces between these two binders were very weak and synergistic effect was not obtained and as discussed earlier, Kollidon® SR is insoluble in water and is independent of the pH of the medium. However, the parameters of Kollidon® SR require an amount of at least 40-55% of the binder in a formulation where a freely soluble active ingredient is used (see table 1.1). In this formulation only 15% w/w of the binder was used and up to 7 hours of sustained release was still achieved. This proved that chitosan was responsible for the sustained release and the properties of Kollidon® SR compromised the integrity of the matrix. Figure 4.2 (a) and (b) shows digital photographs taken at 4 and 7 hours of the dissolution test, respectively.



(a) (b)

Figure 4.2: (a*) Tablet after 4 hours and (b) after 7 hours in the acidic medium.*

In figure 4.2 (a) an off-yellow center remains which confirmed the weak binding force of chitosan and Kollidon® SR, because the Kollidon® SR seemed to have disintegrated and the gel matrix formed in the centre of the tablet was the chitosan. Therefore also confirming that the drug was encapsulated in this gel matrix and that chitosan enabled sustained release. This appearance also confirms that chitosan does not have to be blended with a hydrophilic polymer to aid sustained release. Figure 4.2 (b) shows white fibrinous network, which is the remainder of a compromised matrix tablet. For this formulation, the average drug released was 78.49 %. Thus, a large extent of drug release was achieved, but over a shorter period of time. Drug release continued steadily for up to 7 to 8 hours until it stabilized.

4.4.2.1 Formulations containing various grades of hypromellose

As seen in table 4.2, the formulations containing the hypromellose binders showed very similar initial drug release profiles but variable extent of drug release was seen. The profiles in figure 4.2 showed how drug release was affected when these binders were chosen to enhance the sustained release ability of chitosan. The initial swelling of the tablet was negligible, but as time passed the swelling became extensive and a gel layer could clearly be seen.

It was assumed, that drug release was sustained by diffusion through this gel layer. When the polymer is highly hydrophilic, the rate of absorption of fluid is very large and the dosage form swells, and this swelling is responsible not only for an increase in the dimensions of the dosage form, but also for a very large increase in the diffusivity which enhances the rate of drug release especially at the end of the process. When the swelling is negligible, the diffusion of the drug out of the dosage form can be constant over the whole process of release (Aïnaoui & Vergnaud, 2000:384). Ford *et al.* (1987:224) found that the major factor controlling drug release was the drug:HPMC ratio and for soluble drugs a straight line relationship existed between the release rate and the reciprocal of the weight of HPMC in the matrices. Increasing the polymer content decreased the dissolution rate of the drug. Ford *et al.* (1985:339) said that a straight line relationship

was established between the logarithm of the tablet HPMC content and the logarithm of the release rates ($mg.min^{½}$) and it has been suggested that this relationship has been accounted for by considering that the weight of HPMC directly influences the surface area of the matrix which in turn controls the release rate. Changes in drug particle size insignificantly affected drug release. The actual mechanism of release from HPMC matrices and therefore also hydrophilic matrices, is modified by drug solubility. For water-soluble drugs, release is affected by both diffusion of the drug through the HPMC and by slow dissolution of the matrix itself following hydration, a process known as attrition. Release rate is not modified by the presence of magnesium stearate (as lubricant).

4.4.2.1.1 Methocel K100M

This grade, having a viscosity of 100 cps, had the lowest viscosity of the grades chosen. Thus, a lower sustained release was expected. However, the integrity of the matrix was vastly improved by the presence of chitosan. Chitosan was the primary filler and matrix carrier system, being present in a quantity of 38.36% w/w.

Steady drug release was achieved for up to 16 hours before stabilizing as seen in the above profile. The profile had a %RSD of 0.892 for the extent of drug release (AUC), which can be seen in the low variation among the different test samples. At 8 hours the tablet was still present in the baskets thereafter slow disintegration and dissolution of the tablet occurred. An amount of 62.143% drug was released during this study, but great variation among samples occurred. Beaker 1 only released 23.663% drug where as the other three beakers had an average release of 75% with very little variation.

4.4.2.1.2 Methocel K4M

This grade possesses a viscosity of 4.000 cps. Sustained release was successfully achieved in this formulation as shown in figure 4.4. The extent of drug release (AUC) was 23640.49, which were much lower than for the other hypromellose grade and showed

a %RSD of 4.007. The total drug released during this dissolution study was a mere 9.262%, which is not only low, but also inexplicable. The profile stabilized after 10 hours and the study was discontinued at 14 hours. This formulation has shown the lowest total drug release for all formulations studied. It was assumed that an experimental error had occurred.

As seen above, the initial drug release is as steady as for the other profiles and stabilizes at 10 fours. Digital photographs were taken at 4 and 7 hours as shown in figure 4.3 (a) and (b), respectively.

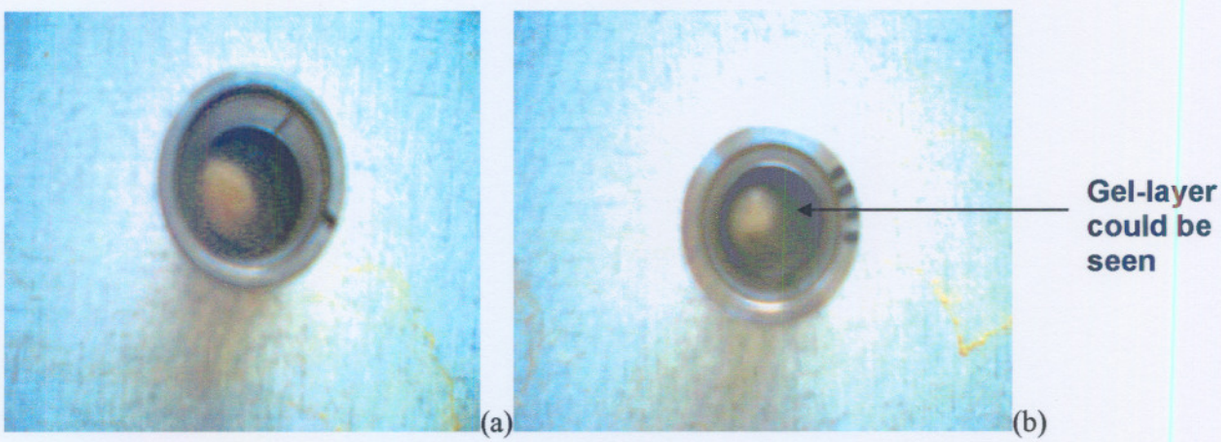


Figure 4.3: *(a) Tablet at 4 hours and (b) at 7 hours. At 7 hours a slight gel layer could still be seen.*

4.4.2.1.3 Methocel K15M

This grade has a viscosity of 15,000 cps and has showed the most favourable results for the duration of this study. The high viscosity of this grade had an excellent synergistic effect with chitosan and 24-hour dissolution was obtained. At 9 hours an extensively swollen sponge-like structure was still visible and at 12 hours this structure was slightly diminished. At the 16-hour reading a small portion of the tablet was still visible.

The total drug release for this formulation was 61.497%. However, the same variation in

beaker 1 occurred leaving the remaining three beakers with an average of 74%. It was thus concluded that an experimental error had occurred in beaker 1. This conclusion was supported by the fact that for all formulations beaker 1 had a total drug release between 20 and 25% compared to above 70% for the other beakers.

From the above profiles it was clear that chitosan used with Methocel K100M and K15M, produced the highest degree of sustained release and is therefore the preferred excipients when a freely soluble drug is used in a sustained released chitosan formulation. The ranking order for excipients used in combination with chitosan is thus K15M>K100M>K4M>Kollidon® SR.

4.5 Conclusion

Khanvilkar *et al.* (2002:604) used a freely soluble drug and both diffusion and attrition contributed to its release from HPMC matrices. Their findings were in agreement with Ford *et al.* (1985:339) who reported that using various viscosity grades of HPMC for a given fixed drug:HPMC ratio did not alter the Higuchi-type release rate significantly. They have therefore concluded that the viscosities of the hydrated higher-molecular-weight HPMC matrices may be identical despite the apparent differences in their viscosity grades. Drug release from these tablets depended on the viscosity of the gel layer formed from the hydrated matrix. It was concluded that drug release from HPMC matrices prepared by direct compression was independent of crushing strength, diffusion controlled and depends mostly on the viscosity of the gel layer.

The findings of the study supported Khanvilkar's conclusions. However, the primary polymer used was chitosan. The amount of drug released was above 60% bearing in mind that discrepancies were found in beaker 1 of all test samples. It can be concluded that drug release took place through diffusion through a gel layer of a matrix system, because the tablet was still partially intact after many hours. The grade of chitosan had a 91.43% degree of acetylation. Sabnis *et al.* (1997:253) suggested that drug release decreased as degree of deacetylation increased.

Chitosan is said to have a more pronounced decrease in drug release in acidic medium and it was previously suggested that chitosan would precipitate out of solution if it were placed in a medium with higher pH. The following study will investigate the effect of pH, if any, on the dissolution rate of chitosan formulations.

4.6 Effect of pH on drug release

For the second phase of the dissolution study, an analysis was done based on the possible effect of pH on drug release from chitosan formulations. At acidic pH values the amino groups become protonated, causing the chitosan to uncoil and become more soluble. As pH values increase above its pK_a of approximately 6.5, chitosan loses this charge, coils up and is likely to precipitate from solution. This was the finding of Schipper *et al.* (1996:1687). However, as the previous studies have shown, with the aid of an additional slow release excipient, it is possible to retain the matrix for up to 6 hours at acidic pH. In this study, the same formulas were used and placed in an acidic medium of pH 1.2 for the first 2 hours. It was then removed from the medium and promptly placed in a second medium, a phosphate buffer of pH 6.8. According to literature, as it has just been mentioned, chitosan is expected to precipitate out of solution. However, the results contradicted these findings.

Kawashima *et al.* (1985:2473) found that chitosan decreased dissolution rates at acidic and slightly acidic pH levels while Akbŭga (1993:259) found that at pH levels of 7.4, chitosan displayed no slow-release properties. The conclusion was made that the effects of chitosan depended on the pH levels. The cationic nature of chitosan has been assumed to be the reason for its effects in different pH media. Mi *et al.* (1997:2502) did an extensive study on the mechanism of action of chitosan. His results showed that hydration of and gel-forming effect of chitosan took place more readily at pH values of 1.2 than at a pH of 7.2. Therefore, it could be concluded that the retardant effect of chitosan is more pronounced in an acidic environment. With regards to these findings, once again, the results of this study proved contradictory. Hypromellose itself is not

thought to be affected by changes in pH, however, the release rates from hypromellose matrices has been said to be dependent on the pH of the dissolution medium. Table 4.3 shows the initial release rate and the extent of drug release.

Table 4.3: *The AUC and DR_i of propranolol hydrochloride tablets in the first 2 hours of dissolution in acidic medium. %RSD is displayed in parentheses.*

Binder type	Dissolution properties	
	DR_i ($\mu g.cm^{-3}.min^{-1}$)	AUC ($\mu g.min.cm^{-3}$)
Kollidon®SR	0.582 (10.78)	201.813 (1.12)
Methocel K100M	0.262 (4.81)	124.570 (8.00)
Methocel K4M	0.324 (5.56)	179.442 (8.79)
Methocel K15M	0.308 (6.94)	163.744 (24.66)

Once again, Kollidon® SR shows an initial drug release that is much higher than the hypromellose binders. The extent of release at 2 hours is very low for all formulations. The following 22 hours in a medium composed of a phosphate buffer is shown in table 4.4.

Table 4.4: *The AUC and DR_i of propranolol hydrochloride tablets in the following 22 hours of dissolution in medium composed of a phosphate buffer. %RSD is displayed in parentheses.*

Binder type	Dissolution properties	
	DR_i ($\mu g.cm^{-3}.min^{-1}$)	AUC ($\mu g.min.cm^{-3}$)
Kollidon®SR	0.215 (5.587)	49974.134 (2.837)
Methocel K100M	0.055 (4.808)	22587.079 (7.810)
Methocel K4M	0.064 (6.155)	24099.675 (5.601)
Methocel K15M	0.056 (1.937)	24955.328 (6.318)

Table 4.4 shows that even in alkaline medium hypromellose is the better choice when used with chitosan. The first reading for this study was taken after 5 minutes. For Kollidon® SR the initial drug release was much higher than the hypromellose

formulations. However, the extent of release for Kollidon® SR was much higher, but as the profiles will soon show, the degree of sustained release was much lower when compared to the release rate of hypromellose. The following profiles are the release rates of the various formulations. Figure 4.4. (a) the release rate of the first two hours at a pH of 1.2 and (b) the following 22 hours at a pH of 6.8.

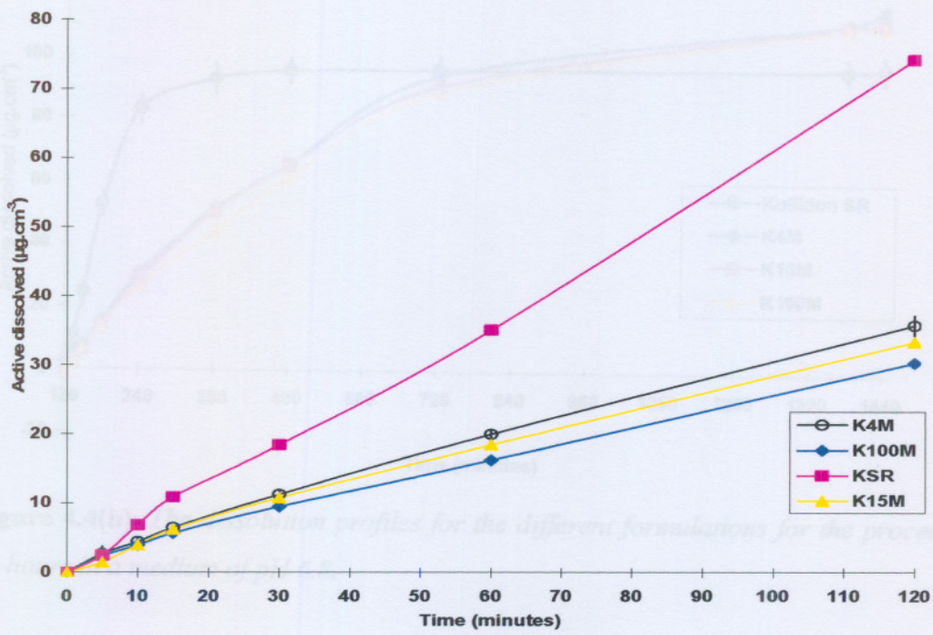


Figure 4.4: (a) *The dissolution profiles of the various formulations after 2 hours in pH* 1.2.

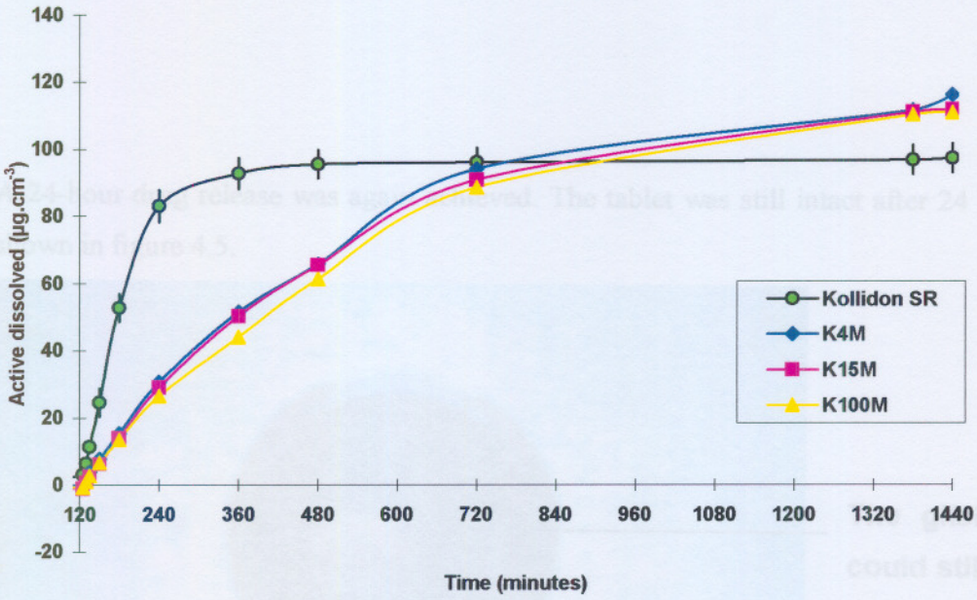


Figure 4.4(b): *The dissolution profiles for the different formulations for the proceeding 22 hours in a medium of pH 6.8.*

In both profiles Kollidon® SR has a very high initial drug release compared to the hypromellose binders which were similar in initial release rate. For Kollidon® SR drug release was stabilized after only 8 hours of the study. This is a slight improvement from the acidic medium study, but still proves that Kollidon® SR is not the first choice when a choice for additional slow release excipient for a chitosan formulation is to be made.

For K100M, a 24-hour release was achieved, with the tablet still intact after 24 hours. The binding strength between chitosan and hypromellose together with the gelling tendency of both polymers strengthened the integrity of the matrix. In a medium of pH of 6.8, the results were inconsistent with the previous studies. It could be assumed that the sum of the viscosity of the two polymers is higher than for a single polymer. Also, hypromellose has to be included in a quantity of 25-45% to be used as a matrix carrier. In this study a mere 15% w/w of hypromellose was added to 38.36% w/w of chitosan, which was the primary matrix carrier. The profiles of K15M and K4M could be compared as they showed similar results.

A 24-hour drug release was again achieved. The tablet was still intact after 24 hours as shown in figure 4.5.

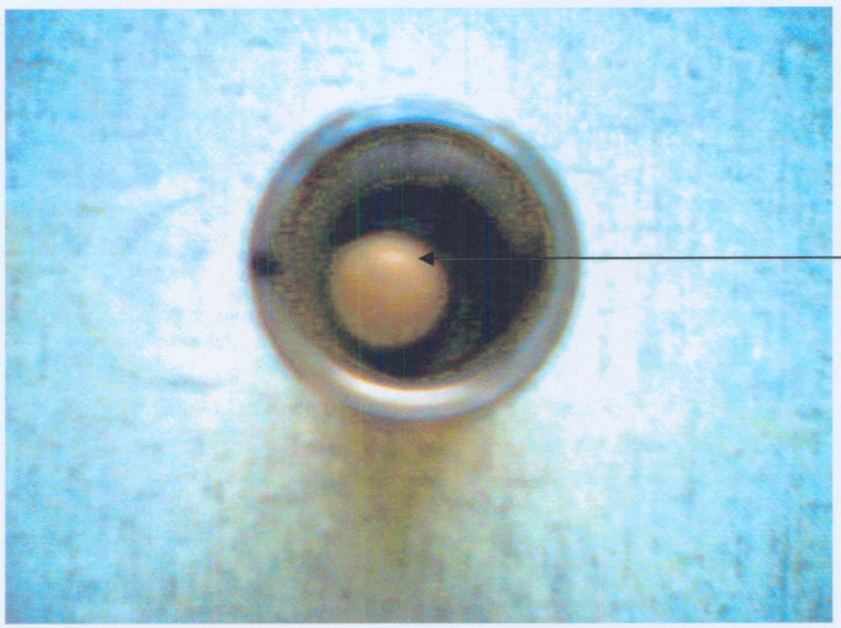


Figure 4.5: *The chitosan formulation containing Methocel K15M after 24 hours of dissolution testing in two media with different pH levels.*

The profiles for the various formulations showed very low variation compared to the previous dissolution profiles when only one medium was used. The drug release proved favourable for hypromellose rather than Kollidon® SR.

4.7 Summary

The chitosan formulations were concluded to be independent of pH, having accomplished sustained release in both media. Chitosan is an excellent matrix carrier and has great potential to be used in once-daily formulations. In study performed by Ford *et al.* (1996:333), it was concluded that the total amount of polymer included in a formulation was the main factor that controls the dissolution rate of propranolol. Propranolol hydrochloride is capable of salting hypromellose into solution and even the presence of phosphate ion may reduce the solubility of hypromellose. Thus, this may also be true for

a polymer such as chitosan. So, a freely soluble drug, in its salt form such as propranolol hydrochloride, may actually contribute to the integrity of the polymer matrix.

5 Recommendations

Oral dosage forms move into the stomach, which is acidic, to a more alkaline environment, which is the rest of the gastrointestinal tract. Bearing in mind that chitosan has a muco-adhesive property, its route through the gastrointestinal tract can only be speculated. If the tablet should adhere to the stomach wall, sustained release can be expected as already been proved in this study. If the chitosan tablet should move into the gastrointestinal tract after two hours as is expected under normal conditions, it will continue to release the drug for duration of 22 hours, ensuring a 24-hour release.

The obvious recommendation would thus be that an *in vivo* study be done to determine the route of a chitosan tablet and also if the drug released over a period of 24 hours is adequate to reach and maintain adequate therapeutic levels in the blood

CHAPTER 5
STABILITY PROPERTIES OF CHITOSAN TABLETS

5.1 Introduction

It is well known that aging of dosage forms and the storage conditions exposed to during aging have a marked effect on both the physical properties of the dosage form and the release profile (both rate and extent) of the drug from the dosage form. Furthermore, it has been reported that chitosan and especially its properties both as a powder and in solid formulations, are significantly influence by storage conditions, and more specific, temperature and the presence of moisture.

As a conclusion to this project (study), the effect of storage conditions on the physical properties of chitosan formulations were evaluated.

5.2 Physical analysis of tablets

For the stability study, the final tablet formulations, containing propranolol hydrochloride (chapter 4) was subjected to a 3-month stability test at 40 °C / 75% relative humidity (RH) and 25 °C / 60% RH. These are the normal conditions utilized during official stability testing.

Tablets were evaluated monthly and only in terms of their physical properties, namely hardness, weight variation, friability and disintegration. All results were compared to the initial properties of the formulations on the day of manufacture (designated as 0 months). The results are presented in table 5.1.

Table 5.1: *The physical properties of the propranolol hydrochloride formulations used for stability testing.*

Time (months)	Physical properties							
	25 °C / 60% RH				40 °C / 75% RH			
	Tablet weight (mg)	Crushing strength (N)	Friability (%)	Disintegration	Tablet weight (mg)	Crushing strength (N)	Friability (%)	Disintegration
	Methocel® K15M							
0	421.1(0.929)	124.39	0.106	Slight	421.1(0.929)	124.39	0.106	Slight
1	416.9(0.526)	108.01	0.067	Relative	422.4(0.634)	112.75	0.116	Relative
2	417.1(0.504)	106.55	0.048	Extensive	422.7(0.859)	104.56	0.064	Relative
3	419.3(0.775)	100.53	0.01	Extensive	421.6(0.771)	108.41	0.01	Extensive
	Methocel® K4M							
0	428.9(0.823)	131.38	0.131	Slight	428.9(0.823)	131.38	0.131	Slight
1	433.2(0.568)	108.70	0.164	Slight	432.7(0.458)	113.23	0.152	Slight
2	433.5(0.705)	106.35	0.323	Extensive	435.5(0.521)	104.86	0.290	Extensive
3	436.4(0.599)	99.83	0.000	Extensive	435.9(0.754)	105.11	0.000	Extensive
	Methocel® K100M							
0	422.0(0.652)	123.77	0.159	Slight	422.0(0.652)	123.77	0.159	Slight
1	420.4(0.623)	109.79	0.120	Slight	426.5(0.503)	109.93	0.123	Slight
2	422.5(0.510)	103.74	0.237	Extensive	425.7(0.487)	110.89	0.130	Slight
3	421.8(0.799)	99.03	0.030	Extensive	426.8(0.696)	109.09	0.010	Extensive
	Kollidon® SR							
0	458.2(1.120)	188.25	0.103	Slight	458.2(1.120)	188.25	0.103	Slight
1	463.6(1.205)	171.43	0.050	Slight	451.7(0.963)	192.41	0.031	Slight
2	465.4(0.734)	181.79	0.097	Extensive	453.6(0.715)	203.08	0.006	Very extensive
3	464.7(1.155)	179.85	0.000	Biconcave lost	452.5(0.743)	215.51	0.020	Very extensive

5.2.1 Effect on tablet weight

The effect of the storage conditions on the tablet weight of the formulations is presented in figures 5.1 and 5.2. for all the formulations containing Methocel®, a steady increase in tablet weight was observed over time at both storage conditions. This could be attributed to the uptake of moisture by the tablet components, especially chitosan and the binders.

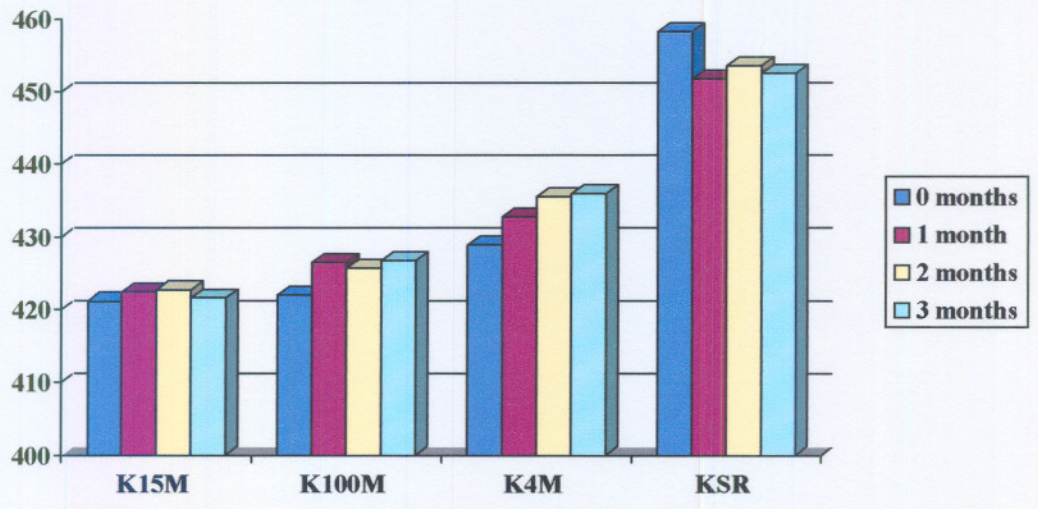


Figure 5.1: *Effect of temperature on weight variation of chitosan tablets in combination with Methocel® K15M, K100M, K4M and Kollidon® SR at a temperature of 40° C.*

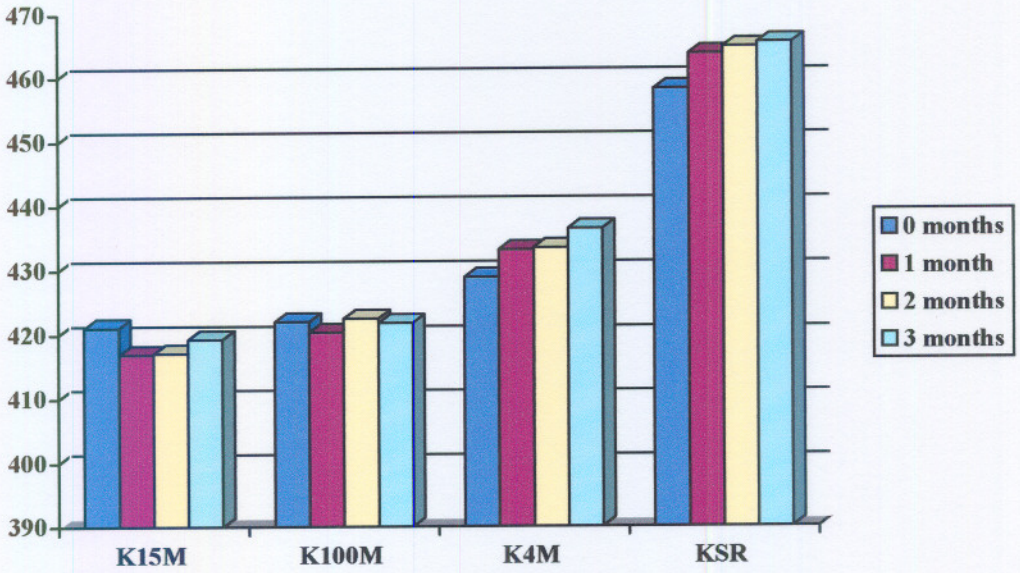


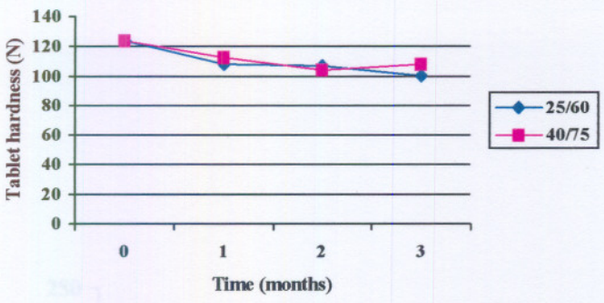
Figure 5.2: *Effect of temperature on weight variation of chitosan tablets in combination with Methocel® K15M, K100M, K4M and Kollidon® SR at a temperature of 25° C.*

For the formulation containing Kollidon® SR, however, tablet weight decreased over time at 40 °C/75% RH, whilst at 25 °C/60% RH, the tablets followed the same trend as the Methocel®, formulations. For all the formulations the first month of storage exhibited the largest change in tablet weight, followed by a smaller increase (or stabilization) in tablet weight. These results could be explained in terms of the equilibrium moisture content of the tablet components being reached within the first month, after which no more moisture was absorbed and tablet weight stabilized.

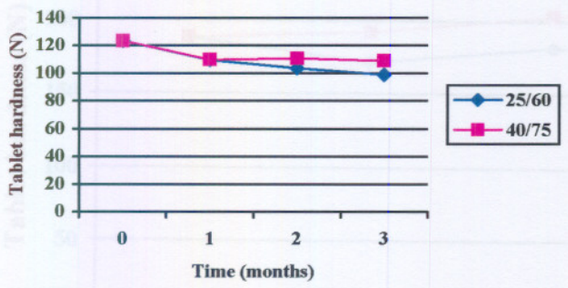
5.2.2 Effect on crushing strength

For all the formulations containing Methocel® as binder, both sets of storage conditions resulted in a decrease in crushing strength with time and all three formulations exhibited the same tendency and magnitude in terms of the decrease in crushing strength. No significant differences occurred between the two conditions for any of the formulations. The decrease in crushing strength during the first month was markedly faster (between 11-17%) than during the following two months (between 6-

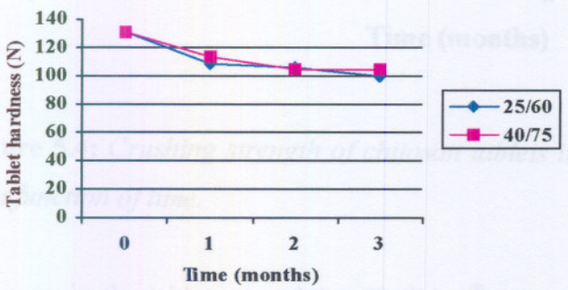
9%) as seen in figure 5.3, which indicated stabilization with time. These results are in correlation with the effect of the storage conditions on the tablet weight as explained in section 5.2.1. It could be concluded that the observed changes in crush strength could be directly related to the absorption of moisture during storage.



(a)



(b)



(c)

Figure 5.3: *Effect of storage conditions on crushing strengths of chitosan tablets containing (a) Methocel®K15M; (b) Methocel®K100M; and (c) Methocel®K4M.*

The friability of all the test samples was between 0 and 0,3 %. Thus, the ability of the tablets to resist mechanical stress was unaffected by varying ambient conditions. Therefore, there were no changes in friability with decreasing crushing strength as

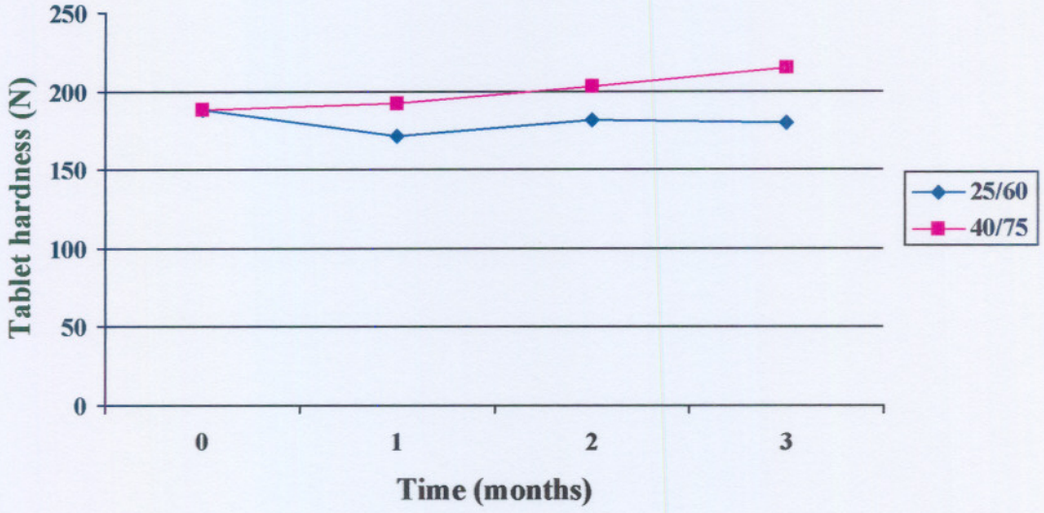


Figure 5.4: *Crushing strength of chitosan tablets in combination with Kollidon® SR as a function of time.*

Once again the tablets containing Kollidon® SR exhibited a different reaction to the storage condition as seen in figure 5.4. At 25 °C/60% RH the crushing strength initially decreased during the first month of storage, after which it slightly increased to reach an average crushing strength after 3 months comparable to the initial crushing strength (at month 0). At 40 °C/75% RH, however, the crushing strength steadily increased and was still increasing at month 3.

Concluding from the results discussed in section 5.2.1 and 5.2.2, it could be concluded that the first month of storage had resulted in the biggest change in tablet properties, after which it stabilized.

5.2.3 Friability

The friability of all the test samples was between 0 and 0,3 %. Thus, the ability of the tablets to resist mechanical stress was unaffected by varying ambient conditions. Therefore, there were no changes in friability with decreasing crushing strength as

discussed in section 5.2.2. This could be explained by the adhesive property of chitosan in that the moisture content at the various conditions increase the binding capacity of the tablet and thus did not become brittle when exposed to mechanical stress.

5.2.4 Disintegration

5.2.4.1 0 months

For all test samples there were no disintegration except for slight swelling. Kollidon® SR, however, lost its original biconcave shape and only a flat disc remained after 15 minutes. These results correlate with the original analysis done for these formulas.

5.2.4.2 1 month

After the first month in stability chambers there was very little differentiation in disintegration testing compared to 0 months.

5.2.4.3 2 months

At this stage of the experiment, the swelling became more extensive at 25/60. There was slight breaking up of the tablet. Kollidon® SR also displayed swelling with similar breaking up around the edges, but as expected, breaking up and loss of tablet shape was much more pronounced for the Kollidon® SR formulation. The formulations tested at 40/75 showed more extensive swelling with swelling more pronounced for Methocel® K100M.

5.2.4.4 3 months

Extensive swelling was seen in all formulations. There was a presentation of a muffin-like swelling which had been seen before, followed by disintegration of the

biconcave shape, although this was not as pronounced as for Kollidon® SR which resulted in a flat disk. The swollen tablet was still present after 15 minutes.

5.3 Conclusion

Weight variation proved more stable at room temperature, i.e. 25°C 60 % relative humidity. Whereas, at 40°C 75 % relative humidity an increase in tablet weight was seen which could be explained by the fact that these formulations has a tendency to swell in an environment with a high moisture content. Kollidon® SR had contradicting results in this regard. Kollidon® SR displayed an increase in crushing strength contradicting the decrease in crushing strength shown by the Methocel® grades. Followed by a subsequent decrease in average weight at room temperature. During disintegration testing, swelling became more pronounced with time and the loss of the biconcave shape for Kollidon® SR tablets. Friability tests produced values as low as 0%, showing the overall excellent mechanical strength of the tablets.

In conclusion, it can be deduced that these tablets can be stored at room temperature in a dry area and be kept away from temperatures higher than 25°C. Bearing in mind that the active ingredient, propranolol hydrochloride, is extremely sensitive to light, these tablets should be stored in amber containers and kept out of direct light. The recommendation at this stage is that a dissolution test be done and the study increased to 6 months, so that the drug release stability can be tested and also the degree of degradation, if any, of the active ingredient.

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Published work

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Comparison of chitosan formulations using different grades of Methocel®: Effect on tablet properties.

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Chitosan and Methocel® are both polymer excipients widely used in sustained-release formulations. Chitosan is a term given to a family of high molecular weight cationic polysaccharides derived from chitin that naturally occurs in crustacean shells. Methocel® (hydroxypropylmethylcellulose) is a binder and predominantly used as a hydrophilic polymer carrier. The purpose of this study is to determine the effect on tablet properties when these two polymers are combined.

All formulations contained chitosan and Emcompress® in a ratio of 90:10 respectively. Emcompress® is a widely used filler in the pharmaceutical industry due to its good flow properties and compressibility. The different grades of Methocel® used were K100M, K15M, K4M and E4M. Various grades of Methocel® exist and Methocel® K type is highly recommended as first to be evaluated when preparing a matrix formulation. The grades were incorporated in concentrations of 20%, 25% and 30% w/w. Due to the physical properties of chitosan, a lubricant such as magnesium stearate was not necessary in these formulations. The highest crushing strength was produced by Methocel® K4M grade followed by E4M, K15M and K100M at a concentration of 30% w/w. The formulations showed negligible weight variation and no disintegration took place. The absence of disintegration is considered a positive result in this case, because the concentrations used is intended for matrix formulation for sustained-release by diffusion through a gel layer. Friability was below 1% in all cases.

From the above results it can be assumed that combining these two polymer blends in a matrix formulation will deliver substantial sustained release with an appropriate drug. The drug properties should be carefully considered because extreme variation in particle size of the active ingredient and excipients will have an impact on the release rate by affecting the dissolution of the drug as well as the efficiency of gel formation. The polymer: drug ratio is also an important factor to consider in sustained-release formulations.

INTRODUCTION

Chitosan and Methocel® are both polymer excipients widely used in sustained-release formulations. Methocel® (hydroxypropylmethylcellulose) is a binder and the most common and predominantly used hydrophilic polymer carrier used in the formulation of oral controlled-release drug delivery systems(1). Chitosan has been proven to produce excellent sustained release properties in vitro, especially at low pH values where a gel matrix is formed(2). The higher the concentration of chitosan, the harder the tablets and the more the sustained the release of the drug(3).

METHODS

Tablet Formulation

➢The formulations contained chitosan (60-70%), binders and EmcompressÒ (10%)
➢The different grades of MethocelÒ used were K100M, K15M, K4M and E4M and were incorporated in concentrations of 20%, 25% and 30% w/w. ➢The tablets were prepared by direct compression using9mm flat-faced punches on an eccentric tablet press.
➢To test the effect on drug release a tracer drug was incorporated into the formula.
➢Mixtures of 36 g was prepared, producing tablets of 450 mg and 160 mg active ingredient.

Dissolution studies

➢A 12-hour dissolution was performed according to the USP six station basket method.

➢Each station contained 900ml of 0.1M hydrochloric acid as medium.

RESULTS AND DISCUSSION

➢The formulations showed negligible weight variation (Figure 1). The effect on crushing strength is depicted in Figure 2

➢No disintegration took place (which is a positive result for a matrix formulation) and friability was less than 1%.

➢A drug release of 12 hours was obtained (Figure 3). The tablets became hydrated and a gel matrix was formed. The tablet matrix remained intact for 7 hours during dissolution.

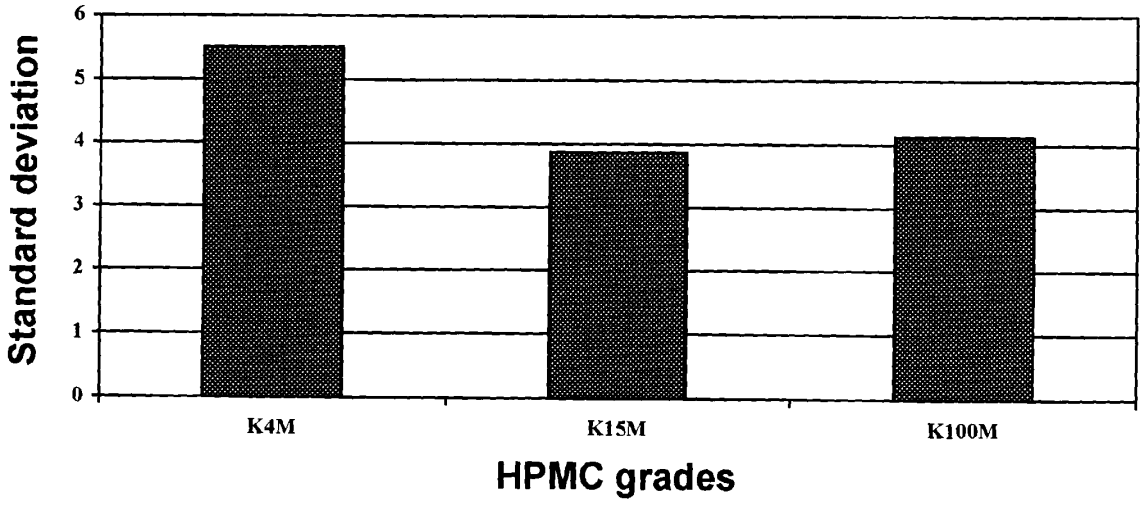

Figure 1: *Effect on weight variation of tablets containing 30% HPMC.*

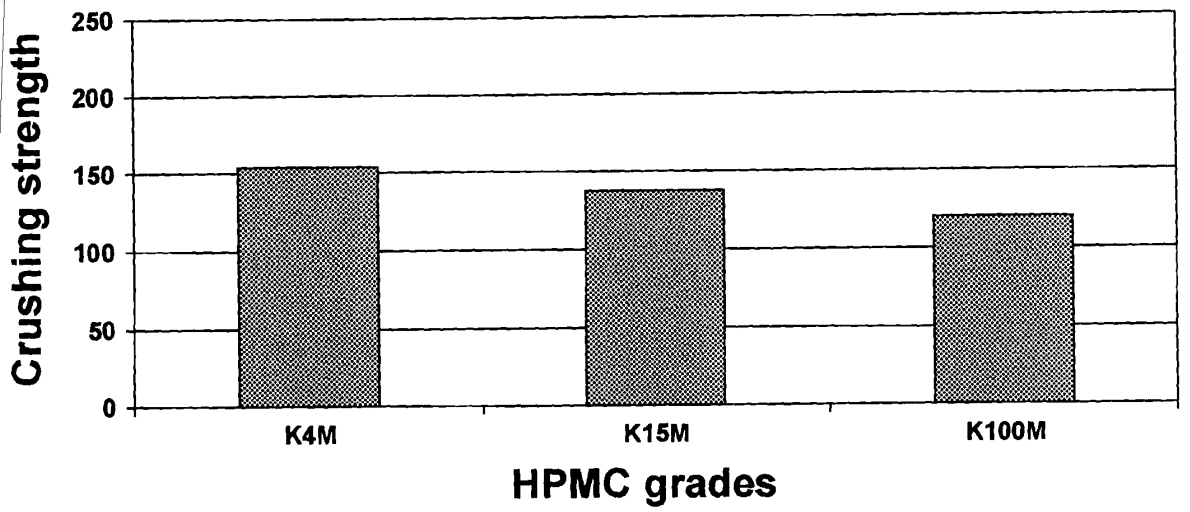

Figure 2: *Effect of 30% HPMC on crushing strength.*

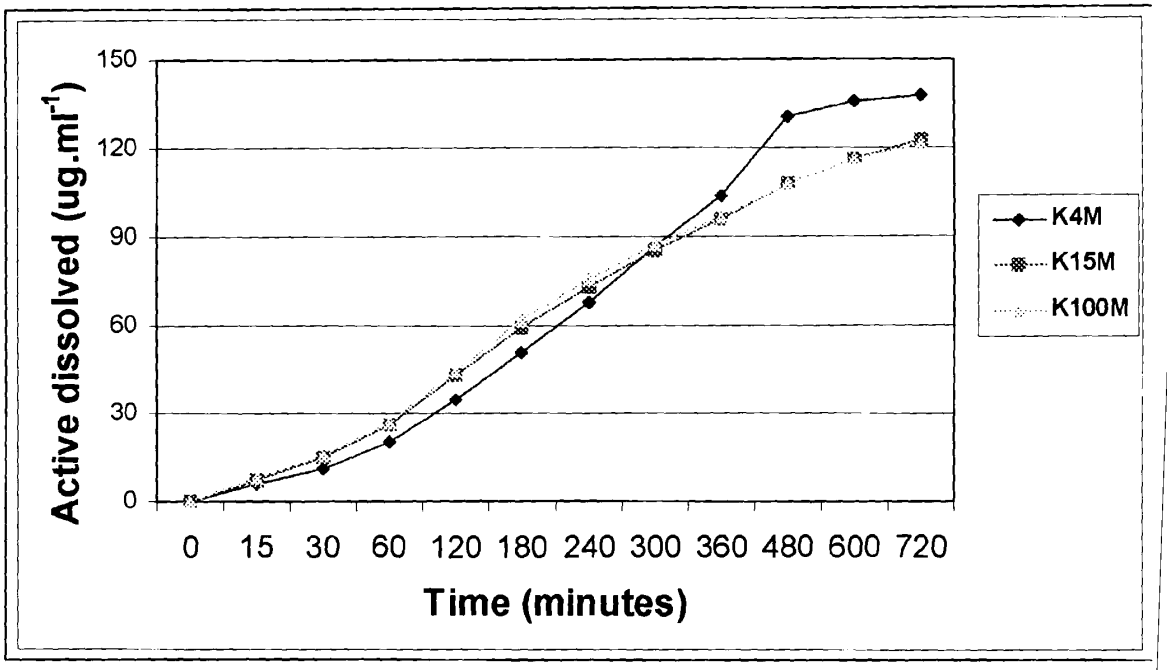

Figure 3: *Dissolution profile of tracer drug from chitosan tablets containing various binders.*

CONCLUSION

From the above results the following can be concluded:

- Chitosan combined with an appropriate binder resulted in directly compressible tablets with acceptable physical properties;
- The formulations containing chitosan needed 10% Emcompress® to assist the compressibility.
- Combination of these two polymer blends in a matrix formulation resulted in substantial sustained release;
- The drug properties should be carefully considered because extreme variation in particle size of the active ingredient and excipients will have an impact on the release rate by affecting the dissolution of the drug as well as the efficiency of gel formation.
- Chitosan, which is the major component in the tablet mixture, contributed, to a large degree, to the matrix formation;
- The extent of the reduction in drug dissolution and therefore the extension of the time of drug release also depended on the viscosity of the binder.

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ANNEXURES

Table B1. 1: *Dissolution data of propranolol hydrochloride from tablet formulations containing chitosan and Methocel K100M at 69 rpm. The tablets were compressed at a compression setting of 50.*

	Beaker 1	Beaker 2	Beaker 3	Beaker 4			
Time(min.)	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	Average	STD	%STD
0	0	0	0	0	0	0	0
15	10.0782	7.3912	7.0150	7.1224	7.9017	1.4596	18.472
30	16.9149	15.2072	15.5275	15.0982	15.6869	0.8387	5.3464
60	27.5515	26.3448	27.2312	26.3964	26.8810	0.6040	2.2470
120	45.8246	43.6976	44.9651	44.0451	44.6331	0.9576	2.1454
180	62.9900	61.0662	62.2064	61.0663	61.8322	0.9406	1.5212
240	76.1934	75.0650	75.7816	75.7369	75.6942	0.4671	0.6171
300	88.0192	86.0246	87.0676	87.5332	87.1612	0.8515	0.9769
360	97.7610	95.4329	95.9712	96.9767	96.5354	1.0377	1.0750
480	108.6317	106.6937	107.0738	108.0043	107.6009	0.8805	0.8183
600	116.7952	115.1152	115.3361	116.2718	115.8796	0.7899	0.6817
720	121.1078	120.2783	121.0379	120.9846	120.8522	0.3859	0.3193
960	124.7458	124.3147	124.0575	124.6219	124.4350	0.3101	0.2492
1440	125.4482	125.0148	124.7561	125.3236	125.1357	0.3118	0.2492
AUC	**60495.674**	**59192.087**	**59772.441**	**59864.082**	**59831.07**	**533.70**	**0.892**
DRi	**0.336**	**0.331**	**0.339**	**0.333**	**0.335**	**0.004**	**1.076**

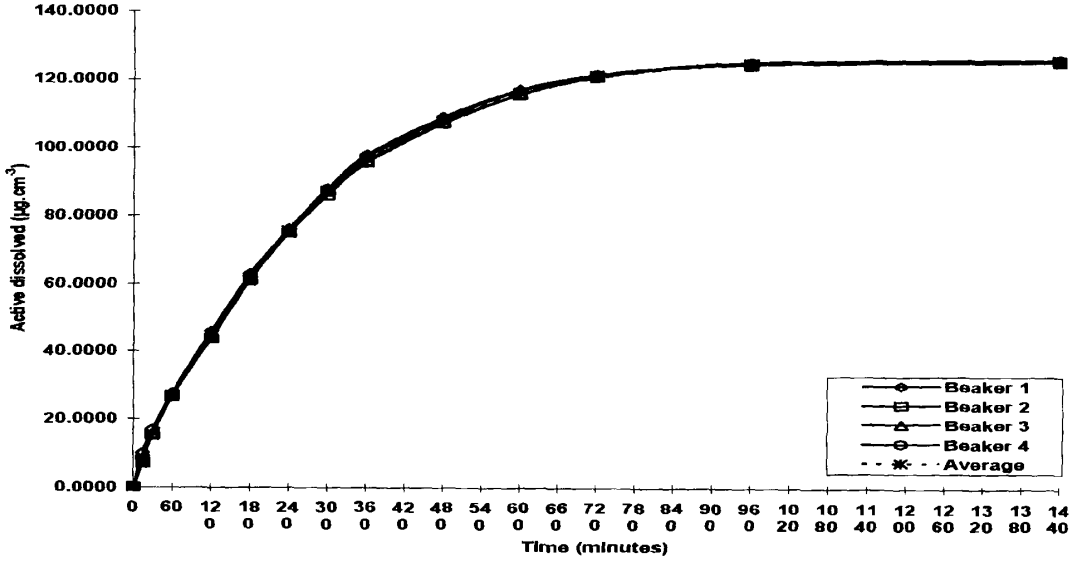

Figure B1.1: *Dissolution profiles of propranolol hydrochloride from tablets containing chitosan and Methocel K100M at 69 rpm and a compression setting of 50.*

Table B1. 2: *Dissolution data of propranolol hydrochloride from tablet formulations containing chitosan and Methocel K15M at 69 rpm. The tablets were compressed at a compression setting of 50.*

	Beaker 1	Beaker 2	Beaker 3	Beaker 4			
Time(min.)	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	Average	STD	%STD
0	0	0	0	0	0	0	0
15	6.0693	7.7355	7.8430	7.6011	7.3122	0.8345	11.4124
30	12.2128	16.1456	15.5819	17.2467	15.2968	2.1691	14.1801
60	22.7709	26.8599	25.8362	28.0478	25.8787	2.2604	8.7345
120	38.1174	46.8246	40.8504	45.3585	42.7877	4.0196	9.3942
180	54.6779	56.4194	56.3780	62.7117	57.5467	3.5376	6.1474
240	68.1861	69.3192	69.2776	77.2589	71.0105	4.1985	5.9126
300	80.5870	81.1889	81.1470	89.9251	83.2120	4.4838	5.3884
360	91.8474	99.4667	91.6043	99.9744	95.7232	4.6214	4.8279
480	105.0784	110.0795	104.5652	110.3750	107.5246	3.1302	2.9111
600	116.4480	114.2210	113.6208	118.0386	115.5821	2.0399	1.7649
720	122.0760	122.4165	120.1200	123.0305	121.9108	1.2575	1.0315
960	125.7735	125.1485	124.8547	125.6046	125.3453	0.4203	0.3353
1440	126.4817	125.8532	125.5578	126.3118	126.0511	0.4227	0.3353
AUC	**57275.002**	**59460.106**	**57218.325**	**61420.268**	**58843.425**	**2010.084**	**3.416**
DRi	**0.298**	**0.314**	**0.302**	**0.338**	**0.313**	**0.018**	**5.811**

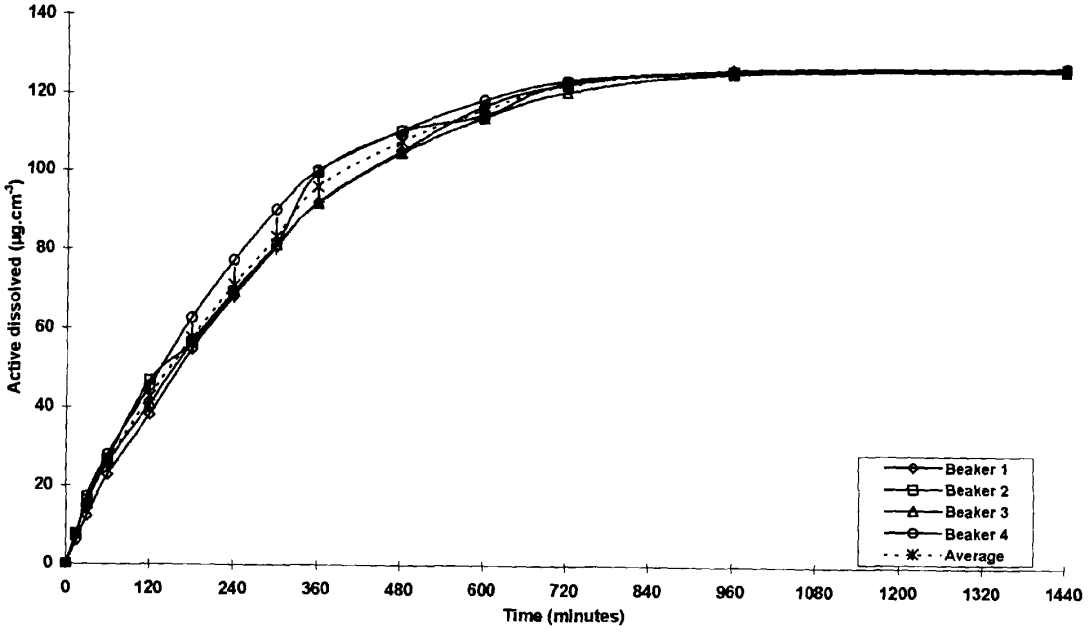

Figure B1.2: *Dissolution profiles of propranolol hydrochloride from tablets containing chitosan and Methocel K15M at 69 rpm and a compression setting of 50.*

Table B1. 3: *Dissolution data of propranolol hydrochloride from tablet formulations containing chitosan and Methocel K4M at 69 rpm. The tablets were compressed at a compression setting of 50.*

	Beaker 1	Beaker 2	Beaker 3	Beaker 4			
Time(min.)	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	Average	STD	%STD
0	0	0	0	0	0	0	0
15	7.3143	5.4529	6.3161	5.1561	6.0599	0.9703	16.0117
30	11.5435	12.1536	11.2142	10.0478	11.2397	0.8848	7.8724
60	20.2473	20.2673	19.3767	19.8493	19.9352	0.4191	2.1025
120	33.8013	35.1433	34.9221	34.6421	34.6272	0.5876	1.6968
180	49.3190	52.3410	50.9586	51.7830	51.1004	1.3164	2.5761
240	66.2718	67.7999	69.6200	68.2909	67.9956	1.3827	2.0335
300	82.2666	87.5799	88.3581	88.2625	86.6168	2.9207	3.3720
360	98.8898	102.2904	105.5007	106.8614	103.3856	3.5574	3.4409
420	114.9850	117.0555	123.2512	117.0659	118.0894	3.5776	3.0296
480	125.7742	132.4153	130.6872	131.3197	130.0491	2.9380	2.2591
600	134.0875	137.8251	135.2242	136.0220	135.7897	1.5720	1.1577
720	136.5661	140.0007	136.5491	136.5960	137.4280	1.7153	1.2481
840	137.3320	140.7857	137.3149	137.5239	138.2391	1.7004	1.2300
AUC	**22371.176**	**23573.508**	**24516.945**	**24235.307**	**23674.23**	**954.47**	**4.032**
DRi	**0.263**	**0.283**	**0.276**	**0.283**	**0.276**	**0.010**	**3.457**

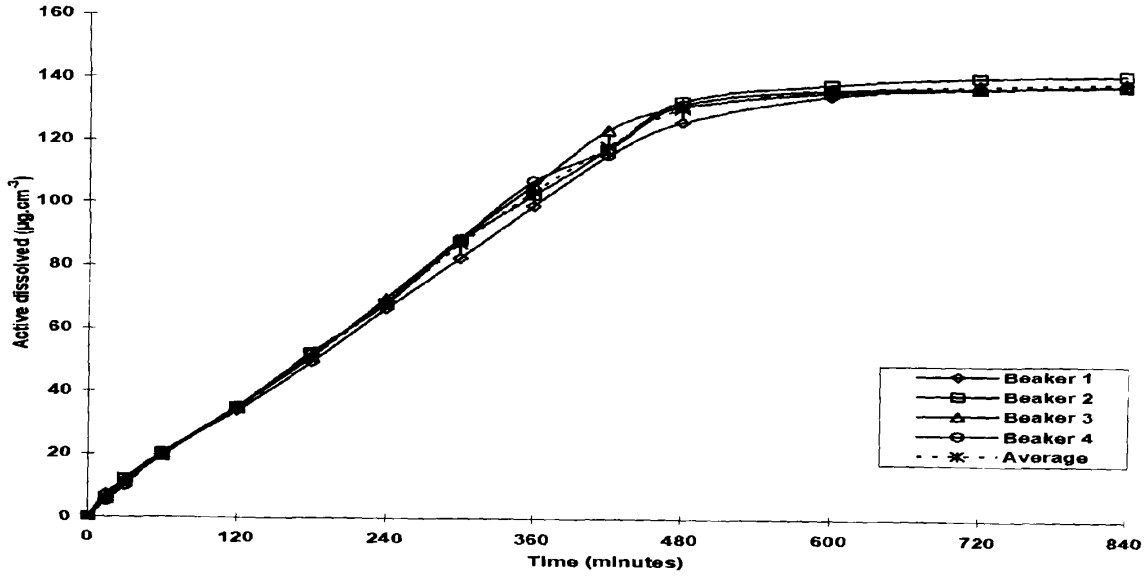

Figure B1.3: *Dissolution profiles of propranolol hydrochloride from tablets containing chitosan and Methocel K4M at 69 rpm and a compression setting of 50.*

Table B1. 4: *Dissolution data of propranolol hydrochloride from tablet formulations containing chitosan and KSR at 69 rpm. The tablets were compressed at a compression setting of 50.*

	Beaker 1	Beaker 2	Beaker 3	Beaker 4			
Time(min.)	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	Average	STD	%STD
0	0	0	0	0	0	0	0
15	5.8202	4.8310	5.2320	5.0181	5.2253	0.4291	8.2120
30	12.7821	11.3328	11.7628	11.3606	11.8096	0.6775	5.7365
60	30.4504	25.8115	26.0834	26.1870	27.1331	2.2172	8.1716
120	68.0018	61.1714	62.0866	60.3459	62.9014	3.4738	5.5226
180	100.6284	93.4393	97.3807	91.1387	95.6468	4.2040	4.3953
240	117.2074	113.0797	110.5194	114.8035	113.9025	2.8199	2.4758
300	125.1089	124.4607	124.7737	124.8573	124.8001	0.2674	0.2142
360	127.3059	127.0285	127.5037	126.9193	127.1893	0.2653	0.2086
480	130.2104	130.0651	130.0884	130.0622	130.1065	0.0702	0.0540
600	130.9386	130.7925	130.8159	130.7896	130.8341	0.0706	0.0540
720	131.6708	131.5239	131.5474	131.5210	131.5658	0.0710	0.0540
960	132.4071	132.2594	132.2830	132.2564	132.3015	0.0714	0.0540
1440	133.1475	132.9990	133.0228	132.9960	133.0413	0.0718	0.0540
AUC	**76653.863**	**75201.694**	**75435.875**	**75150.970**	**75610.600**	**706.49**	**0.934**
DRi	**0.574**	**0.531**	**0.550**	**0.518**	**0.543**	**0.024**	**4.436**

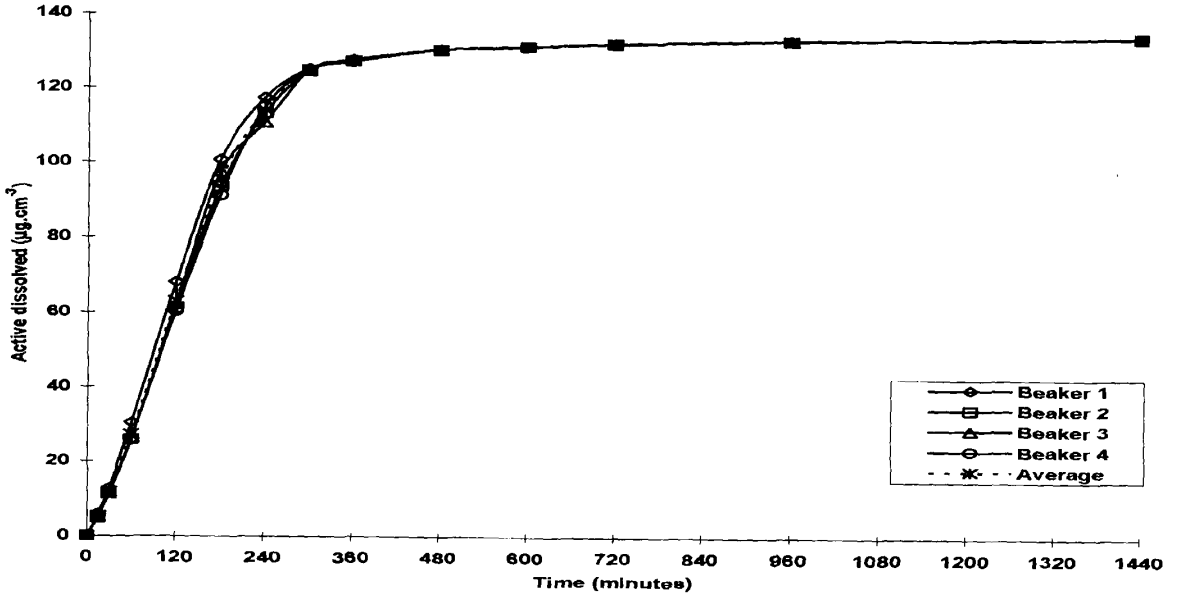

Figure B1.4: *Dissolution profiles of propranolol hydrochloride from tablets containing chitosan and KSR at 69 rpm and a compression setting of 50.*

Table B1. 5: *Dissolution data of propranolol hydrochloride from tablet formulations containing chitosan and Methocel K100M during a two medium dissolution of pH 1.2 for the first 2 hours at 69 rpm. The tablets were compressed at a compression setting of 50.*

	Beaker 1	Beaker 2	Beaker 3	Beaker 4			
Time(min.)	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	Average	STD	%STD
0	0	0	0	0	0	0	0
5	1.9884	2.8259	2.3666	2.2045	2.3464	0.3553	15.140
10	4.0602	4.1730	4.0083	3.4941	3.9339	0.3011	7.6552
15	6.1166	5.7166	5.6051	5.2231	5.6653	0.3676	6.4891
30	9.8864	9.7273	9.1559	9.1230	9.4731	0.3910	4.1273
60	17.1892	16.1918	15.6442	15.9083	16.2333	0.6753	4.1600
120	29.6657	29.5542	28.4092	33.3216	30.2377	2.1329	7.0538
AUC	**197.395**	**153.027**	**145.643**	**2.216**	**124.570**	**84.711**	**68.003**
DRi	**0.280**	**0.258**	**0.250**	**0.259**	**0.262**	**0.013**	**4.808**

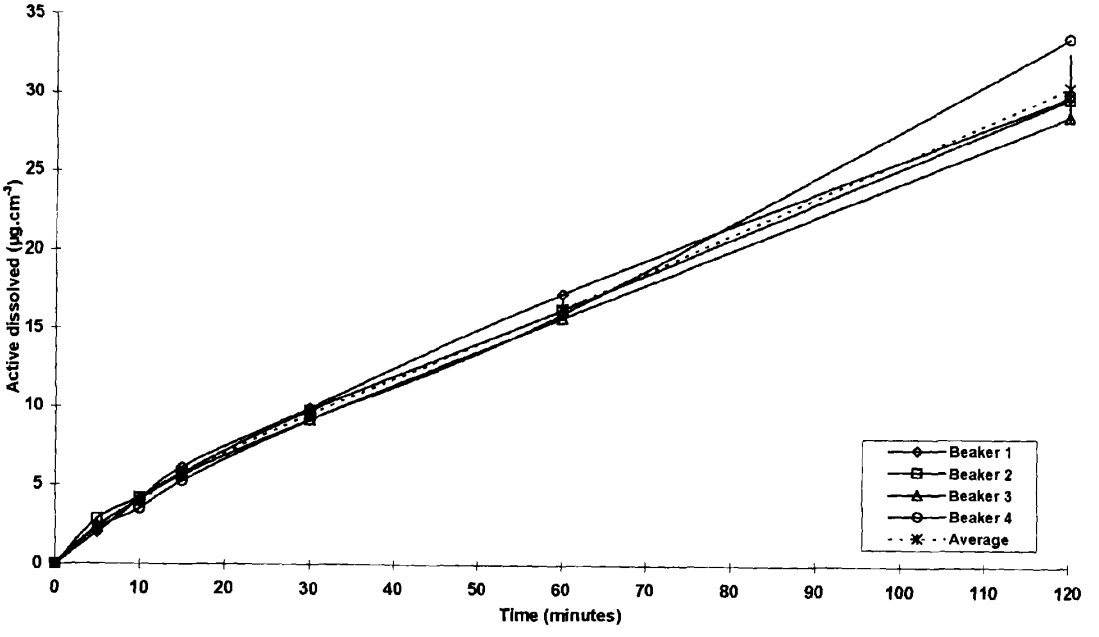

Figure B1.5: *Dissolution profiles of propranolol hydrochloride from tablets containing chitosan and Methocel K100M during a two medium dissolution of pH 1.2 for the first 2 hours at 69 rpm and a compression setting of 50.*

Table B1. 6: *Dissolution data of propranolol hydrochloride from tablet formulations containing chitosan and Methocel K100M during a two medium dissolution of pH 6.8 for the following 22 hours at 69 rpm. The tablets were compressed at a compression setting of 50.*

	Beaker 1	Beaker 2	Beaker 3	Beaker 4			
Time(min.)	[µg.cm^{-3}]	[µg.cm^{-3}]	[µg.cm^{-3}]	[µg.cm^{-3}]	Average	STD	%STD
0	0	0	0	0	0	0	0
125	0.9553	0.7016	0.9835	0.1378	0.6946	0.3922	6.4699
130	0.9171	1.0313	0.9452	1.3163	1.0525	0.1825	7.3387
135	2.4617	2.9712	2.9128	2.9195	2.8163	0.2378	8.4445
150	6.5803	6.6697	6.9210	6.5614	6.6831	0.1655	2.4768
180	12.1594	13.8844	14.2217	14.1137	13.5948	0.9672	7.1147
240	24.1405	27.0873	27.7084	27.5435	26.6199	1.6737	6.2873
360	41.9110	42.7880	45.6396	46.0939	44.1081	2.0704	4.6938
480	57.8350	62.3253	62.8811	62.5204	61.3904	2.3815	3.8792
720	83.7705	90.0618	89.7186	90.7090	88.5650	3.2226	3.6387
1380	107.6795	111.1866	110.7851	110.6253	110.0691	1.6105	1.4632
1440	108.2949	111.8215	111.4178	111.2571	110.6978	1.6195	1.4630
AUC	**20012.452**	**22953.217**	**23432.440**	**23950.210**	**22587.079**	**1764.041**	**7.810**
DRi	**0.050**	**0.056**	**0.058**	**0.057**	**0.055**	**0.003**	**6.155**

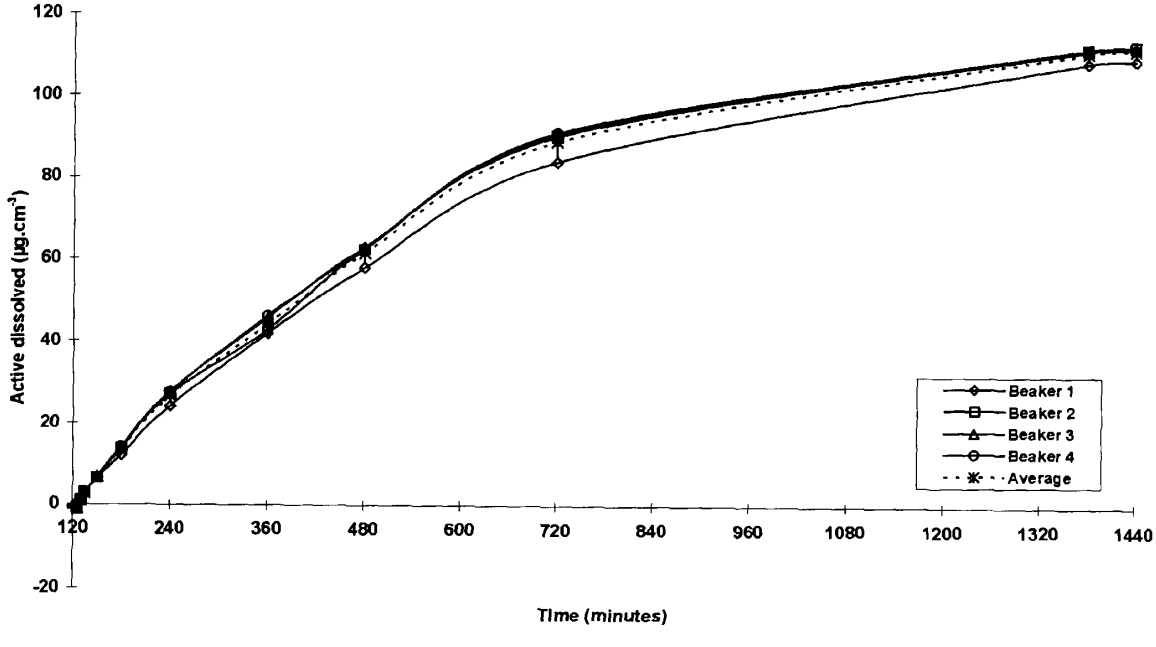

Figure B1.6: *Dissolution profiles of propranolol hydrochloride from tablets containing chitosan and Methocel K15M during a two medium dissolution of pH 6.8 for the following 22 hours at 69 rpm and a compression setting of 50.*

Table B1. 7: *Dissolution data of propranolol hydrochloride from tablet formulations containing chitosan and Methocel K15M during a two medium dissolution of pH 1.2 for the first 2 hours at 69 rpm. The tablets were compressed at a compression setting of 50.*

	Beaker 1	Beaker 2	Beaker 3	Beaker 4			
Time(min.)	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	Average	STD	%STD
0	0	0	0	0	0	0	0
5	1.4211	1.5831	1.6372	1.1779	1.4548	0.2062	14.1730
10	3.8950	4.1660	4.0583	3.6505	3.9425	0.2243	5.6889
15	6.0855	6.7903	6.2497	5.7856	6.2278	0.4214	6.7662
30	10.6656	11.5094	10.8577	9.9858	10.7546	0.6270	5.8299
60	18.2159	19.9829	18.8413	16.8029	18.4608	1.3254	7.1798
120	32.1840	35.0145	34.1367	31.7627	33.2745	1.5541	4.6705
AUC	**181.607**	**204.409**	**159.033**	**109.927**	**163.744**	**40.378**	**24.659**
DRi	**0.304**	**0.333**	**0.313**	**0.281**	**0.308**	**0.021**	**6.936**

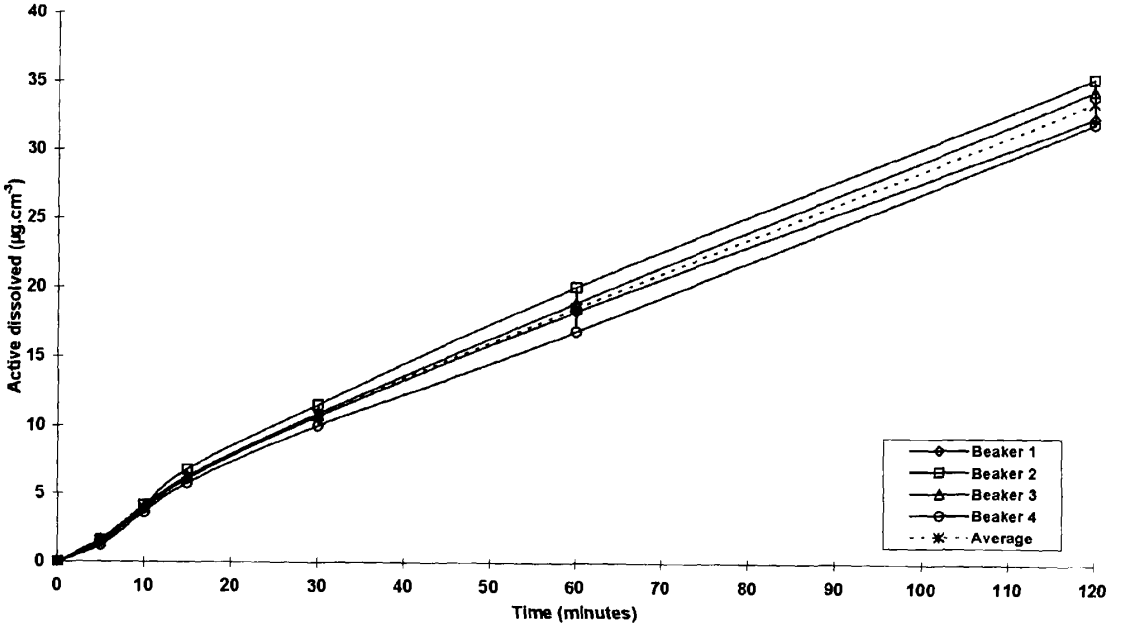

Figure B1.7: *Dissolution profiles of propranolol hydrochloride from tablets containing chitosan and Methocel K15M during a two medium dissolution of pH 1.2 for the first 2 hours at 69 rpm and a compression setting of 50.*

Table B1. 8: *Dissolution data of propranolol hydrochloride from tablet formulations containing chitosan and Methocel K15M during a two medium dissolution of pH 6.8 for the following 22 hours at 69 rpm. The tablets were compressed at a compression setting of 50.*

	Beaker 1	Beaker 2	Beaker 3	Beaker 4			
Time(min.)	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	Average	STD	%STD
0	0	0	0	0	0	0	0
125	0.7580	1.4064	0.9271	1.1245	1.0540	0.2786	6.4322
130	0.9746	0.3790	0.8609	0.8034	0.7545	0.2602	4.4908
135	2.6323	2.2307	3.0254	2.5447	2.6083	0.3272	12.5441
150	5.6805	6.3761	6.5832	6.3254	6.2413	0.3901	6.2511
180	14.1583	13.8993	14.2767	14.1584	14.1231	0.1593	1.1282
240	26.4324	30.8235	29.5961	29.9282	29.1950	1.9133	6.5535
360	45.5124	53.8463	49.6802	52.1003	50.2848	3.6112	7.1814
480	64.2472	66.7920	63.9842	67.0379	65.5153	1.6228	2.4770
720	88.5270	89.7891	91.1661	93.6447	90.7817	2.1919	2.4145
1380	110.2071	110.3486	111.2258	111.8858	110.9168	0.7876	0.7101
1440	111.2876	111.3735	111.5508	112.2709	111.6207	0.4471	0.4006
AUC	**22875.000**	**25242.787**	**25003.228**	**26700.295**	**24955.328**	**1576.663**	**6.318**
DRi	**0.055**	**0.055**	**0.057**	**0.056**	**0.056**	**0.001**	**1.937**

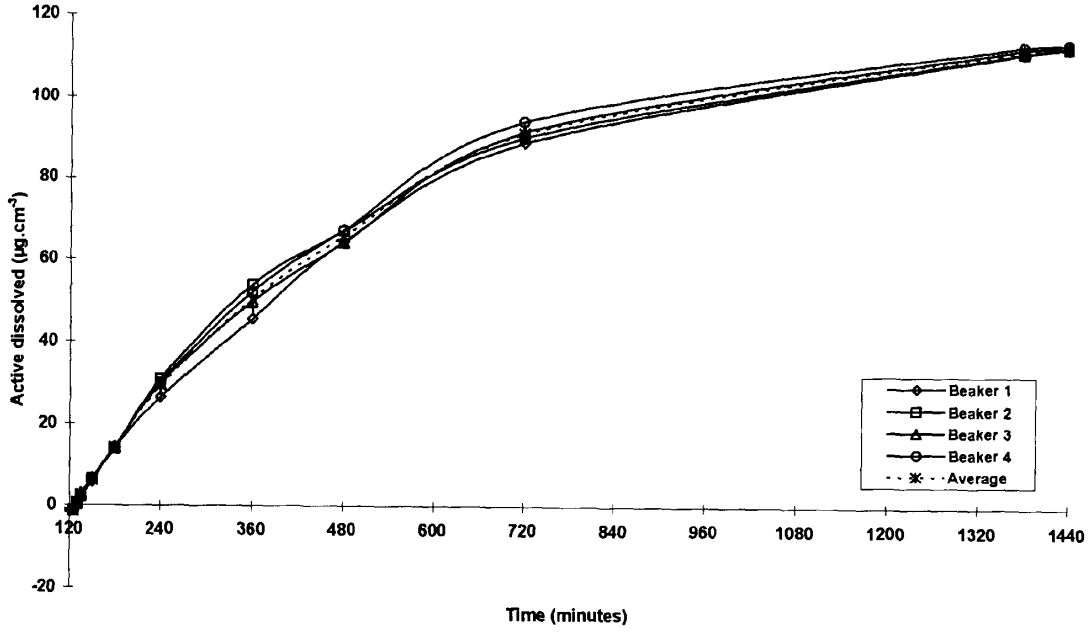

Figure B1.8: *Dissolution profiles of propranolol hydrochloride from tablets containing chitosan and Methocel K15M during a two medium dissolution of pH 6.8 for the following 22 hours at 69 rpm and a compression setting of 50.*

Table B1. 9: *Dissolution data of propranolol hydrochloride from tablet formulations containing chitosan and Methocel K4M during a two medium dissolution of pH 1.2 for the first 2 hours at 69 rpm. The tablets were compressed at a compression setting of 50.*

	Beaker 1	Beaker 2	Beaker 3	Beaker 4			
Time(min.)	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	Average	STD	%STD
0	0	0	0	0	0	0	0
5	2.5017	4.2037	2.0424	1.8803	2.6570	1.0642	4.0510
10	4.0631	5.0992	4.5468	3.8165	4.3814	0.5666	12.9312
15	6.1735	6.5399	6.7409	6.1957	6.4125	0.2758	4.3016
30	11.1593	10.8794	11.8380	10.9115	11.1970	0.4452	3.9764
60	19.8740	19.3764	20.9077	19.5168	19.9187	0.6918	3.4731
120	35.9586	35.2151	37.3222	33.9243	35.6050	1.4202	3.9886
AUC	**161.217**	**172.186**	**187.892**	**196.473**	**179.442**	**15.772**	**8.789**
DRi	**0.326**	**0.301**	**0.345**	**0.323**	**0.324**	**0.018**	**5.562**

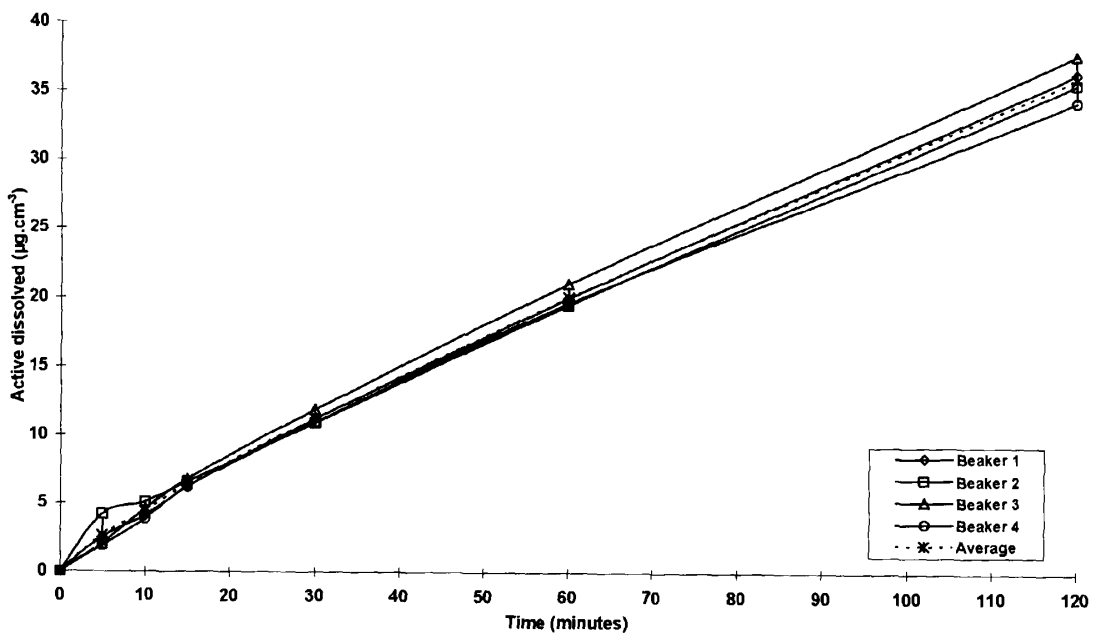

Figure B1.9: *Dissolution profiles of propranolol hydrochloride from tablets containing chitosan and Methocel K15M during a two medium dissolution of pH 1.2 for the first 2 hours at 69 rpm and a compression setting of 50.*

Table B1. 10: *Dissolution data of propranolol hydrochloride from tablet formulations containing chitosan and Methocel K4M during a two medium dissolution of pH 6.8 for the following 22 hours at 69 rpm. The tablets were compressed at a compression setting of 50.*

	Beaker 1	Beaker 2	Beaker 3	Beaker 4			
Time(min.)	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	Average	STD	%STD
0	0	0	0	0	0	0	0
125	0.3633	0.0814	0.1660	0.5388	0.0180	0.3895	3.4773
130	1.7098	1.5986	2.0210	2.3350	1.9161	0.3316	17.3055
135	3.6534	3.5698	3.9945	4.3949	3.9032	0.3758	9.6274
150	7.8068	7.1589	7.7269	8.4677	7.7901	0.5360	6.8808
180	15.7325	14.6300	15.1730	16.1153	15.4127	0.6496	4.2148
240	31.8494	29.4721	30.2719	31.0784	30.6679	1.0249	3.3419
360	54.2295	47.8078	51.7411	52.6085	51.5967	2.7284	5.2879
480	68.0794	64.3565	64.6751	66.1112	65.8056	1.6972	2.5791
720	96.1862	91.5969	93.1858	95.3064	94.0688	2.0741	2.2048
1380	110.8612	112.4483	111.6217	110.7941	111.4314	0.7749	0.6954
1440	116.2585	116.2194	115.5292	116.1065	116.0284	0.3390	0.2922
AUC	**25508.787**	**22340.014**	**23873.141**	**24676.758**	**24099.675**	**1349.857**	**5.601**
DRi	**0.065**	**0.060**	**0.063**	**0.068**	**0.064**	**0.003**	**5.073**

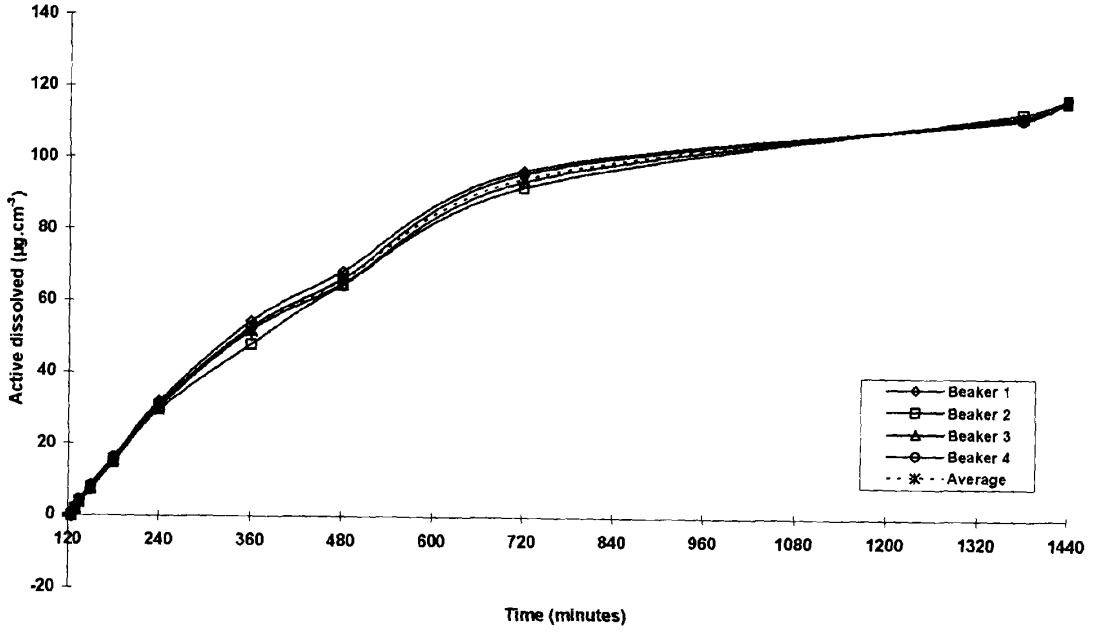

Figure B1.10: *Dissolution profiles of propranolol hydrochloride from tablets containing chitosan and Methocel K4M during a two medium dissolution of pH 6.8 for the following 22 hours at 69 rpm and a compression setting of 50.*

Table B1.11: *Dissolution data of propranolol hydrochloride from tablet formulations containing chitosan and KSR during a two medium dissolution of pH 1.2 for the first 2 hours at 69 rpm. The tablets were compressed at a ompression setting of 50.*

	Beaker 1	Beaker 2	Beaker 3	Beaker 4			
Time(min.)	**[µg.cm^{-3}]**	**[µg.cm^{-3}]**	**[µg.cm^{-3}]**	**[µg.cm^{-3}]**	**Average**	**STD**	**%STD**
0	0	0	0	0	0	0	0
5	2.5827	2.7989	2.2045	2.2856	2.4679	0.2741	11.1054
10	7.1704	7.3067	6.3578	6.4123	6.8118	0.4964	7.2872
15	11.2702	11.7585	10.1289	10.3458	10.8759	0.7688	7.0693
30	19.5803	20.3955	16.8658	17.0568	18.4746	1.7805	9.6377
60	36.6359	39.5358	31.8259	32.1261	35.0309	3.7229	10.6274
120	76.5067	78.5583	70.5354	70.4050	74.0014	4.1629	5.6254
AUC	**44.563**	**49.374**	**160.314**	**135.748**	**72.813**	**5.473**	**1.121**
DRi	**0.610**	**0.658**	**0.528**	**0.533**	**0.582**	**0.063**	**10.781**

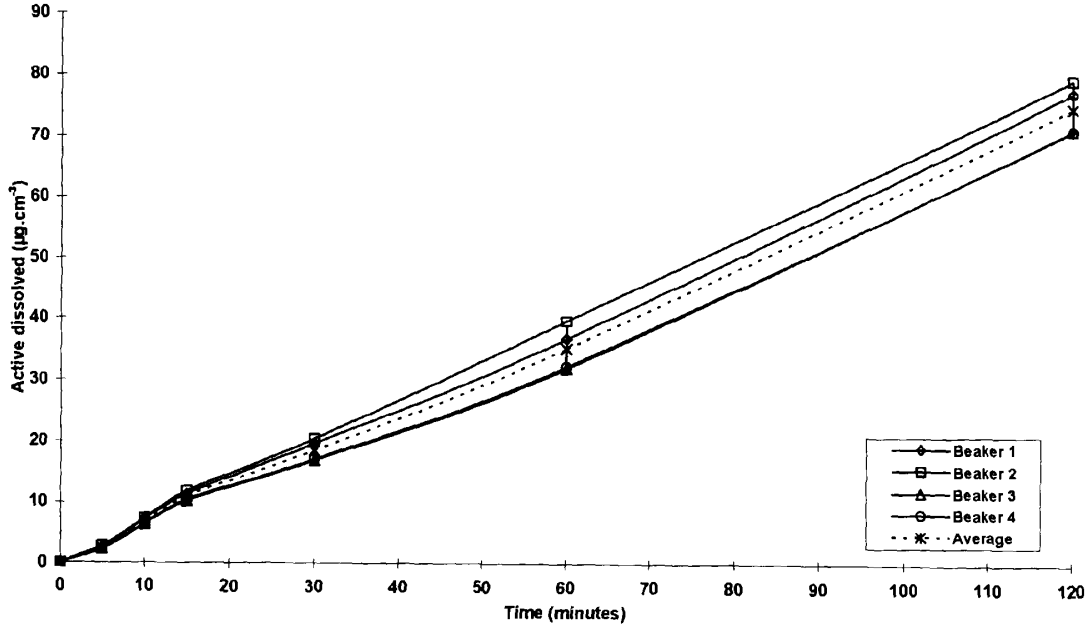

Figure B1.11: *Dissolution profiles of propranolol hydrochloride from tablets containing chitosan and KSR during a two medium dissolution of pH 1.2 for the first 2 hours at 69 rpm and a compression setting of 50.*

Table B1. 12: *Dissolution data of propranolol hydrochloride from tablet formulations containing chitosan and KSR during a two medium dissolution of pH 6.8 for the following 22 hours at 69 rpm. The tablets were compressed at a compression setting of 50.*

	Beaker 1	Beaker 2	Beaker 3	Beaker 4			
Time(min.)	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	[$\mu g.cm^{-3}$]	Average	STD	%STD
0	0	0	0	0	0	0	0
125	2.2302	2.2302	3.8089	3.8089	3.0195	0.9114	30.1851
130	5.6709	4.4868	6.3844	8.8370	6.3448	1.8365	28.9458
135	10.7657	10.3926	10.2146	13.8366	11.3024	1.7050	15.0855
150	24.1204	28.3488	18.8303	26.9547	24.5636	4.2076	17.1296
180	49.4458	56.6774	55.8817	48.7720	52.6943	4.1618	7.8980
240	82.3260	87.9910	84.8792	76.6869	82.9708	4.7870	5.7695
360	88.2414	91.6262	91.5699	99.2316	92.6673	4.6536	5.0218
480	93.6258	91.6168	94.8867	101.4633	95.3981	4.2618	4.4674
720	94.1631	92.1430	95.4310	102.0442	95.9453	4.2854	4.4666
1380	94.7035	92.6721	95.9784	102.6284	96.4956	4.3093	4.4658
1440	95.2468	93.2041	96.5289	103.2157	97.0489	4.3332	4.4650
AUC	**48646.051**	**49380.433**	**49918.420**	**51951.631**	**49974.134**	**1417.731**	**2.837**
DRi	**0.204**	**0.232**	**0.216**	**0.210**	**0.215**	**0.012**	**5.587**

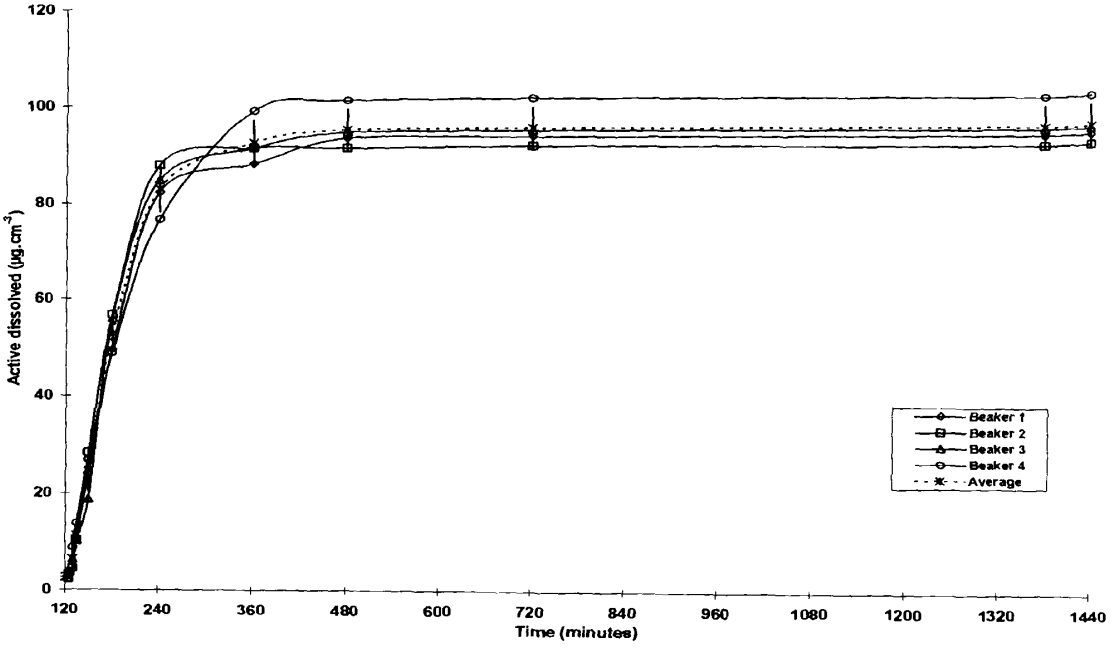

Figure B1.12: *Dissolution profiles of propranolol hydrochloride from tablets containing chitosan and KSR during a two medium dissolution of pH 6.8 for the following 22 hours at 69 rpm and a compression setting of 50.*