DESIGN OF FILMS FOR ORAL DOSAGE FORMULATIONS

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Doctor of Philosophy

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Pharmaceutical dosage forms, more specifically tablets, are typically coated in order to taste mask and protect the core from *e.g.* light. Conventionally tablets are film-coated where an aqueous/organic solution is sprayed onto the tablet. This may cause stability and safety issues, for example, if the tablet core is moisture-sensitive while on the other hand, the use of organic solvents may increase the cost and introduce safety issues. Also there may be a need for alternative and possibly more effective coating method in pharmaceutical industry therefore a novel method for tablet coating was studied where a thin polymer film was cast (pre-formed film), dried and applied as a coating hence eliminating the need for using any solvent during the actual coating process. A pre-formed film is initially heated to a temperature where it becomes flexible, a vacuum is applied and the film is then pulled around the tablet. The aim of this work was to evaluate, initially, the effect of coating on dissolution of drug from commercially available/outsourced film-coated solid-dosage forms as well as design novel fast dissolving film formulations for the new coating process. The proposed films (gelatin or cellulose-based) were characterised in terms of their dissolution, swelling, mechanical and thermal properties prior to using them in the novel coating process; selected films were then coated onto tablets containing paracetamol or ibuprofen and the effect of the film on the subsequent dissolution was evaluated. It was found in this study that the pre-formed films could be designed to be fast dissolving and mechanically strong to withstand the stress from the coating process. Also metoclopramide was incorporated in a gelatin film-coating formulation which was then successfully coated on paracetamol-containing core. Gelatin-based films were found to be successful in the novel coating process therefore to be suitable as finished coatings for immediate release dosage forms.
Orally disintegrating dosage forms have been identified as a favourable dosage form due to following reasons: fast onset of drug release, easy to use, not painful and possible increase of amount absorbed to systemic circulation. Selected films formulated for coating studies were also successfully formulated to contain active ingredient suitable for orally disintegrating dosage form; cellulose-based naratriptan-films were studied as orally disintegrating dosage forms where the effect of formulation on the film properties was studied. It was found that strength of the film can affect the dissolution of the film but it may be the inclusion of specific excipients in the formulation which affect the penetration of the drug through mucosa.
In conclusion, identified polymer films can be utilised as film coatings (with or without active ingredient) as well as orally disintegrating dosage forms.

Keywords: film-coating; oral films; tablet coating; dissolution; paracetamol; ibuprofen

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Abbreviations

5-ASA	5-aminosalicylic acid
ADP	Adenosine diphosphate
AMVn	Automated Microviscometer
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
ATP	Adenosine triphosphate
BCA	Bicinchoninic acid
BCS	Biopharmaceutical Classification System
BSE	Bovine Spongiform Encephalopathy
COX	Cyclooxygenase
DL-LA	DL-lactic acid
DR	Delayed release
DSC	Differential scanning calorimetry
EM	Elastic modulus
f_2	Similarity factor
GI	Gastrointestinal
GORD	Gastro-oesophageal reflux disease
GSK	GlaxoSmithKline
H-bonding	Hydrogen bonding
HCl	Hydrochloric acid
HEC	Hydroxyethylcellulose
HPC	Hydroxypropylcellulose
HPLC	High performance liquid chromatography
HPMC	Hydroxypropylmethylcellulose
HyperDSC™	High scan speed DSC
IDS	Intraoral delivery system
IMMC	Interdigestive migrating motility complex
IOD	Intraoral dosage form
IR	Immediate release
IS	Internal standard
IUPAC	International Union of Pure and Applied Chemistry
K_d	Rate of dissolution
K_s	Rate of swelling
LC/ESI-MS/MS	Liquid chromatographic-electrospray tandem mass spectrometry
LOD	Limit of detection
LogP	Partition coefficient
LOQ	Limit of quantitation

MC	Methylcellulose
MCG	Membrane coating granules
MFT	Minimum film formation temperature
MR	Modified release
MRU	Medicines Research Unit
MW	Molecular weight
Na CMC	Sodium carboxymethylcellulose
NaOH	Sodium hydroxide
NDA/ANDA	New Drug Application/Abbreviated New Drug Application
NSAID	non-steroidal anti-inflammatory drug
p	Significance level
PAT	Process Analytical Technology
PBS	Phosphate buffered saline
PEG	Polyethyleneglycol
PG	Propylene glycol
pKa	Acid dissociation constant
PVP	Polyvinylpyrrolidone
QbD	Quality by Design
RFID	Radio frequency identification
RH	Relative humidity
rpm	Revolution per minute
RT	Room temperature
S.D.	Standard deviation
SPE	Solid phase extraction
SR	Sustained release
t	Time
TEA	Triethanolamine
T_g	Glass transition temperature
TGA	Thermogravinetric analysis
t_{lag}	Lag time
USP	United States Pharmacopeia
UV/VIS	Ultraviolet/visible
w/v	Weight/volume
w/w	Weight/weight
$\varepsilon_{p/t}$	Puncture/tensile strain
$\sigma_{p/t}$	Puncture/tensile strength

Chapter 1-

Introduction

1.1 Introduction to oral dosage forms

The need for new medicines and development of new drugs and formulations is a major driver for growth in pharmaceutical industry. There are several routes for drug administration into humans and animals such as oral, topical, inhalation, intravenous, ocular, vaginal and nasal. The use of these drug delivery routes requires an appreciation of drug absorption *via* the respective routes as well as patient compliance with different methods. Only intravenous drug delivery will guarantee 100 % bioavailability of the dose in the systemic circulation and all other delivery methods require the drug to pass several barriers (*e.g.* fluids, membranes and tissues) before reaching systemic circulation. This provides a challenge for formulators to design suitable delivery system for a particular medication allowing maximum bioavailability.

Today over 70% of pharmaceutical formulations are in a tablet form, comprising from tablets, caplets, effervescent tablets, chewable tablets and lozenges. In 1843 the first patent was filed describing a machine that compressed powder into compacts by William Brockedon which was soon exploited by pharmaceutical industry. Reasons for the popularity of tablets as a dosage form are that they are quick and simple to manufacture, contain accurate amounts of the active ingredient, are easily administered and generally are more stable than, for example, liquid formulations. Orally administered solid-dosage forms must be able to withstand the stomach's acidic conditions and gastrointestinal (GI) enzymatic challenges as well as being able to be absorbed through GI membranes.

Solid-dosage forms, mainly tablets, can be divided into two categories: modified release (MR) and immediate release (IR) formulations. Modified release dosage forms can be formulated so that the drug release is sustained (the active is released at certain rate over a period of time) and/or delayed (the active is released after a period of time) (Figure 1.1). Sustained release (SR) formulations are used, for example, to avoid constant administration of immediate release formulations whereas delayed release (DR) products can be used to avoid taking medication, *e.g.* during the night. IR oral dosage forms are designed to be released as quickly as possible after administration and typically the rate of dissolution depends on the physicochemical properties of the drug and the site of release in GI tract. They are required to disintegrate, deaggregate and dissolve quickly in order for drug to be available for absorption. Often, dissolution of the drug in the GI fluids can be rate limiting step prior to the drug being in solution as disintegration and deaggregation can be controlled by inclusion of excipients (*e.g.* disintegrants, lubricants *etc.*) and control of process variables but dissolution of the drug is dependent on physicochemical properties of the drug and behaviour

in GI fluids. All above factors are considered by formulators when designing oral dosage forms (Florence and Attwood, 1998b; Ashford, 2002a).

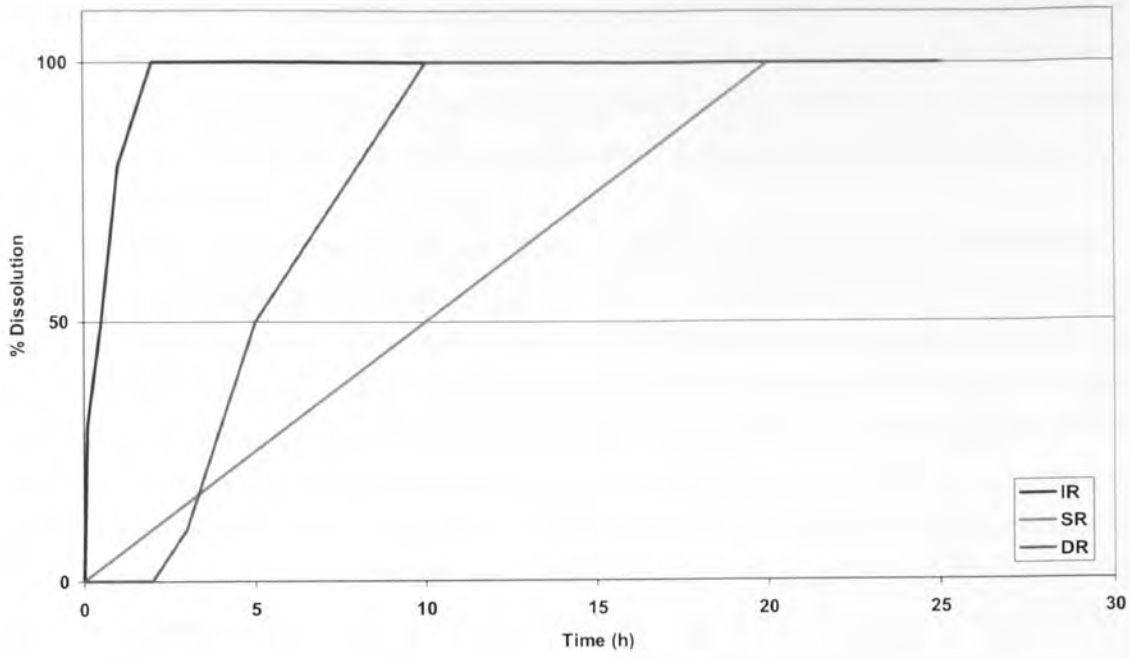


Figure 1.1- Schematic of immediate release (IR), sustained release (SR) and delayed release (DR) profiles

In this thesis, novel film formulations were designed for utilisation as tablet coatings and as individual orally disintegrating dosage forms therefore the film formulations were analysed as pre-formed films and additionally, for example, the effect of tablet coating on the tablet core dissolution was studied. The aim of this introductory Chapter 1 is to give sufficient background information for the issues related to oral dosage forms (*e.g.* formulatory effects on core and tablet coating), their analysis and physiological conditions which can affect the behaviour of the oral dosage form in the GI tract. Also model drugs used in the studies are described at the end of this chapter. Prior explaining more in depth the solid-dosage forms and issues relating to them, drug transit through the GI tract (section 1.2), mechanism of solid form to dissolved drug (section 1.3) and absorption of drugs from the GI tract (section 1.4) will outlined.

1.2 Drug transit through the GI tract

To lay an overall picture, it is necessary to discuss the route for solid-dosage forms from administration to a pharmacological effect or clearance. This section describes the transit of

solid-dosage form and the stages it may have to go through before reaching the absorption site.

Transit of the solid-dosage forms through human GI tract is a complex process depending on the formulation, properties of the drug and physiological conditions at the time of administration. Transfer of the drugs is dependent on oesophageal transit, gastric emptying, small intestinal transit and large intestinal transit as well as formulation of the dosage form and dosing conditions.

Generally small dosage forms are passed through a healthy oesophagus within 2 minutes of the swallowing (oesophageal transit), and this can be improved by standing while taking the drug with water. However, if the solid-dosage form is hydrated easily and quickly it may cause problems by adhering to the oesophagus and therefore starting to disintegrate leading to oesophageal damage. Alternatively if the dosage form is designed to be mucoadhesive to extend residence times in the stomach, this may present problems in oesophagus due to possible adhesion to it. It has been reported that uncoated and sugar-coated tablets adhered less to oesophagus compared to gelatin capsules when an *ex-vivo* model to study adhesion was utilised (Marvola *et al.*, 1982). These findings were similar to Swisher and his co-workers who reported adherence in the oesophageal tissue depending on the surface material of the dosage form where hard gelatin capsules were found most adhesive, followed by film-coated, then sugar-coated and leaving uncoated tablets the least adhesive (Swisher *et al.*, 1984). McCargar *et al.* found a similar trend again *in-vitro* but when the experiments were performed *in-vivo* in humans and monitored by gamma scintigraphy, the opposite trend was revealed (McCargar *et al.*, 2001). The adhesion process may be more complicated in human subjects due to the swallowing mechanism and therefore the *in-vitro* results do not correlate well with *in-vivo* results. Also human to human variations, dosage form size, shape and mass as well as coating material might have an effect on the adhesion process.

When the drug has successfully passed through oesophagus it will end up at the top part of the stomach (fundus). If the dosage form is small and has been taken with less than 50 ml of water into an empty stomach, the residence time depends which phase of the interdigestive migrating motility complex (IMMC) is dominating because drug and small volumes of water do not trigger the digestion process. The IMMC consists of 4 phases where Phase I can last 40-60 minutes with no contractions in the stomach, Phase II 25-40 minutes with occasional contractions, Phase III with continuous strong contractions for 15-25 minutes leading to gastric emptying and Phase IV with decreasing contractions for few minutes; therefore it can be seen that the residence time can vary. In the fed state small particles (up to 5 mm in diameter) can empty with the liquid fraction of the meal but larger particles (> 5 mm) stay in

the stomach until digestion is finished and the fasted state is reached with Phase III contractions, hence food uptake with administration of drug can affect the transit times for the solid-dosage form. Gender, age, diseases, other drugs *etc.* can affect the gastric emptying rate, for example metoclopramide can accelerate the gastric emptying (Nimmo *et al.*, 1973).

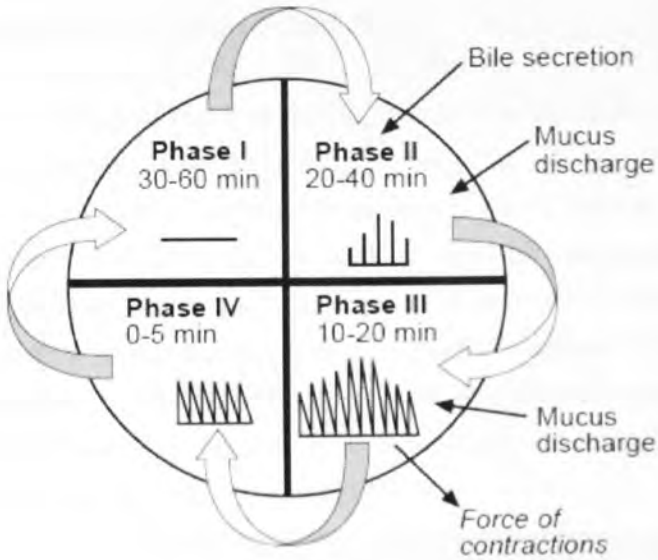


Figure 1.2- Diagram of IMMC phases (Reproduced from Batchelor and Conway 2007)

Small intestinal transit is much more constant compared to gastric emptying due to regular size and structure of the small intestine. Normally transit times through the small intestine are 3-4 hours.

Large intestinal transit times can vary greatly. Large particles pass through quicker (15-30 h) whereas smaller particles can take up to 40 hours before passing through completely. This phenomenon is due to the mucus secreting cells in large intestine allowing small particles to get stuck in the mucosa and therefore taking longer for clearance (Macheras *et al.*, 1995).

Modification of the transit times in the upper GI tract can be achieved by adjusting the dosing conditions, formulating a product which swells in the stomach causing extended residence time and using bioadhesive polymers where the dosage form can adhere to gastric mucosa

inhibiting the dosage form from emptying with the rest of the food stuff (Singh and Kim 2000; Jackson *et al.*, 2001; Jackson and Perkins, 2001).

Once the solid-dosage form has reached the site of absorption, the drug must dissolve in order to be absorbed through membranes. The next section discusses the processes involved with dissolution and what affects it.

1.3 From solid form to dissolved drug

In order drugs to be absorbed, they need to be dissolved in the GI fluids. Generally, IR solid-dosage forms are formulated so that they disintegrate and deaggregate as soon as the solid-dosage form reaches the GI fluids. Depending on the drug, the rate limiting step could be either dissolution or absorption of the drug; if the drug is poorly soluble in aqueous medium (saturated solubility << 0.1 mg ml^{-1}) then dissolution might be rate limiting whereas another drug may dissolve quickly in the GI fluids but stay in the ionised form leading to precipitation not absorption. If a drug has a low solubility in aqueous medium, inclusion of dissolution enhancing excipients may increase the dissolution rate. The Biopharmaceutical Classification System (BCS) categorises drug substances into four classes according to solubility and permeability of active pharmaceutical ingredient (API):

- **Class I** "high solubility and high permeability"
- **Class II** "low solubility and high permeability"
- **Class III** "high solubility and low permeability"
- **Class IV** "low solubility and low permeability"

Dissolution of solid drug can be expressed as solid coming in touch with solvent (diffusion layer) where drug particles are then released to the bulk solution (Figure 1.3), the Noyes-Whitney model. The rate limiting step in this model is the rate of transfer of the dissolved particles in the diffusion layer to the bulk solution from which the dissolved drug can be available for absorption. The Noyes-Whitney model can be expressed as the mathematical equation:

Equation 1.1 $$\frac{dw}{dt} = k(C_s - C)$$

Equation 1.2 $$k = \frac{DA}{h}$$

Equation 1.1 describes how mass of solid dissolved in time t (dw/dt) is dependent on dissolution rate constant, k, and the difference between the concentration of saturated bulk solution, C_s, and concentration of the dissolved drug, C. The rate of the dissolution is dependent on the relationship between the diffusion coefficient, D, and exposed surface area of the solvate, A, in relation to thickness of the diffusion layer, h. In order for the model to be valid, so called sink conditions should apply in which term (C_s-C) can be simplified to C_s. This is allowed only if solute is removed from dissolution medium at a faster rate than solid drug dissolves into the dissolution medium or if the volume of the medium is large enough for the concentration of dissolved drug (C) never to exceed 10% of the saturated bulk solution concentration (C_s). If the sink conditions are not valid then the *in vitro* dissolution profile may not reflect reality as, for example, the dissolution of a solute can be hindered due to concentration of dissolved drug nearing saturation.

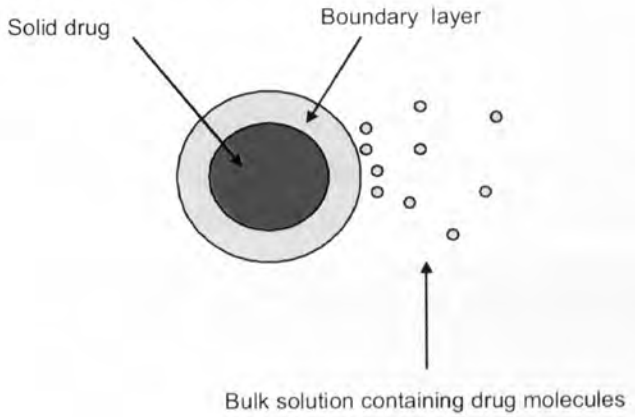


Figure 1.3- Diffusion model of dissolution mechanism according to Noyes-Whitney model (Reproduced from Macheras *et al,*. 1995)

Many other factors can affect the dissolution process. For example, if the drug is administered together with food or after food consumption, the diffusion coefficient can be decreased due to an increase in the viscosity of the fluids in the GI tract which can lead to decreased dissolution. Other factors such as increased surface area of the drug (by micronisation) or increased agitation in the gut can lead increased dissolution of the drug. If the drug is prone to biotransformation, alternative delivery systems should be considered in order to avoid enzymatic attacks in the GI tract (Macheras *et al.*, 1995; Florence and Attwood, 1998a).

Formulation of solid-dosage forms can be optimised so that desired effects are obtained from the dosage form. Inclusion of excipients can either hinder or accelerate dissolution of the

drug, for example inclusion of disintegrants generally leads to increased dissolution rates due to fast disintegration of the solid-dosage form with increased surface area of the solid drug allowing immediate dissolution. Generally all solid-dosage forms are coated in order to protect them from light and humidity, mask the unpleasant taste of the formulation and increase mechanical strength to ease handling at the manufacture stage. Normally a conventional hydroxypropylmethylcellulose (HPMC) -coating is utilised as it provides advantages mentioned above without presenting a physical barrier resulting in decreased dissolution due to increased lag times. Although these coatings are widely used they also introduce problems of their own either in the production or once in the market place (see sections 1.6.2 and 1.6.5).

Once solid-dosage forms have dissolved the drug needs to be able to cross the physiological membranes in order to reach systemic circulation and lead to a pharmacological effect. The next section discusses absorption of drugs within GI tract.

1.4 Absorption of drugs from the GI tract

Absorption of orally administered drugs is a complex process due to digestion and absorption of foods and nutrients, presence of enzymes, bile salts, fat and microbial flora, pH of the GI fluids and physicochemical properties of drugs. Hence it is impossible to predict an exact mechanism for absorption of drugs but in majority of the cases it is thought to be a passive diffusion through GI epithelium.

The GI tract consists of the stomach, small intestine and large intestine and GI tract can be considered as muscular tube having a mucosal lining consisting of three layers (epithelium lining, lamina propria and muscularis mucosa). The stomach digests food and is not the primary site for drug absorption because the mucosal area is small, the surface of the epithelium is covered in mucosal cells rather than absorptive cells and the residence time can vary in the stomach, but it still provides an absorption site for example for weakly acidic drugs in unionised form with prolonged residence times.

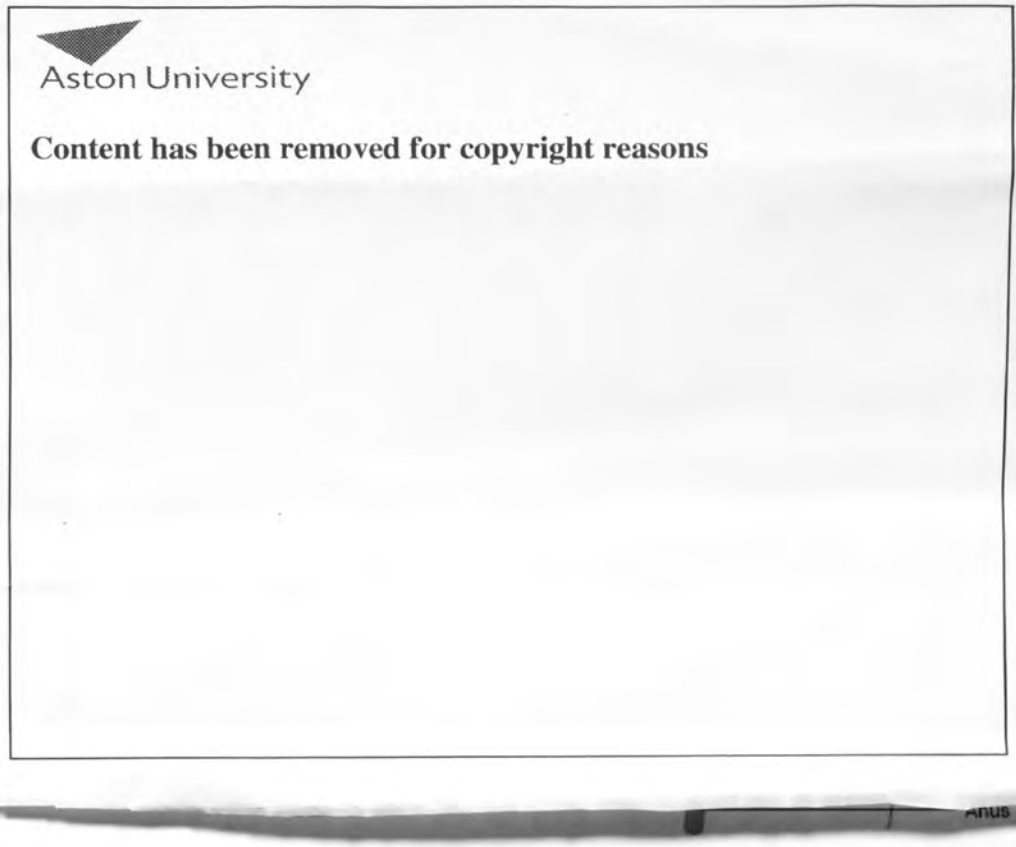


Figure 1.4 Illustration of GI tract (reproduced from Batchelor and Conway 2007)

The main absorption site for drugs is the small intestine. The epithelium lining in the mucosa of the small intestine consists of columnar cells involved in absorption and the mucus-secreting goblet cells. This lining provides a vast surface area for drug absorption because of folds of villi and microvilli. Villi are finger-like shapes on the mucosal surface covered in microvilli which comprises a brush border hence increasing the total surface area available for absorption. The microvilli are coated with glycocalyx made of mucopolysaccharides, which is covered in mucus produced by goblet cells, and an unstirred aqueous layer. For drug to be absorbed it has to pass these layers in order to reach columnar cells of the epithelium lining, then diffuse through basal membrane at the bottom of the columnar cells and basement membrane before reaching the lamina propria which contains connective tissue, blood and lymph vessels (Figure 1.5).

The function of large intestine is to absorb water and produce mucus to aid the movement of intestinal contents down the GI tract. However drugs which have not been absorbed (intentionally or unintentionally) from stomach or small intestine may be absorbed in the large intestine.

There are two possible routes for drug to pass through epithelium, transcellular transport (through the cells) or paracellular transport (in between the cells). Transport between the cells has been noted for water, electrolytes and small molecules which is thought to be due to extension of the pore size under specific conditions, for example elevation of the local pH. Another theory for paracellular transport is a solvent drag effect whereby small molecules are dragged through with natural fluid absorption (Krugliak *et al.*, 1989). The paracellular route can also provide an alternative route for drugs which are polar therefore unable to pass through the lipophilic cell membrane. Transcellular transport is the primary route for drug absorption. One possible mechanism is carrier-mediated transport across the cell where drug reversibly interacts with *e.g.* a protein of the membrane, which then acts as a carrier for drug. This process is very complex and requires high specificity, may not be guaranteed due to competition between molecules for the carrier and it needs energy to be able to function (generally energy release obtained from the conversion of ATP to ADP). It is suggested that the main mechanism for transport could be passive diffusion of drug through the columnar

cells in the epithelium lining but for this to be effective the drug needs to be lipophilic *i.e.* in its unionised form to be able to cross the lipophilic cell membrane. There is a relationship between the partitioning coefficient (P) of drug expressed as log P and permeability of drug through the cell membrane: drugs with higher log P values possess more lipophilic characteristics and therefore readily diffuse across the cell. This process is controlled by equilibrium reactions where a concentration gradient is required so that the unionised form is favoured in the GI tract and the ionised form is favoured once drug has been absorbed through the cell into the bloodstream to allow more unionised species to cross the membrane. This mechanism also prevents the flow of unionised species back to GI tract (Figure 1.6).

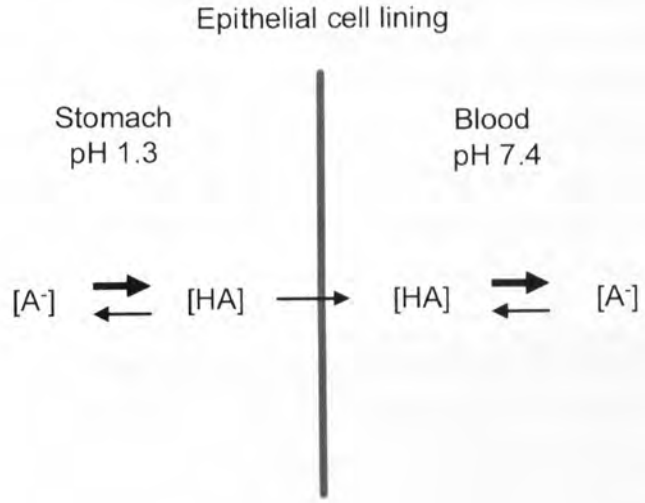


Figure 1.6- Diagram of ionised and unionised forms of a weakly acidic drug in the stomach and blood (thicker arrows describe more favourable reaction at each physiological conditions)

Ionisation of the drug is also dependent on the pH of the GI fluids, this and above observations led to pH-partitioning theory which states that only unionised species can cross the lipophilic membrane. The pH-partitioning theory utilises the Henderson-Hasselbalch equation for weakly acidic/basic drugs where pK_a is the negative logarithm of the acid dissociation constant of the drug, [HA] and [A^-] are fractions of unionised and ionised forms of the weakly acidic drug ([BH^+] and [B] for weakly basic drugs). Two equations can be used to predict the fraction ionised/unionised at given pH where Equation 1.3 can be used for weakly acidic drugs and Equation 1.4 for weakly basic drugs.

Equation 1.3 $$\log\frac{[A^-]}{[HA]} = pH - pK_a$$

Equation 1.4 $$\log\frac{[BH^+]}{[B]} = pK_a - pH$$

Although the pH-partitioning approach gives a general picture what might be happening at certain absorption sites it is not completely representative of the complex drug absorption process in the GI tract. As pH of the absorption site is crucial for ionisation, it cannot be known for sure how these conditions vary between individuals and if the dosage form has been taken together with other drugs or foods. The pH of stomach can vary between 1-3 but it has also been noted that in extreme cases the pH in the stomach might be as high as 7 which would greatly affect the drug dissolution (Florence and Attwood, 1998b). The pH variations in the small and large intestine are not as substantial as in the stomach. Also the epithelium lining of mucosa in the small intestine is coated with an unstirred aqueous layer and protective mucus layer which is thought to have pH of 5.3, that being lower than the bulk pH (Florence and Attwood, 1998b; Ashford 2002b). This may explain why some weakly acidic drugs have high absorption within these regions. Inclusion of strong acidic/basic excipients in the formulation, or simultaneously taken antacids, can change the pH of the GI fluids therefore the pH conditions may be different than during the fasted state. There are other complex reactions constantly taking place in the human body which all may influence the drug absorption, but although there can be variations, the pH-partitioning theory provides a general guide to absorption of drugs. Figure 1.7 summarises various processes taking place after drug administration which can all affect the rate of dissolution and absorption. For example before reaching the systemic circulation, drug can go through transformation reactions in the GI tract (intestinal metabolism) or the liver (hepatic metabolism) caused by enzymatic breakdown, inactivation and therefore a lack of pharmacological effect. Drugs such as penicillin which undergo hydrolysis reactions in the stomach's acidic conditions can be enteric coated, protecting the active ingredient from the acid and inhibiting dissolution until it has reached a higher pH in small intestine keeping the drug in its active form, enhancing bioavailability of the drug. Also design of prodrugs (chemical derivations of parent drug) can solve the problem of biotransformation due to insolubility at gastric pH but release of parent drug can occur at intestinal pH hence leading to pharmacological effect (Macheras *et al.*, 1995; Florence and Attwood, 1998b; Ashford, 2002b).

Figure 1.7- Diagram of possible processes which may affect solid-dosage form after administration (reproduced from Florence and Attwood, 1998)

1.5 Introduction to tablet core formulation

It is very rare that drug by itself is compressed into a solid-dosage form because the physico-chemical properties may not allow it; the active ingredient may be sticky therefore powder flow would be poor hence an excipient may be added to improve the flow characteristics. Thus, tablet core formulations contain active ingredient and excipients which have a specific function; excipients can enhance flowability, compressibility, disintegration, solubility *etc.* of the resulting powder mix or the excipients may have several functions, like starch which can be used as diluent, binder or disintegrant. The main categories of excipients are diluents, binders, adhesives, lubricants, glidants, antiadherents, (super)/disintegrants, colour and flavour agents. Although excipients are considered to be nonactive ingredients, they can still react with other excipients or drug leading to undesired effects (Banker *et al.*, 1980). It is also possible that excipients are slow dissolving therefore they can retard the onset of drug release (Vueba *et al.*, 2004).

Diluents such as lactose and starch are used in the tablet formulations variably; if dose of the active ingredient is small then there may be need for larger amounts of diluent to ease the tabletting process and to obtain tablets which are a reasonable size. Other tablets may

contain large amounts of active therefore there might be only small amounts of diluent, if any. Diluents can also affect the dissolution of product; a study on ketoprofen-containing matrix tablets showed that formulations containing lactose produced slightly decreased mean dissolution times compared to formulations with β-cyclodextrin as diluent (Vueba *et al.*, 2004).

Binders, as well as *adhesives*, add cohesive properties to the tablet providing adhesion to the powders, and they can be either water soluble or insoluble. Such examples are methylcellulose (MC) as a water-soluble binder and polyvinylpyrrolidone (PVP) as water-insoluble binder. Binders can be used as solutions or dry powders and are required to be evenly distributed in the powder mix to allow uniformity throughout batch.

Lubricants such as talc or stearic acid are used to reduce the friction between the tablet and the die. Typically lubricants are water-insoluble therefore high concentrations of lubricants may lead to increased disintegration times and decreased onset of drug release. Talc can also be classed as an *antiadherent* which is used if the formulation has got tendency to pick during the compression process. Alternative antiadherents are *e.g.* DL-leucine and colloidal silicon dioxide (Banker *et al.*, 1980).

The function of the *glidant* is to enhance the flow of granules in such way that the composition remains uniform and the granules do not separate because of vibrations during the tabletting process.

Disintegrants such as microcrystalline cellulose are used to promote disintegration of the tablet by swelling which results from water absorption *via* capillary action. Water entering into the tablet breaks hydrogen-bonds between cellulose molecules leading to disintegration. The typical range of disintegrant in formulations is 5 to 20%. Disintegration using lower levels is possible if so called *superdisintegrants* are exploited. These act same way as disintegrants but are more powerful, thus lower levels are sufficient. Croscarmellose sodium is a superdisintegrant, and levels of less than 5% are enough for activating disintegration as it swells up to 4-8 times its original volume when in contact with water (Guest, 2005). Another excipient that can aid rapid tablet disintegration is sodium bicarbonate (Grattan *et al.*, 2000); the sodium bicarbonate reacts violently with acid and water resulting in the disintegration of the solid-dosage form.

Colours and flavours do not act as enhancers in the tablet manufacture process, other than colour may be used to identify products in the production line. Also colours can be beneficial

for the end user for the same identification reasons. Flavours are used to mask unpleasant tastes of the active ingredient or excipients: as an example of colour is yellow iron oxide (Hogan, 2001) and flavour a natural blackberry type flavour W.S. #2705 (GSB Flavor Creators, 2008).

Excipients listed above aid the process of tablet manufacture and depending of the physico-chemical characteristics of the drug, some of the above may be included in the tablet formulation. Also manufacture method of the granules for tabletting can affect the behaviour of the solid-dosage form *in vitro* and *in vivo*. The tablet mass can be prepared by mixing active ingredient with excipients which is then tabletted (so called direct compression). If the excipients and drug mix in homogeneously and the mass is compressible, this is most preferred way of manufacture as the process is simple and straight forward. Typically the direct compression requires direct compression-grade excipients which flow well and compress into tablets easily. Alternative way to prepare tablet mass is to make well flowing granules. Typically formulations then require at least a binder which ensures that the excipients and drug are sufficiently bound together. Also glidants are often used to ensure good flowability of the tablet mass. Granules can be prepared either in a dry process or wet process; in wet granulation a solvent together with a binder is used for the granule formation.

Careful consideration of the tablet core formulation can lead to desired effects, *e.g.* requirements for fast dissolving drug and requirements for colon specific product formulation are very different as one needs a fast action where the latter would need to survive the upper GI tract intact. Tablet cores are often coated for example in order to mask the unpleasant taste of the tablet core or protect it from the acidic environment in the stomach; next section discusses tablet coatings in general.

1.6 Introduction to tablet coatings

The aim of this thesis was to investigate tablet coatings as pre-formed films as well as coatings therefore it is essential that issues relating to tablet coatings are discussed.

The popularity of tablet coatings has increased despite the additional cost of manufacture. This may be due to patient compliance as well as advantages in medication lifetime due to coating. Some drugs can be bitter tasting therefore additional coatings will allow the patient to swallow the medicament without tasting the active ingredient and it has been also claimed that these coatings ease the swallowing of the tablet. Oval shaped film coated tablets (in comparison to uncoated caplets, tablets and gelatin capsules) have been found to be easier to swallow and show less lodging and less extended transit times in a study carried out by

Colorcon Inc. (NewsBlaze, 2006). It was identified that the tablet shape and size together with the coating can enhance swallowability of the dosage form but the effectiveness of coating on its own as a factor was not studied. Jones and Francis studied patient preference for softgels *versus* solid-dosage forms and found that patients perceived Gelcaps® (see also Chapter 3) as easier to swallow which might be an indication that people prefer coated formulations over uncoated ones (Jones and Francis, 2000). The coating can also protect the active ingredients from light and moisture which can cause premature aging of the product. The coating also protects the formulation from chipping during packaging in manufacture therefore guaranteeing the correct dose in the tablet. An additional advantage of tablet coating is the aesthetics of the product, making it easier to identify by the patient and the pharmacist.

Previously organic solvents were used in the tablet coating process as organic solvents were cheap and convenient to use due to low latent heat of vaporisation allowing easy drying conditions for the coating process. When the requirement for aqueous based coating became prevalent, mainly due to increased costs and hazardousness of organic solvents and introduction of increased safety measures, it became apparent that current coating and drying methods were inadequate. Improvement of processes and drying conditions has led to use of water as a coating solvent even for moisture sensitive cores.

1.6.1 Coating technologies

There are three main methods for coating tablets: pan coating, perforated pan coating and fluidised bed coating methods. *Pan coating* consists of a round (hexagonal or pear-shaped) pan, rotated at a constant speed in which a bed of uncoated tablets is sprayed, allowing uniform coating. To dry the tablets, dry air is blown onto the surface of the tablets and the resulting moist air exhausted from the pan *via* ducts. The drying process in the conventional pan coater is not ideal (only top of the tablet bed is getting dried) hence the Glatt immersion sword was developed in order to improve the drying conditions. The sword is immersed into the bed of tablets containing inlet and exhaust air ducts, allowing more efficient drying of the coating. This type of pan coating is still used but mainly for sugar coated tablets.

Perforated pan coating was developed in order to improve the drying conditions further by perforating the coating pan to allow exhaust air to be withdrawn in several parts of the pan underneath the tablets and not only at the top of the tablet bed. The perforated bed can utilise various types of drying air inlet *e.g.* supplying of air underneath and/or on top of the tablet bed and this method is used for application of aqueous tablet coatings.

Fluidised bed technology has been used for granulation and rapid drying of powdered materials for decades in the pharmaceutical industry and its use has been extended for application of tablet coatings. There is a spray nozzle in the middle of the bottom of the coating chamber, with air flow from bottom to top. The air inlet is higher in the middle of the chamber allowing tablets to rise through the inner partition through sprayed solution. Due to decreased air flow on the sides of the chamber, the tablets fall back down due to gravity where the process of coating starts again. This method is highly efficient, leading to decreased drying times and increased uniformity of the tablet coating (Figure 1.8). This method is based on the first patent of the design by Wurster in the 1950s (Wurster, 1953). Depending on the functionality of the coating, the process variables need to be optimised to achieve the optimum process with desired outcome. For example, the fluidised bed process can be divided into 3 different spraying processes: bottom spray (Wurster), top spray or tangential spray and depending on the function of the coating and/or the properties of the coating materials, the suitable coating method can be chosen. The top spray comprises a fairly small coating chamber therefore does not necessarily provide a uniform tablet coating and the tangential spray method can induce mechanical stress on the tablets, and therefore can lead to friability issues. Due to its widest application range, uniformity and reproducible film characteristics, the Wurster model is most widely used, although it is impossible to access the spray nozzle whilst running the experiment. These so called film-coating technologies are preferred over sugar-coating because there is a reduced weight increase due to coating (from over 50% to 2-4%), faster processing times, easier automation and there is a greater range of materials and systems available (Porter and Bruno, 1990; Mehta, 1997).

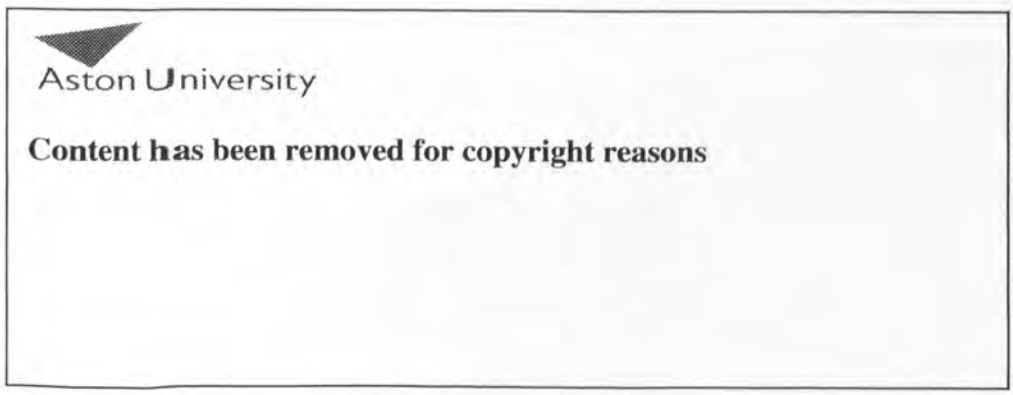


Figure 1.8- Wurster's fluidised bed coating principle (reproduced from Porter and Bruno, 1990)

Some pharmaceutical dosage forms, especially capsule shaped tablets (caplets), are dip-coated. This process is straight forward as the solid-dosage form is dipped into a polymeric solution, one end at the time and dried. The same is then repeated on the other end (or side) of the solid-dosage form. The thickness of the coating is controlled by the viscosity of the polymer solution or the dipping process is repeated until the desired level of coating is reached. Disadvantages of the dipping method are that the core has to be either pre-coated to protect the core or it has to be solvent resistant whether it is an aqueous or organic based polymer solution.

Although the coating methods described above are widely used and very common, they still can be time-consuming especially at the method development stage. Depending on the tablet surface properties, the process and the coating formulations have to be optimised for each product individually which is crucial to avoid sticking of the tablets. This has led to the search for an alternative coating methods consisting of more straight forward processes with fewer variables to complicate the system and where the technologies could be used also for immediate release coatings as well as functional coatings without extensive process optimisation between different coatings.

Press-coating has been available for decades and was originally used for water-sensitive cores where dry granular material would be pressed around the core in the tableting machines (Hogan, 2002). Waterman and Fergione utilised a press-coating technology where an IR tablet was coated with controlled release (CR) powder utilising a Manesty F-press. They filled the die with CR powder, placed the IR tablet on top and added remaining CR powder on top before compressing it, forming a new combination dosage form without friability issues due to adhesiveness of the press-coating (Waterman and Fergione, 2003). Although film coating is more popular today, the press-coating is still used for chemically incompatible materials (Hogan, 2002).

Another technology for coating tablets was patented by Kessel *et al.* who described a process where a thin, dry, polymer film was wrapped around tablets by applying a vacuum one side at a time, forming a thin polymer coating and providing an alternative to the spray coating process (Kessel *et al.*, 2002). This coating principle was studied in this thesis (Chapter 5) and pre-formed film work (Chapter 4) was carried out to identify how film characteristics were altered with inclusion of different excipients. For the coating process to be successful, it may be that the films need to be flexible in order to be able to pull around tablet when the vacuum is applied but they need to be strong enough for handling and for the coating process so that the film does not break before it is coated onto the tablet. In this

work, this particular coating method by wrapping the film around the tablet is called wrap-coating.

1.6.2 Functions of coatings

As presented in section 1.1, solid-dosage forms can be divided into two main categories: immediate release and modified release dosage forms. Immediate release dosage forms are required to dissolve quickly and therefore be available for absorption as soon as possible. Immediate release products are generally coated with a conventional HPMC-coating to provide taste masking and ease the handling of the solid-dosage form without delaying the release of active, therefore not producing a physical barrier for dissolution. Modified release can be obtained either by delaying release and/or sustaining release of the drug. Delayed release can be obtained for example by coating the solid-dosage form with gastric-resistant polymers hence the active would be protected from stomach's acidic conditions and the active could then dissolve in small intestine avoiding pre-systemic metabolism. For example, Eudragit L30 D-55 is a delayed release polymer comprising methacrylic acid and ethyl acrylate monomer units in a 1:1 ratio.

In addition coating can be used to identify the solid-dosage form during manufacture, in the pharmacy and by the patient. It has been suggested that solid-dosage forms without unique embossing or coating can be easily faked *e.g.* uncoated tablets and conventional HPMC-coated tablets are reproducible outside authentic manufacturing companies. This presents a real problem as pharmacies and patients may be supplied with counterfeit products which, in the worst case, may not even have the right active ingredient or the dose. Thus unique coatings could also help patients to identify medication and help elderly people to distinguish one medication from another.

1.6.3 Film formation

Conventionally films sprayed on tablets are considered to be continuous films although the coatings are generally built-up using several layers until an homogeneous coating is achieved. The process of conventional film coating consists of droplets of polymer reaching the substrate and wetting the surface. The droplets start to spread and coalesce, forming a thin polymer film once completely dried (Figure 1.9). The structure of the film depends greatly on the rate of solvent evaporation; initially the rate of solvent evaporation is fast resulting in a high polymer concentration followed by further but much slower solvent evaporation through the polymer matrix until a solidification point is reached and the remainder of the solvent is

evaporated. Total removal of the solvent is impossible without application of heat, requiring temperatures much higher than the glass transition temperature, T_g, (where polymer becomes rubbery and can deform without breaking) hence it is expected that the coating may contain some moisture. It should be noted that any evaporation much past the solidification point can result in shrinkage and therefore introduce internal stress into the film which might lead to problems in the coating (Rowe, 1981).

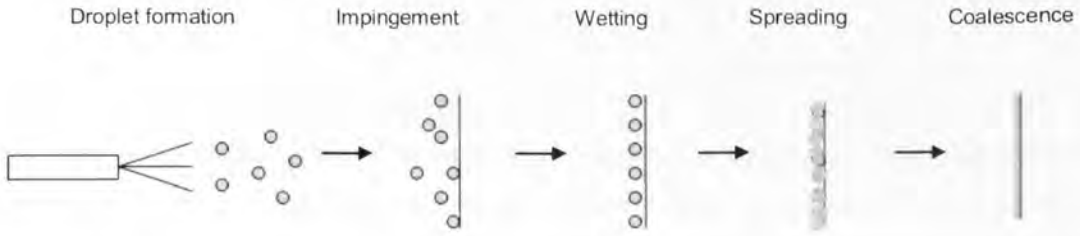


Figure 1.9- Process of film formation from spray (reproduced from Aulton and Twitchell, 1995)

Other factors affecting film formation from a sprayed solution are the properties of the polymer formulation such as the wetting power of the sprayed droplets, wettability of the surface and properties of the solution. For example, the surface tension of the solution can affect how the droplets form and behave prior forming the continuous film, and if other possible physical properties are ignored, it can be said that a reduction in the surface tension would result in better droplet forming and spreading of the droplets. The film formation process, as a whole, includes very many variables leading to a complex process which might not be completely predictable but individual variables can be measured and used to understand the processes taking place (Porter and Bruno, 1990; Aulton and Twitchell, 1995).

The film-forming process described above is mainly for films which are formed by spraying. If a pre-formed film is utilised as a coating material, some of the above issues do not apply. A film can be made by casting, where polymer solution is poured onto an inert, even plate and left to dry, so wetting properties and issues relating to droplets play minor role. Successful film formation is greatly dependent on the stability of the solution formulation and vaporisation of the solvent. If the polymer solution is physically and thermally stable, *i.e.* does not separate on standing, or on heating (if dried in an oven), then the drying conditions can be optimised. Some polymer solutions may become less viscous on heating which can lead to migration of the polymer solution. This can cause an uneven film thickness which is not desirable when the requirement is for a uniform coating. The temperature of the drying

conditions can affect the film formation, *i.e.* higher temperatures will lead to increased evaporation rates for the solvent but can also introduce stability issues.

Minimum film formation temperature (MFT) depends on the T_g (for definition, see section 1.6.6.3) of the polymer system and film formation can only take place above this temperature as the polymer exists in a softer and more rubbery state instead of being hard and glassy (Hogan, 1995; O'Donnell and McGinity, 1997).

1.6.4 Excipients for tablet coating

A typical film formulation consists of a solvent and a polymer which form the basis of the film. These can be chosen according to the function of the coating, properties of the substrate (*i.e.* tablet surface) and the process to be used for the coating. Additional excipients can be used to refine the properties of the film such as strength and flexibility which can be enhanced, for example, by inclusion of a plasticiser or surfactant to increase the wetting power. Also if the coating is for light protection then it may be crucial to add dyes or pigments to the formulation.

1.6.4.1 Polymers

Polymers can be divided into three categories according their origins: I) synthetic polymers II) semi-synthetic polymers and III) biopolymers. Examples of *synthetic polymers* are acrylic polymers which are commonly used for gastric insoluble coatings or to obtain controlled release properties. Acrylic polymers are water insoluble and were used in combination with organic solvents but the pressure to move towards use of cheaper and safer solvents (water) led to the development of acrylic polymers as an aqueous dispersion for use in film formation. Eudragits® are widely used acrylic polymers which are often aimed for modified release formulations as they generally are not soluble in GI fluids but are swellable and/or permeable. Depending on the grade, they consist of ethyl acrylates and methyl methacrylate and by addition of quaternary ammonium groups, the aqueous solubility can be enhanced, *i.e.* these polymers can be designed to provide the desired solubility profiles. Although acrylic polymers are mainly used in modified release formulations, particular Eudragit® polymers (*e.g.* grade RS 30D) can be combined with water-soluble excipients such as polyethylene glycol for use in immediate release formulations and the opposite effect can be obtained by addition of hydrophobic excipients (Ghebre-Sellassie *et al.*, 1997). Bodmeier and Paeratakul showed Scanning Electron Micrograph (SEM) pictures of Eudragit® RS 30D polymer films plasticised with water-soluble triethyl citrate or water-insoluble acetyl tributyl

citrate. After exposure to 0.1 M NaCl solution, it was clear that the formulation with triethyl citrate formed pores in aqueous media whereas the film containing the water-insoluble excipient was not pore forming, therefore there was no leaching of ingredients and no increase in the dissolution rate of the film (Bodmeier and Paeratakul, 1993).

Examples of *semi-synthetic polymers* are cellulose-based polymers. Cellulose is practically insoluble in water but methylation or carboxymethylation increases its aqueous solubility, and therefore a range of grades of cellulose based polymers with varying properties is available. Hydroxypropyl methylcellulose (HPMC) is probably the most widely used cellulose polymer because the films produced are tough, uniform, can add protection from light and mask unpleasant tastes. Additionally, it is soluble in some organic solvents, water and at all pHs in the GI tract. Another reason for its popularity is because it has been used in food industry for decades, it is therefore regarded as safe for human consumption. Cellulose polymers are generally characterised by their molecular weight determined by Gel Permeation Chromatography (GPC) but because this technique is slow and time consuming it is much more common to characterise these polymers according their viscosity as this is directly correlated to the molecular weight. Typically the viscosity is based on a 2% solution at 20 °C, *i.e.* the viscosity of low substituted HPMC might be 3 mPa.s for a 2% solution at 20 °C. Low viscosity cellulose polymers are used in coatings, especially for IR solid-dosage forms, and generally viscosity of the formulations does not exceed 100 mPa.s. There is a relationship between the viscosity of the polymer and percentage used in the formulation *e.g.* grades 3, 6, and 15 mPa.s would have a maximum concentration of 14, 7.5, 4.5% respectively in coating formulations (Nagai *et al.*, 1997).

Other cellulose based polymers include hydroxypropylcellulose (HPC) and hydroxyethylcellulose (HEC) which are both water-soluble polymers but possess lower mechanical strength compared to HPMC (Hercules Inc., 2005) and are less widely used in film coating applications. In comparison elasticity of the polymers HPC and HEC is much higher compared to HPMC (Hercules Inc., 2005).

The third category of the polymers according to their origin is *biopolymers*. These polymers occur naturally or they are obtained from plant or animal sources. Regarding pharmaceutical applications and especially solid-dosage forms, gelatin, obtained from animal collagen, is a widely used biopolymer due to its excellent film forming properties, glossy appearance, ability to hold dyes and neutral taste as well as its solubility in biological fluids at body temperature (Rama Rao and Pakhale *et al.*, 2003). Gelatin is also regarded as a non-toxic and non-irritant material (Singh *et al.*, 2002) and has a low cost (Maurer, 1954) which promotes its use in

pharmaceutical formulations. Gelatin is characterised by its bloom strength, which describes the rigidity of the gel [definition: "The bloom strength is a measure of gel rigidity and is expressed as the load in grams required to push a standard plunger a set distance into a prepared gelatin gel (6.66% (w/w) solution at 10 °C)" (Jones, 2002)] and generally lower bloom strength corresponds to lower viscosity and strength. Despite the desirable physicochemical properties of gelatin, the UK Foods Standards Agency (FSA) had stated that any gelatin-containing products, like vitamin supplements, should not be fed to animals as it is an animal-derived product, *i.e.* preventing intra-species recycling and therefore contributing to the Bovine Spongiform Encephalopathy (BSE)-related safety measures (Hind, 2001). Due to the ethnical reasons relating to the source of gelatin, the pharmaceutical industry has been looking for alternatives to replace gelatin.

A number of alternative biopolymers have been reported in the last 10 years. Starches are widely used in solid-dosage form applications as fillers, binders and disintegrants. Amylose-rich maize starch has a low oxygen permeability, is cheap and safe, and therefore was studied for its aqueous film forming properties in a theophylline IR tablet (Krogars *et al.*, 2002). The drug release was found to be pH-dependant and theophylline was rapidly released from the amylose-rich maize starch in an acidic medium. This could be advantageous for drugs requiring a fast release in the stomach's acidic conditions. However amylose-rich maize starch needs specially designed equipment for preparation of polymer solutions and for the coating process, which might limit its applicability. Phaechamud and his co-workers reported the use of chitosan citrate in film coated formulations and found that these coatings display pH-dependent behaviour which could also be altered by addition of excipients (Phaechamud *et al.*, 2000). Chitosan is obtained from the bio-waste of shellfish and due to high biocompatibility, biodegradability, low toxicity and structural similarities with celluloses, chitosan and its derivatives may be considered as an alternative for gelatin. Use of gellan, a microbial polysaccharide secreted by bacterium *Sphingomonas elodea*, in pharmaceutical applications (Balasubramaniam *et al.*, 2004) and in the food industry (Yang and Paulson, 2000) has been reported. Balasubramaniam *et al.* (2004) used gellan in film formulations for implants, investigating effects from plasticisers and crosslinking with calcium chloride and found that crosslinking was an effective tool for providing extended release in gellan films as implants. Yang and Paulson formed gellan films for biodegradable and edible food packaging and showed the potential of these films due to ease of manufacture of the film and variable properties depending on the excipients in the film formulation (Yang and Paulson, 2000).

Another biopolymer, pullulan, produces films which are biodegradable, transparent and resistant to oxygen which allows its use in the food and pharmaceutical industry (Lazaridou *et al.*, 2003). Pullulan is a polysaccharide produced from starch through a fermentation process. Capsugel® provides alternative capsules for gelatin made from pullulan or HPMC (Pfizer Inc., 2006) although pullulan can be expensive as well as difficult to source.

1.6.4.2 Solvents

Polymer and solvent are the only required excipients in film coating, solvent allows the polymer to dissolve and form a solution which can then be applied as a coating. The pharmaceutical industry has moved towards aqueous-based coating formulations due to environmental, safety and financial issues and encourages the use of water where it is possible. There are issues with use of water such as the latent heat of vaporisation is much higher for water than for organic solvents (alcohols, ketones, esters, chlorinated hydrocarbons) which caused problems initially when organic solvents were replaced with water in the coating processes. This was overcome by development of coating pans and the drying mechanisms applied (section 1.6 and 1.6.1). It has been also shown that solvent choice can affect the adhesion of the dry film on the substrate, and the trend is that there is less adhesion with aqueous-based films than organic (Fung and Parrott, 1980). This can depend on the surface characteristics of the substrate; aqueous-based films may not adhere to the tablet surface and the problem may have to overcome by process development or development of alternative formulations. In order to have a successful solvent-polymer system the solvent should be able to penetrate the polymer mass to allow sufficient dissolution. It should be thermodynamically stable and not too volatile (which does not present a problem in case of aqueous solvent systems) (Hogan, 1995).

1.6.4.3 Plasticiser

Plasticisers are typically non-volatile liquids or low melting point solids which are commonly used in film formulations to alter the physical properties of the polymer, generally making the polymer softer and more pliable, and to improve mechanical properties of dry polymer films *i.e.* making films less strong but more flexible. Inclusion of plasticiser may be crucial in the wrap-coating technology as some flexibility will be required for the polymer film to wrap tightly around the tablet (sections 1.6.1 and 4.1).

An example of this is if gelatin is plasticized with glycerol, the higher the plasticiser content, the weaker but more flexible the films become until the polymer-plasticiser ratio is too low

and a continuous film cannot be formed (Chapter 4). The plasticiser molecules move in between the polymer strands, weakening the polymer-polymer interactions and hence allowing the polymer strands move past each other. Therefore a plasticiser must be able to diffuse into polymer and not to migrate or leak out of the polymer. It is possible that plasticisers interact intermolecularly with the polymer chains, for example, by forming hydrogen bonds (H-bonding) between them (Bruce *et al.*, 2005). H-bonding can form in between hydrogen atoms and electronegative atoms such as oxygen, nitrogen and fluorine. H-bond is a force between the atoms, not a covalent bond. The addition of plasticiser can decrease the glass transition temperature (T_g) of the polymer, which makes it more workable at lower temperatures, and also lowers the minimum film formation temperature (MFT). Plasticisers are divided into two categories I) water soluble (*e.g.* glycerol, triacetin) and II) water insoluble plasticisers (*e.g.* tributyl citrate).

1.6.4.4 Colourants

Colourants are often used in film formulation to enhance the appearance of the final product. Branding and specific colours can also help the consumer and the manufacturer to identify the products. Colourant can be either a dye (water-soluble) or a pigment (water-insoluble). Phaechamud *et al.* investigated the compatibility of chitosan with various dyes and how the incorporation of dyes affected the thermal properties of the film, disintegration and dissolution properties of the coated tablets (Phaechamud *et al.*, 2000). They reported no problems associated with the use of dyes although it is thought that when the film is dried, the water molecules leave the film which can cause the water-soluble colour molecules to follow the flow therefore resulting in an uneven colour coating. This migration does not happen with pigments, hence the use of pigments is much more common in tablet coatings. Also pigments are much more opaque and therefore give more protection against the light and it is known that organic dyes are less stable compared to inorganic pigments (Hogan, 1995). Pigments also can increase the shelf-life of the product as they can decrease the permeability of the films to water vapour and oxygen. Maul and Schmidt (1995) studied the effect of pigments on Eudragit L 30 D-based film coatings and the drug release from the coated formulations. They concluded that the shape and size of the pigment affects the dissolution of the enteric-coated tablets; platelet-shaped particles decreasing bisacodyl release from Eudragit L 30 D-coated formulations (Maul and Schmidt, 1995).

1.6.5 Coating defects

All coating processes result in the solid-dosage forms undergoing certain stresses which can lead to batch rejection if process parameters are not optimised. Also, interactions between the core and coating are complex hence core characteristics (surface porosity and energy) and properties of coating formulation (viscosity and surface tension) need to be optimised. There are number of possible problems associated with film coating and the coated core. Coating processes can affect the properties of the core itself causing for example chipping due to mechanical stress and the following defects have been listed in the literature: picking, edge-wear, roughness, infilling, film cracking, bridging and film peeling (Porter and Bruno, 1990; Aulton and Twitchell, 1995).

Picking occurs when two coated solid-dosage forms touch too early in the coating process, *i.e.* when the surface is still tacky, resulting in temporary twinning. When the coatings dry, the solid-dosage forms break apart and pull the film off the core at the site of twinning, leaving pockets in the coating. Sometimes the twinning can be permanent. When coated solid-dosage forms' edges can become chipped (*edge wear*), it leaves the core exposed. This phenomenon could be due to friability of the core or film formulation producing brittle and/or weak films leading to these edge effects. Both picking and edge-wear may be resolved by changing processing conditions, increasing air inlet or decreasing pan rotation speed respectively.

Roughness (also called orange peel) of the film can be the result of an unsuitable film formulation (viscosity), unsuitable process conditions (temperature) and/or surface roughness of the core. Roughness appears as non-glossiness of the film and the surface looks like the skin of an orange. A problem associated with embossed solid-dosage forms is *infilling*. This occurs when the polymer solution, once sprayed, forms air bubbles which are protected from shear stress at logos or break lines and do not burst. This leads to accumulation of the coating material in the embossment until it reaches the actual surface of the solid-dosage form therefore making the embossment illegible or invisible. These problems associated with roughness and infilling can be corrected by altering the formulation or the process conditions.

Film *cracking, bridging and peeling* occur when internal stresses within the film change, *e.g.* in cracking, the internal stress overcomes the tensile strength of the film leading to cracks on the surface. In bridging, associated with embossing, the internal stress increases so that it causes the film to detach itself from the surface of the core in order to relieve the stress, thereby diminishing the effect of the embossing. *Peeling* of the film is due to increased

internal stress as in the case of cracking and bridging, and these can be very problematic especially in the case of functional coatings and can be overcome by increasing tensile strength of the formulation and/or reformulating the core and/or changing process conditions (Porter and Bruno, 1990; Rowe, 1997).

All defects relating to spray coated tablets can lead to batch rejection and in order to avoid this all the parameters and conditions have to be carefully optimised.

1.6.6 Characterisation of coatings

In order to prevent prolonged development processes or rejection of batches, it is beneficial to characterise films prior to the actual coating process. This can provide important information on mechanical properties such as tensile strength and elastic modulus, on stability issues as well as on interaction between excipients. Pre-coating studies can also offer information on dissolution, moisture or gas permeability and thermal properties of the film. These studies are generally carried out for pre-formed films (*i.e.* films sprayed/cast on inert support, dried and peeled ready for testing) but prior to forming a film, the method of making the film needs to be outlined. The majority of coating methods utilise spraying where the solid-dosage forms are sprayed layer by layer until a uniform film is produced. This method is probably the most representative of the actual coating process but cannot be directly represented by formation of a pre-formed-film so a direct correlation is not possible. Another method to produce a film is where the polymer solution is poured onto an inert plate, dried and peeled off for tests. If the solid excipients are completely dissolved in the solvent then an even film should result but again questions arise as to how representative to this film is compared to a film sprayed onto a solid-dosage form. Also it is not possible produce multi-layered films by a casting method because earlier layers may dissolve or interact with fresh layers (Obara and McGinity, 1994).

Although there are known problems relating to the correlation of pre-formed-film studies they still provide valuable information on properties of the film such as quality of the film, stability of the film, strength or softness of the film and aqueous permeability of the film. It is widely accepted that pre-formed films are suitable to use to study the characteristics of the films.

1.6.6.1 Mechanical characterisation

Mechanical characterisation is useful to analyse such properties of the films as tensile strength, puncture strength, strain, elastic modulus and toughness. The mechanical strength

of the coating film can be crucial in order for it to perform as expected without breaking during the coating process, packaging, transport or storage.

Tensile strength (σ_M) can be expressed according to Equation 1.5 where tensile force, F, in Newtons, before breakage divided by cross-sectional area of the sample (A) in mm^2, results in maximum tensile strength (MPa). Tensile stress can be calculated similarly, replacing maximum tensile force with tensile force at any given moment.

Equation 1.5 $$\sigma_M = \frac{F}{A}$$

Nominal tensile strain (ε_t, dimensionless ratio or %) is the increase in the length of the film (ΔL in mm, measured by distance between the grips holding the sample during measurement) per initial length of the gauge (L in mm) (Equation 1.6). The tensile strain at breakage point can be calculated similarly using the maximum length of the film before breakage as ΔL.

Equation 1.6 $$\varepsilon_t = \frac{\Delta L}{L}(*100\%)$$

Elastic modulus (EM in MPa) is a measurement of stiffness and rigidity of the film. It can be defined as the change in stress ($\Delta\sigma$ in MPa) divided by corresponding change in strain ($\Delta\varepsilon$) in the linear region of the curve (Figure 1.10, Equation 1.7). Generally the elastic modulus is calculated from the beginning of the curve but if a non-linear stress-strain curve is obtained, possibly due to viscoelastic behaviour being time dependent, then approximation of the placement for the tangent is operator-dependent which can lead to unreliable results. Therefore ISO 527-1 recommends using the region from -0.05% to 0.25% for the strain values and respective stress values in order to obtain reliable results. The lower value should not be zero in order to avoid any onset effects at the beginning of the curve (ISO 527-1 1993; Aulton, 1995).

Equation 1.7 $$EM = \frac{\sigma_2 - \sigma_1}{\varepsilon_2 - \varepsilon_1}$$

Together, tensile strength, strain at break and elastic modulus describe elasticity, strength and toughness of the film. Depending on the application the film may be required to be hard but strong and these mechanical characterisations can help in prediction of performance (Figure 1.10).

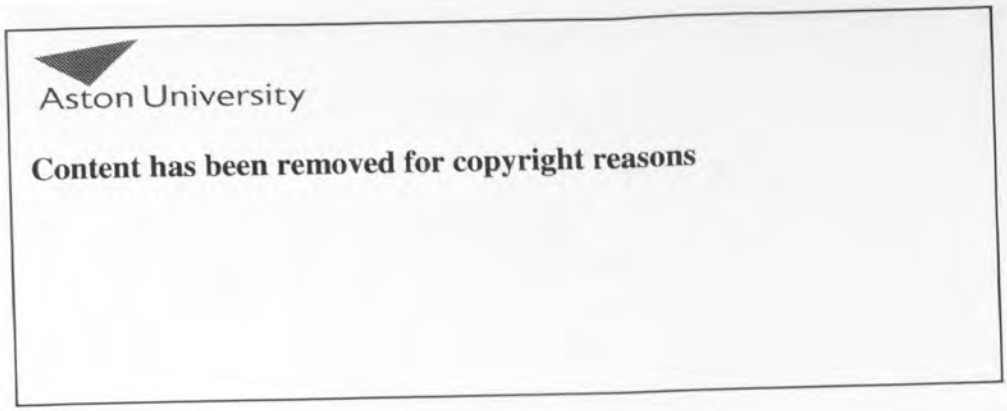


Figure 1.10- Stress-strain profiles owing different viscoelastic properties (reproduced from O'Donnell and McGinity, 1997)

Another mechanical strength test is the puncture test which determines the puncture or rupture characteristics of the film. A probe is driven through the film until it ruptures or an elongation limit is reached. Yang and Paulson used puncture testing to characterise plasticised gellan films under dry conditions (Yang and Paulson, 2000) and Bussemer and his co-workers devised a method to measure puncture strength following immersion in acidic fluids to assess the suitability of a film as a pulsatile release coating (Bussemer *et al.*, 2003). Puncture strength (σ in MPa) is defined as the force at a given moment (F in Newtons) per cross-sectional area of the film (A in mm^2) similarly to tensile strength. The % puncture strain can be defined be following equation, which takes into consideration the displacement of the radius instead of the length of the film (Radebaugh *et al.*, 1988):

Equation 1.8 $$\varepsilon_p = \frac{(r^2 + D^2)^{0.5} - r}{r} * 100$$

where r is radius of the film exposed (in mm^2) and D is the distance between initial contact of probe with the film and the probe position at the break of the film.

1.6.6.2 Permeation, dissolution and swelling characterisation

Although measurement of the mechanical properties is probably the most common characterisation, other properties can offer an insight into the behaviour of the film. For example, dissolution of the film can become important for functional coatings for solid-

dosage forms and gas/water vapour permeation studies can be valuable for polymer films intended for use in food products. Arvanitoyannis *et al.* (1996) studied the mechanical and permeation properties of chitosan/gelatin films in relation to characteristics of other polymer films employed in the food industry (Arvanitoyannis *et al.*, 1996) and Sobral *et al.* (2001) studied the mechanical, water vapour barrier and thermal properties of gelatin films formulated with sorbitol as edible films for the food industry (Sobral *et al.*, 2001). Generally, however, dissolution of polymer films is not studied (as pre-formed films) unless the film itself contains an active ingredient (i.e. drug). For example, dissolution of polymer films containing lidocaine has been studied utilising a dissolution bath with a paddle and disc to which the film is attached (Danjo *et al.*, 1995; Repka *et al.*, 2005). Generally dissolution of coatings for solid-dosage forms are not investigated in isolation but instead as a complete coated formulation (Phaechamud *et al.*, 2000). A reason for this may be the lack of appropriate analytical techniques for characterisation of the polymer release in isolation, where there are no interfering factors such as excipients. For example, dissolution of gelatin can be analysed by a bicinchoninic acid (BCA) assay for protein determination but interference is possible from excipients or drug. For fast dissolving dosage forms, it is important to choose a polymer for the formulation which is water soluble or soluble at physiological pHs. The dissolution of polymer then occurs when water (or suitable solvent for dissolution) diffuse into the polymer forming a swelling gel layer from where the polymer dissolves to the solvent (Miller-Chou and Koenig, 2003).

Swelling of the polymer can contribute to its disintegration and dissolution and is therefore generally characterised whatever the application (Bigi *et al.*, 2004; Yoo, Dharmala *et al.*, 2006). Typically the swelling is measured by weight gain of the film in a solution, *i.e.* pre-cut film is weighed and immersed into a solution for a given time, then the film is blot dried and the weight gain is measured (Equation 1.9; W_t weight at time t, W_0 weight initially).

Equation 1.9 $$\frac{W_t - W_0}{W_0} * 100$$

1.6.6.3 Thermal characterisation

The thermal properties, such as the glass transition temperature (T_g), crystallisation and/or melting of polymer films and materials are important, as well as determination of moisture content and degradation during heating of a material. During differential scanning calorimetry (DSC) the sample is subjected to a constant rate of heat increase and the changes in the sample, *i.e.* the energy difference in order to keep the temperature of the sample and inert reference material identical, is measured. Thermal techniques are widely used in the

pharmaceutical industry and other industries (*e.g.* plastics/polymer) because they provide information of the processes as a function of time and temperature at the molecular level. As DSC detects the heat flow differences between the sample and the inert reference material either at constant temperature or at constant change of temperature, the resultant curve shows exothermic and endothermic changes in the sample, *e.g.* melting of the sample is seen as an endothermic peak because melting absorbs energy. T_g of the sample can be obtained by DSC and this is the temperature at which brittle material (glass) turns into a rubbery material on heating which greatly affects the mechanical properties of the material hence widely used in characterisation of polymer films. The glass transition temperature can be seen as a change in baseline on a DSC thermogram and typically onset of transition temperature, T_g and ΔCp (change in heat capacity during transition) are acquired form the software.

Also Hyper-DSC™ as alternative for conventional DSC method has been established by Perkin-Elmer (McGregor *et al.*, 2004; Gramaglia *et al.*, 2005; McGregor and Bines, 2008). The hyper-DSC™ method differs from the conventional DSC method in the speed of the temperature scan where Hyper-DSC™ utilises heating scan rates up to 500 °C/min and a conventional DSC method typically uses scan rate of 10-20 °C/min. Hyper-DSC™ can only be used on power compensation DSC where the heat flow is measured directly and no mathematical manipulation of the results is needed. High speed temperature scanning makes the analysis more sensitive and the sample size needed is smaller (microgram samples can be used). Hyper-DSC™ is a useful tool for characterisation of drug molecules and also for studying changes in polymers *i.e.* T_g of the polymer (Goth *et al.*, 2003).

Thermogravimetric analysis (TGA) detects weight changes in a sample at a certain temperature or when temperature is increased. It can measure degradation of the material, moisture content and presence of volatile components in the sample. Although TGA is a valuable technique on its own, it is also a useful tool for analysis of materials prior DSC analysis as changes in the sample are established and degradation of samples within the pans can be avoided.

Another thermal technique is thermomechanical analysis (TMA) which records the sample dimensions as a function of temperature *i.e.* any changes in the sample size when the sample is heated/cooled are recorded (*e.g.* extension, flexibility and penetration).

1.7 Introduction to the oral cavity

A number of pre-formed film studies were carried out (Chapter 4) and suitability of these polymer films as a buccal delivery system was investigated (Chapter 6). Therefore a thorough introduction to issues relating to drug delivery to oral cavity is discussed.

Drug absorption *via* the oral cavity was first reported over 100 years ago when positive effects of nitroglycerin were noted in the treatment of angina pectoris when administered sublingually (Murrell, 1879). It has been only during the last decade when the popularity of the intraoral delivery systems (IDS) has grown leading to increased number of patents in the area as well as products in the market. Fast-dissolving formulations are most popular in U.S. and there is the scope for increasing their market share in other countries. Oral solid-dosage forms are still the most popular route and form for drug administration but for example first-pass metabolism and poor absorption can lead to decreased bioavailability of the drug. Delivery *via* the buccal cavity has the potential to improve bioavailability.

There are several sites for targeted drug delivery in the oral cavity: buccal, sublingual, periodontal, periodontal pocket, peribuccal, tongue and gum, and there are also several methods of delivering the drug at the target site: gels, ointments, powders, chewing gums, solutions, sprays, patches, bioadhesive tablets, lozenges, injections *etc.* The drug delivery sites in the oral cavity are divided into three specific areas: I) sublingual delivery, II) buccal delivery and III) periodontal, gingival and odontal delivery where first two provide sites for systematic and local delivery and the last for local delivery only, due to the specific mucosa covering it (masticatory mucosa).

Figure 1.11- Oral cavity (Reproduced from Washington *et al* 2001)

Sublingual delivery allows rapid drug absorption due to thinness of the epithelium on the floor of the mouth as well as large veins near the surface. Additionally, it is easy to access and convenient for administration. Studying drug penetration through animal/human sublingual tissue can be challenging *in-vitro* due to availability of the tissue but disintegration and dissolution characterisation *in-vitro* can help in understanding the properties of the dosage form *e.g.* Das and Das (2004) used a USP II dissolution bath in the investigation of buprenorphine release from a mucoadhesive film for treatment of drug addiction. Sublingual penetration studies are generally carried out *in-vivo* (Artusi *et al.*, 2003).

Intraoral dosage forms (IODs) can provide enhanced bioavailability due to absorption through the buccal membrane, avoiding the low pH and the stomach's metabolic enzymes as well as providing a dosage form which is conveniently administrated. Transit time is not delayed as the drugs are at the site of absorption immediately, and toxicity and irritation issues are minimised due to the relatively high turnover of cells compared to skin (Squier and Wertz, 1996). These kinds of IODs could be beneficial for children, animals and elderly, especially if the taste of the product is pleasant. Another great advantage is that IODs placed in the oral cavity can be removed at any time; this terminates absorption and as there are fewer variables concerned in the drug absorption through oral cavity, the drug delivery process can be more controlled and reproducible.

Although there are many advantages, there are also limitations associated with intraoral drug delivery. The size of the dose can be limited due to size of the IOD and the mouth has a small surface area (0.01 m^2) compared to the GI tract or skin, 301 m^2 and 1-2 m^2 respectively (Pfister and Ghosh, 2005). Another limiting factor is the constant saliva flow in the mouth which can be up to 1000 ml *per* day and therefore the IOD could be washed in to the stomach due frequent swallowing. The drug is then subjected to metabolism and potential losses in bioavailability. Also taste masking is mandatory if the drug is bitter-tasting. Therefore it is a challenge to design IODs so the drug is rapidly absorbed or the IOD can adhere to the oral tissue, maximising absorption but not causing any local irritation.

IODs designed for buccal delivery have been studied more frequently in recent years, mainly for local delivery of drugs, *e.g.* treatment of bacterial or fungal infections (Tallury *et al.*, 2007; Giunchedi *et al.*, 2002). The buccal mucosal area can be utilised for local and systemic delivery of drugs although permeability of the buccal mucosa is lower than the sublingual mucosa (which is almost three times thinner) but it is still a potential absorption site being much more permeable than other transepithelial routes. Utilisation of permeation enhancers can allow enhanced absorption or the use of mucoadhesive polymers in the dosage form formulations can provide prolonged action (Washington *et al.*, 2001). Buccal delivery avoids the acidic conditions of stomach and can increase the bioavailability of the active and drug absorption through buccal mucosa is independent of food consumption.

1.7.1 Structure of the oral cavity and absorption of drugs

All human and animal tissues have an epithelial top surface of the oral tissue protecting underlying sections but it can be structured differently depending on the region. As described in section 1.4, the GI tract lining consists of a single layer of epithelium cells but the epithelium in the oral cavity as well as the oesophagus is very similar to that of skin consisting of a multilayered epithelium (stratified epithelium between 40-50 layers). There are three types of mucosa with varying characteristics in the oral cavity: masticatory (gingiva and hard palate), lining (floor of the mouth, cheek, soft palate, underside of the tongue and lips) and specialized mucosa (tongue). The masticatory mucosa covers about 25 % of the total surface area of the oral cavity and it is keratinized similar to human skin (Squier and Wertz, 1996). The lining mucosa is non-keratinized, can vary significantly in thickness (190-580 µm) and is rougher and more permeable than keratinized regions. Similar mucosae can be found only in the oesophagus and uterine cervix. A specialized mucosa is found on the tongue and it consists of non-keratinized and keratinized epithelium (15% of the surface area of the oral cavity) (Squier and Wertz, 1996).

The general structure of oral epithelium is a stratified cell layer at the top, followed by cellular membrane-coating granules (MCGs) which produce lipid and glycolipid providing epithelial cohesion and the bottom of the epithelium consists of a basal layer which is the major permeability barrier for drugs. Similar to absorption for drugs from the GI tract, the drugs need to dissolve in the fluid saliva, and then there are two pathways for the drug to be absorbed through the mucosa: *via* transcellular or paracellular paths which depend on the physicochemical properties of the drugs such as polarity or molecular weight (see section 1.4).

1.7.2 Characterisation of orally dissolving dosage forms

As orally dissolving dosage forms are fairly new to the market there are no standard guidelines on what kind of characterisation is necessary for these products. Generally it can be seen from the literature that *in-vitro* studies include drug release studies utilising USP dissolution baths or Franz Cell types of arrangement, permeation, adhesion, swelling and thermal studies; *in-vivo* and *ex-vivo* studies include bioadhesion and drug release studies on human/animal subjects and substrate respectively (Li Wan Po and Mhando, 1984; Nicolazzo *et al.*, 2003; Das and Das 2004; Ikinci *et al.*, 2004). The dissolution, swelling and thermal studies are carried out similarly to the characterisation of the films (see section 1.6.6).

Franz diffusion cells consist of two compartments which are separated by a tissue (*e.g.* animal tissue, silicone membrane *etc.)* allowing passive diffusion through it. The receiver compartment contains a stirred solution which can mimic, for example, conditions in the blood (buffer at 37 °C) and the donor compartment contains the dosage form, possibly with a donor solution. The drug concentration in the receiver must always be much lower than the saturated solubility of the drug in that medium (*i.e.* sink-conditions need to apply) and the receiver fluid is sampled at certain time points and analysed to produce drug released *versus* time curves (Ikinci *et al.*, 2004).

Adhesion of the dosage form to the tissue can be measured using modified tensiometers, modified texture analyzers or similar as there is no standard method for determination of adhesive properties of mucoadhesive dosage forms. For example, the use of a tensiometer was reported where the ring was replaced with a "hanging plate" to which a tablet was secured. Mucin gel was placed at the bottom of the tensiometer and the hanging plate system was lowered as if measuring surface tension and the force needed to separate the tablet from the mucin was recorded (Das and Das, 2004).

1.7.3 Technologies for fast dissolving intraoral dosage forms

Orally dissolving and absorbed dosage forms can be beneficial for children, elderly patients, people with dysphagia due to a disease, *e.g.* gastro-oesophageal reflux disease (GORD), or if there is no access to the water to aid administration of oral dosage forms. The fast-dissolving intraoral dosage forms should allow rapid dissolution in the saliva, and absorption *via* tissues in the oral cavity, possibly through the oesophagus once swallowed with saliva and from the stomach. The majority of the quick dissolving intraoral dosage forms are produced as tablets but there are several other intraoral dosage forms in the pipeline: sprays, films, powders and wafers, and all comprise different manufacturing procedures. For example, WOWTAB® (Yamanouchi Pharmaceutical Co. Ltd., Japan) is produced by a standard compression method which allows exact doses but the carefully designed formulation can allow high dissolution rates as well as the product being tough enough to handle and pack.

Another quick dissolving tablet technology intended for intraoral dosing is Zydis® (Catalent) but the product is formed by freeze-drying instead of compression. This technology has been utilised for odanzeron (Zofran Zydis) which is formulated as a thin wafer leading to even faster disintegrating and dissolution rates (Pharmaca Fennica, 2008). Due to the freeze-drying process, the products are relatively fragile leading into problems in packaging, transport and handling.

Also a spray could be an alternative dosage form for intraoral delivery, for example, a nitroglycerin spray for the treatment of angina. Although very convenient and painless, it is not possible to guarantee the right dose as the dosage (spray action) depends entirely on the patient.

The concept of thin polymer films for intraoral delivery is not new as local delivery of lidocaine as a polymer film was studied in the 1970s but the booster for further development of thin polymer films was Listerine Pocket Paks ™, breath fresheners, by Warner-Lambert healthcare division. Active-containing, thin film drug delivery technologies have been developed and reported since for example Quick-Dis™ and Slow-Dis™ by Lavipharm Laboratories which utilise the formation of a large film which is then cut into right size containing right dose. Also Dinke and Nagarsenker (2008) studied incorporation of triclosan into a thin polymer film. These films, like wafers and tablets, dissolve rapidly in the mouth producing fast drug release and a possible quick onset of action.

Drug containing polymer films may be utilised as tablet coatings (Chapter 5) and as the polymer films for coating procedure had similar requirements as orally dissolving films, the suitability of these films as buccal delivery systems was investigated (Chapter 6). The next section outlines the properties of paracetamol, ibuprofen, metoclopramide hydrochloride and naratriptan hydrochloride, the drugs studied in combination with film-coatings and as orally disintegrating dosage forms in this thesis.

1.8 Drugs for the study

Paracetamol and ibuprofen solid-dosage forms are common pain killers/anti-inflammatory drugs available over-the-counter, and are used to treat acute pain or inflammation where rapid onset of drug action is desirable. Dissolution of paracetamol and ibuprofen formulations was investigated (Chapters 3 and 5) and this section describes the relevant properties of paracetamol and ibuprofen. In addition metoclopramide hydrochloride and naratriptan hydrochloride are described here as metoclopramide hydrochloride was formulated in the thin polymer film which was then coated on paracetamol-containing solid-dosage form and naratriptan hydrochloride was applied in the films designed for orally disintegrating dosage form.

1.8.1 Paracetamol

Paracetamol, also called acetaminophen, is an analgesic and antipyretic drug used to reduce fever and pain. It can be used instead of aspirin (in cases other than anti-inflammatory) as it is less of an irritant to stomach, thus preferred by the elderly and those on regular medication and interactions with other medicines are not generally a problem (PharmWeb, 2006). Its chemical name is N-(4-hydroxylphenyl) acetamide (Figure 1.12) and it has a melting point of 169 °C and pK_a of 9.5 at 25 °C. The aqueous solubility of paracetamol has been reported 14.7 mg ml^{-1} (at 20°C) and 23.7 mg ml^{-1} (at 37 °C) (Etman and Naggar, 1990). Its mechanism of action is different from non-steroidal anti-inflammatory drugs (NSAIDs), which block cyclooxygenase enzymes (COX-1 and COX-2) therefore restricting prostaglandin production. It has been suggested that COX-3 exists in the brain and spinal cord, and that paracetamol selectively blocks this enzyme, unlike NSAIDs, thus this may be the mechanism of action for paracetamol (Chandrasekharan *et al.*, 2002; Botting and Ayoub, 2005).

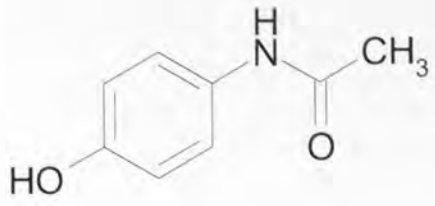


Figure 1.12- Molecular structure of paracetamol (MW 151.17 g mol^{-1})

The routes of administration for paracetamol are oral, intravenous and rectal, where the rectal route is considered to provide a slow and irregular absorption (Bannwarth and Pehourcq, 2003). Paracetamol is available as solid-dosage forms, typically as IR formulations, but is also available as effervescent tablets and syrups or suspensions. The dose of paracetamol can vary from 100 – 500 mg but the effective dose for an adult is 1 g (Bannwarth and Pehourcq, 2003). Paracetamol has 100% bioavailability although absolute bioavailability has been found between 62 – 89%. The decrease in the bioavailability is thought to be due to clearance in the liver prior reaching the systemic circulation *(Kalantzi et al.*, 2006).

1.8.2 Ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects which makes it preferable medication in treatment of fever in combination with inflammation (BNF, 2003). The side effects of NSAIDs are well known, *e.g.* they may cause bronchospasm and trigger asthma attacks (Debley *et al.*, 2005). Also interactions of NSAIDs with other medication are well reported; ibuprofen in combination with aspirin can reduce the effect of aspirin in patients with high risk of cardiovascular diseases leading to injury in the gastric mucosa (Gaziano and Gibson, 2006). Racemic ibuprofen is a non-selective COX-inhibitor therefore inhibiting prostaglandin production in case of inflammation.

The chemical name for ibuprofen is (RS)-2-(4-Isobutylphenyl) propionic acid and it has a melting point of 75-77 °C and pK_a of 4.55 (Fini *et al.*, 1995). Typically ibuprofen is administered in its racemic form, although S (+)-ibuprofen is thought to results in a faster therapeutic effect than the racemic compound (Dionne and McCullagh, 1998; Potthast *et al.*, 2005). Solubility of ibuprofen is low below its pK_a (~0.05 mg ml^{-1}, (Shaw, 2001)) but solubility is increased at higher pH 5-8 (Potthast *et al.*, 2005).

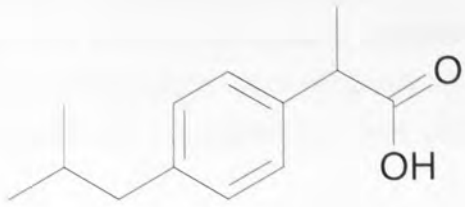


Figure 1.13- Molecular structure of ibuprofen (MW 206.3 g mol^{-1})

The dose of ibuprofen varies between 200 to 800 mg and it is available as solid-dosage formulations as well as liquid preparations and chewable tablets for children.

1.8.3 Metoclopramide hydrochloride

Metoclopramide hydrochloride is dopamine receptor antagonist and used as antiemetic drug for example as treatment of nausea and vomiting caused by migraine attack. Dose for adult with symptoms is 10 mg and can be used as combination with paracetamol. It can be administered as injection, oral solution and tablets (British Pharmacopoeia, 2008).

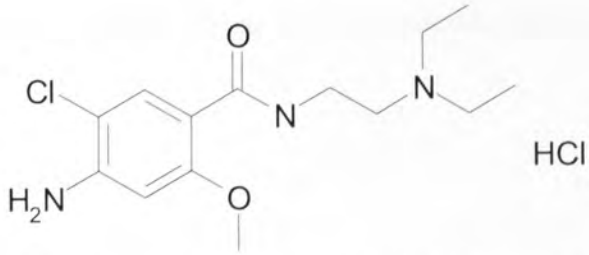


Figure 1.14- Molecular structure of metoclopramide hydrochloride (MW 299.8 g mol^{-1})

Its IUPAC name is 4-amino-5-chloro-*N*- (2-(diethylamino)ethyl)- 2-methoxybenzamide. It is very soluble in water, 200 mg L^{-1} and experimental Log P is 1.8 and pKa 9.27 (Drugbank-website, 2008). Melting point is 183 °C with decomposition (British Pharmacopoeia, 2008).

1.8.4 Naratriptan hydrochloride

Naratriptan hydrochloride is used for acute migraine attacks, and it belongs to group of $5HT_1$ agonists. It acts on the 5HT 1B/1D receptors which mediate the serotonin levels in the body. The $5HT_1$ agonists are typically used if conventional analgesics and anti-emetics are not sufficient enough. The onset of therapeutic effect of naratriptan hydrochloride is slower than for other triptans (*e.g.*sumatriptan and rizatriptan) but there are fewer side effects (Bateman 2000).

Naratriptan hydrochloride has got a melting point of 246 °C, it is soluble in water (35 mg ml^{-1}) and has logP value of 1.564 and pKa is 9.7. Naratriptan hydrochloride is a low dose medicament (2.5 or 5 mg), and it is studied in buccal delivery system (Chapter 6).

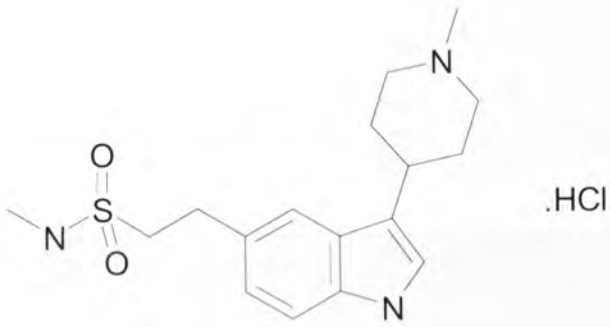


Figure 1.15- Molecular structure of naratriptan hydrochloride (MW 371.93 g mol^{-1})

1.9 Aims and objectives

The aim of this thesis work was to design novel pre-formed thin polymer films which could be utilised as fast dissolving film coatings. The pre-formed films were also studied as orally disintegrating dosage forms as it was thought that these polymer films could contain an active ingredient and therefore could be additionally formulated as oral dosage forms disintegrating in the oral cavity.

The objective was to investigate different kinds of coated solid-dosage forms in order to see if the coating plays a role in the onset of the drug release (Chapter 3). A new coating method had been established (Kesser *et al.*, 2002) where a dry pre-formed film was utilised as film

coating. Novel formulation design of these pre-formed films was carried out (Chapter 4) to formulate fast dissolving film for the wrap-coating technology as well as probe the actual wrap-coating method and its suitability with the designed film formulations as alternative tablet coating method (Chapter 5). Finally the formulated pre-formed films were applied as orally disintegrating dosage forms containing an active ingredient (Chapter 6).

Chapter 2-

General materials and methods

2.1 HPLC assay for paracetamol

Paracetamol has been analysed and well characterised hence a number of high performance liquid chromatography (HPLC) assays for paracetamol exist. A reversed-phase HPLC method was developed within Medicines Research Unit (MRU) (Shaw, 2001) and an optimised method was used here.

2.1.1 Materials

Potassium dihydrogen phosphate, di-sodium hydrogen orthophosphate dihydrate and caffeine were purchased from Sigma-Aldrich, UK. HPLC grade methanol, hydrochloric acid (HCl) S.G 1.18 (37%) and glacial acetic acid were obtained from Fisher Chemicals, UK. Water was double distilled in the laboratory using Fisons Fi-Streem 4 litre bi distillation unit. Paracetamol was supplied by GlaxoSmithKline Healthcare, Weybridge, UK.

2.1.2 Standard preparation

All standards were freshly prepared on the day of the analysis. Caffeine was used as an internal standard (IS) for tablets which did not contain caffeine in the formulations and caffeine containing tablet core formulations were analysed without internal standard. The IS solutions were prepared in methanol and acetic acid (95:5). The concentration of IS was chosen approximately in the middle of paracetamol standard range (typically 0.01- 0.4 mg ml $^{-1}$). The paracetamol standard solutions were prepared in the dissolution media used for the experiment (pH 5.8 Sørensen's phosphate buffer or 0.05M HCl, pH 1.3) by serial dilution. The samples and standards for HPLC were filtered using 0.45 μm nylon Syringe filters (Kinesis, UK) prior analysis and consisted of equal volumes of the sample and IS solution.

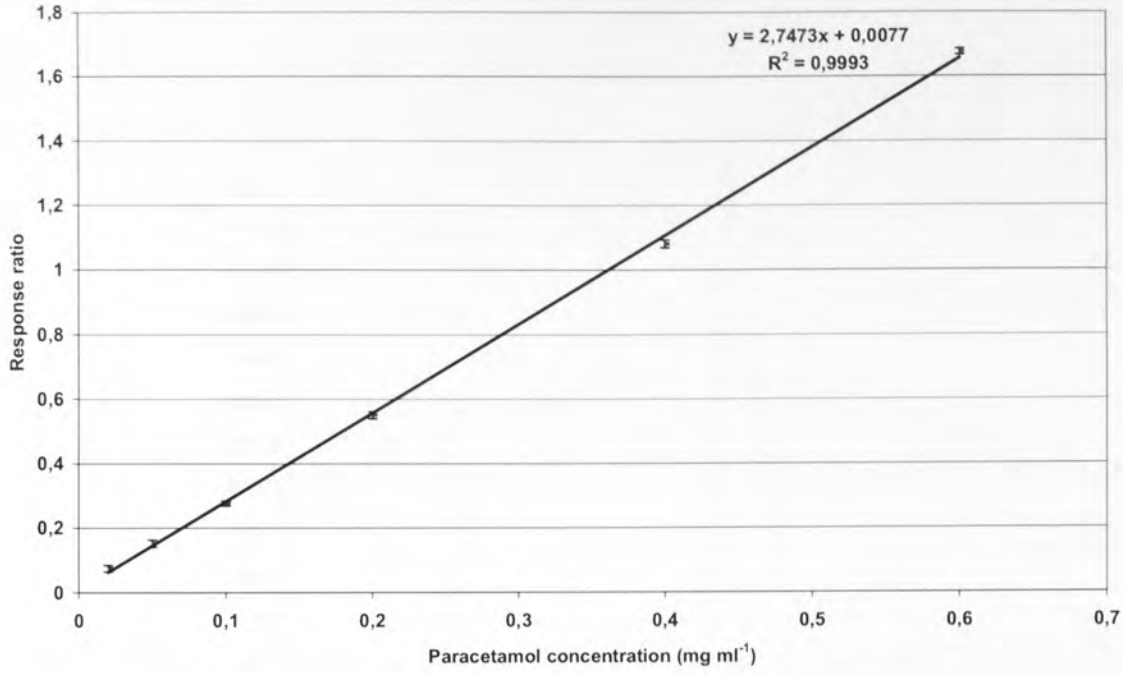


Figure 2.1- A typical calibration line for paracetamol assay

2.1.3 Method and chromatographic conditions

The reversed-phase HPLC method was used to determine the quantity of paracetamol in the dissolution samples. The HPLC system comprised a Waters 600E system controller, Erma ERC-3312 degasser, Waters WISP 712 autoinjector, Thermo Electron Corporation ODS-2 Hypersil column (150 x 4.6 mm, 5 μm) and Severn Analytical SA 6500 UV/VIS absorbance detector. The chromatograms were integrated on JCL 6000 for Windows.

The chromatographic conditions were based on the method by Krieger (Krieger, 1987). The mobile phase consisted of methanol and 0.75% acetic acid (1 to 3). The injection volume was 15 μl, flow rate 1 ml min^{-1} and the wavelength was set to 280 nm. The peaks for paracetamol and caffeine were approximately at 2.9 and 4.8 minutes respectively (Figure 2.2).

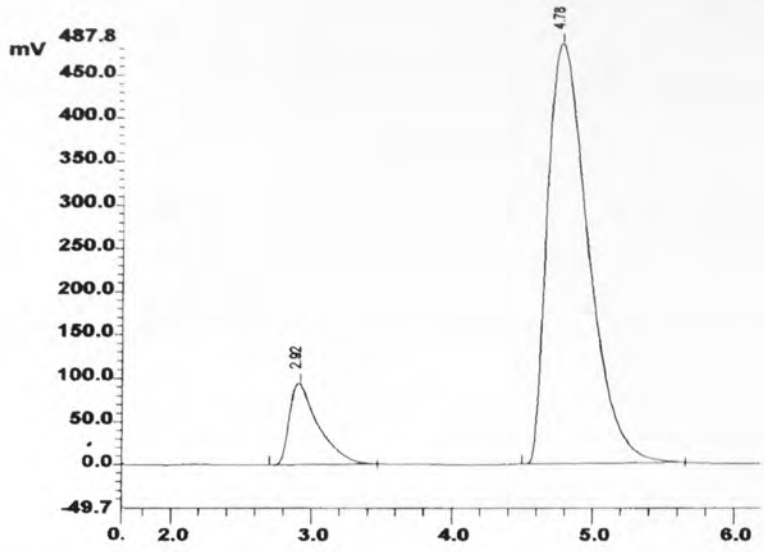


Figure 2.2- Paracetamol and caffeine chromatograph

2.2 HPLC assay for ibuprofen

HPLC method used for ibuprofen was developed previously within MRU (Shaw, 2001).

2.2.1 Materials

Potassium dihydrogen phosphate, di-sodium hydrogen orthophosphate dihydrate and caffeine were purchased from Sigma-Aldrich, UK and phosphoric acid (85%) was bought from Acros Organics, UK. HPLC grade acetonitrile was obtained from Fisher Chemicals, UK. Water was double distilled in the laboratory using Fisons Fi-Streem 4 litre bi distillation unit. Iburofen was supplied by GlaxoSmithKline, Dungarven, Ireland.

2.2.2 Standard preparation

The standards were prepared and analysed on the day of the experiment. Standard solutions ranging between 0.001-0.05 mg ml^{-1} were prepared by serial dilution in the dissolution media for the experiment (Sørensen's phosphate buffer pH 6.8). The samples and standards for HPLC were filtered using 0.45 μm nylon Syringe filters (Kinesis, UK) prior analysis.

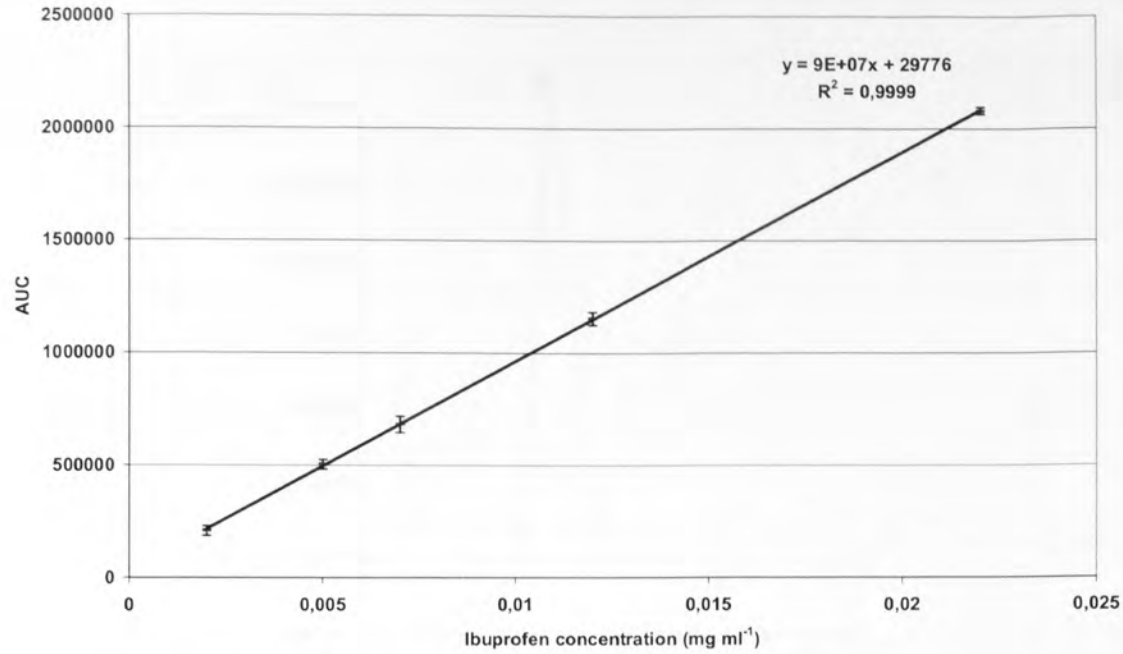


Figure 2.3- A typical calibration line for ibuprofen assay

2.2.3 Method and chromatographic conditions

The reversed-phase HPLC method was used to determine the quantity of ibuprofen in the dissolution samples. The HPLC system comprised a Waters 600E system controller, Erma ERC-3312 degasser, Waters WISP 712 autoinjector, Thermo Electron Corporation ODS-2 Hypersil column (150 x 4.6 mm, 5 μm) and Severn Analytical SA 6500 UV/VIS absorbance detector. The chromatograms were integrated on JCL 6000 for Windows.

The mobile phase consisted of acetonitrile, double distilled water and phosphoric acid (85%) in ratio 60:40:1. The injection volume was 100μl, flow rate 1 ml min^{-1} and the wavelength was set to 225 nm. The peak for ibuprofen was approximately at 5.5 minutes (Figure 2.4).

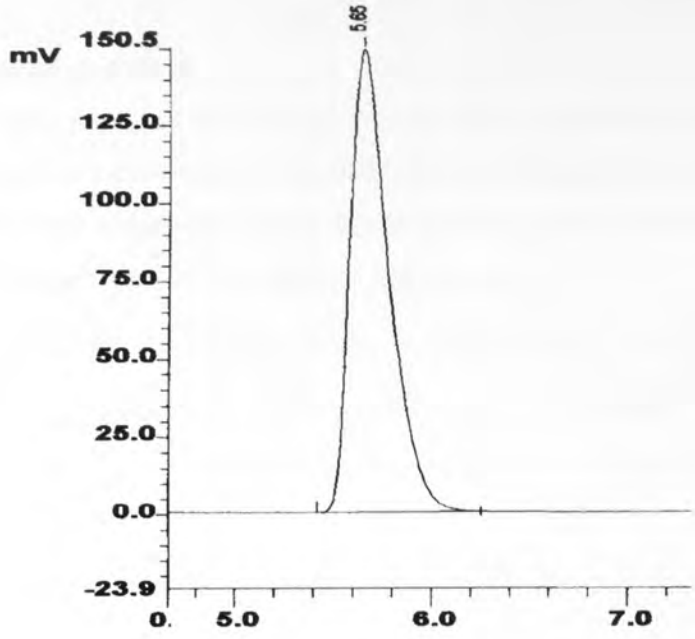


Figure 2.4- Ibuprofen chromatograph

2.3 HPLC assay for naratriptan hydrochloride

Naratriptan has been quantitated by liquid chromatographic-electrospray-mass spectrometric (LC/ESI/MS) (Dulery *et al.*, 1997) and solid phase extraction (SPE) in combination with liquid chromatographic-electrospray tandem mass spectrometric (LC/ESI-MS/MS) (Vishwanathan *et al.*, 2000) assays in rabbit and human plasma respectively. Naratriptan has ultraviolet (UV) absorbance maximum at 281 nm which was used as a base for developing a rapid reverse phase HPLC assay for detection of naratriptan *in vitro* or *ex-vivo* samples which has not been reported in the literature to date.

2.3.1 Materials

Phosphate buffered saline (PBS) tablets (pH 7.4), potassium dihydrogen phosphate, potassium bicarbonate and sodium chloride were purchased from Sigma-Aldrich, UK. Phosphoric acid (85%) and calcium chloride were bought from Acros Organics, UK. HPLC grade acetonitrile, citric acid and di-sodium hydrogen orthophosphate were obtained from Fisher Chemicals, UK. Magnesium chloride hexahydrate was purchased from BDH Chemicals Ltd., Poole, UK. Water was double distilled in the laboratory using Fisons Fi-

Streem 4 litre bi distillation unit. Naratriptan hydrochloride was supplied by GlaxoSmithKline, UK.

2.3.2 Standard preparation

The standards were prepared in PBS solution or artificial saliva by a serial dilution. The standards and samples were filtered using 0.45 μm nylon Syringe filters (Kinesis, UK) prior to analysis. The standard range was found linear in the range of 0.25-100 μg ml^{-1} but a typical calibration curve ranged from 0.25-50 μg ml^{-1} (Figure 2.5).

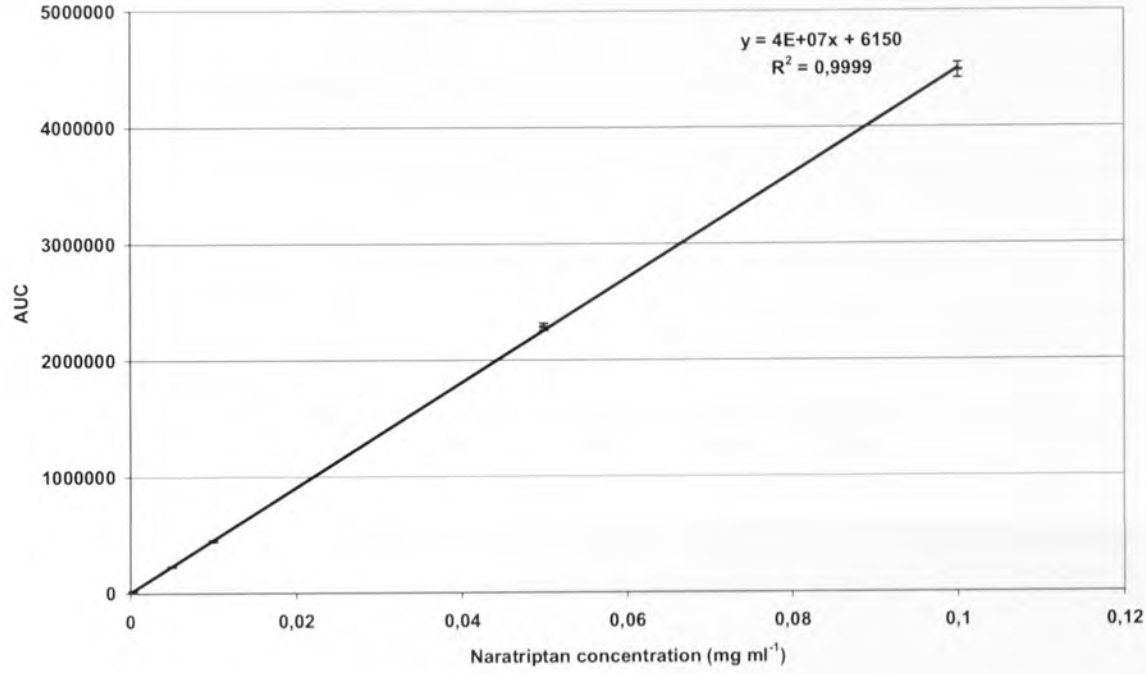


Figure 2.5- A typical naratriptan hydrochloride calibration curve

2.3.3 Method and chromatographic conditions

The reversed-phase HPLC method was used to determine the quantity of naratriptan hydrochloride in the drug release and penetration samples. The HPLC system comprised a Waters 600E system controller, Erma ERC-3312 degasser, Waters WISP 712 autoinjector, Thermo Electron Corporation ODS-2 Hypersil column (150 x 4.6 mm, 5 μm) and Severn Analytical SA 6500 UV/VIS absorbance detector. The chromatograms were integrated on JCL 6000 for Windows software.

The mobile phase consisted of acetonitrile, double distilled water and phosphoric acid (85%) in ratio of 200:800:7. The injection volume was 100μl, flow rate 1 ml min^{-1} and the

wavelength was set to 281 nm. The peak for naratriptan hydrochloride was approximately at 4.4 minutes (Figure 2.6).

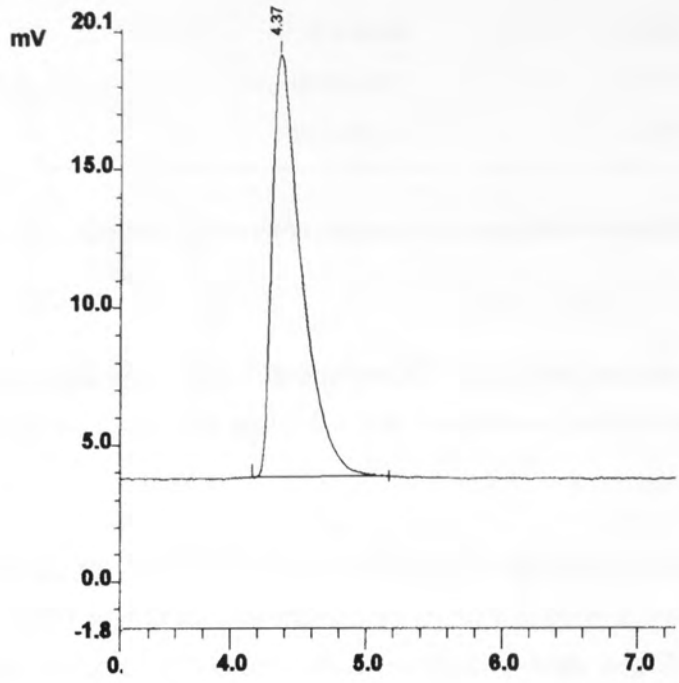


Figure 2.6- Naratriptan hydrochloride chromatograph

2.3.4 Method validation

Naratriptan hydrochloride was assayed for its linearity, range, accuracy, precision, detection limit and quantitation limit in order to validate the HPLC method. Linearity of standard naratriptan solutions were found in between 0.25-100 μg ml^{-1} using 6 standard samples. Calibration samples (5 standards) were injected 5 times to determine accuracy of the method by calculating relative error of known concentrations and it was found that all five replicates were within acceptable limits (± 10 %) (Table 2.1).

Theoretical concentration ($\mu g\ ml^{-1}$)	Actual concentration ($\mu g\ ml^{-1}$) (mean ± S.D.)	Accuracy (%)
0.25	0.235 ± 0.013	6.093
5	4.99 ± 0.471	0.179
10	9.91 ± 0.604	0.939
50	49.5 ± 2.57	1.034
100	99.2 ± 5.04	0.777

Table 2.1- Accuracy of the HPLC method for naratriptan hydrochloride (n=5)

Precision was determined intra- and interday (n=36) where the relative standard deviation (RDS %) was found to be 6.4 ± 2.04 and 2.0 ± 0.47 respectively which complies with < 10 % variation.

The limit of detection (LOD) and the limit of quantitation (LOQ) were calculated based on the calibration curves. LOD and LOQ was calculated using Equation 2.1 and 2.2 respectively where σ is standard deviation of y-intercepts of regression lines and S is the slope of the calibration curve (ICH Topic Q 2 B, 1996). The LOD and LOQ were found to be 0.072 $\mu g\ ml^{-1}$ and 0.22 $\mu g\ ml^{-1}$ respectively.

Equation 2.1 $$LOD = \frac{3.3\sigma}{S}$$

Equation 2.2 $$LOQ = \frac{10\sigma}{S}$$

Stability of the HPLC samples was investigated under various conditions and was concluded that samples can be kept up to a week before analysis but although the variation is not great between the treated samples it is still good practice to analyse the samples as soon as possible.

Storage Condition	Day 2 (%)	Day 5 (%)	Day 9 (%)
Light (RT)	100.68 ± 0.629	99.87 ± 0.115	94.38 ± 4.171
Dark (RT)	100.58 ± 0.538	100.24 ± 0.222	103.33 ± 3.172
Dark (4 °C)	99.58 ± 0.384	101.48 ± 1.356	104.47 ± 4.252
Dark (- 20 °C)	98.77 ± 1.140	104.09 ± 3.741	108.05 ± 7.660

Table 2.2- Stability data at varying conditions as % recovery

2.4 pH Measurements

All pH measurements were performed with Mettler Toledo MP230 pH meter at ambient temperatures. The Mettler Toledo inLab®413 pH probe was immersed in sample solution, left to settle and the measurement was taken with three significant numbers.

Chapter 3-

Commercial solid-dosage forms

3.1 Introduction

Counterfeit products are a problem for the pharmaceutical industry, patients and consumers. Over 70 % of drug products are solid-dosage formulations and a large part of these are in the form of a tablet. In the simplest form, tablets are white, uncoated, or with a thin coating and no specific embossing; such products are fairly easy to mimic and therefore to produce outside authentic pharmaceutical companies. Worryingly, counterfeits might not contain any active ingredient or they may contain some but not at the right dose, and some counterfeits have been found where the medicament contains the wrong active ingredient resulting in serious problems (New Scientist, 2006).

Pharmaceutical industry has been looking into ways of identifying the products from the counterfeits, *e.g.* looking to tag their products so they can identify where the product ends up. Stora Enso and Orion in Finland tested radio frequency identification (RFID) on pharmaceutical products where the products were tracked through the supply chain to the pharmacies to allow safety, reliability and efficiency of the supply chain and additionally the technology could be used to identify products (Collins, 2006). A possible drawback with this technology is that sometimes the tag is attached to the original packaging, not the formulation but the technology may still be useful in other types of dosage forms such as liquid preparations.

Another way to increase the threshold for copying is by designing the tablets in such way that they are easy to identify but not easy to replicate. Colorcon, for example, offers brand protection (5D ID™) where tablets can be identified by adding a printed text or a bar code on the surface with, for example, details of the drug and what it is for, or the tablets have a unique size and shape with recognisable colours *etc.* adding to the safety of the product (Colorcon Inc., 2003a; Colorcon Inc., 2003b). Phoqus, a drug delivery company, markets coatings which are recognisable by addition of a pattern or image (UniQ™) (Phoqus Ltd.).

Another problem concerning solid-dosage forms is the possibility of the formulation lodging in the oesophagus, resulting in irritation and damage. The sticking of solid-dosage forms in the oesophagus is a significant problem and it was reported that 40 % of American adults experience difficulties when swallowing solid-dosage forms (Harris Interactive Survey, 2003) and these problems are also associated with children and the elderly. It may be that hydration of polymer-coated solid-dosage forms induces sticking and therefore adherence to the oesophagus (Swisher *et al.*, 1984), and this can be a significant problem for people suffering from heartburn which can weaken peristaltic movement (Bontempo *et al.*, 1994). Adhesion and transit times *in vitro*, *in vivo* and *ex vivo* in relation to solid-dosage form shape,

size and coating have been studied (Marvola *et al.*, 1982; Swisher *et al.*, 1984; Al-Dujaili *et al.*, 1986b; Al-Dujaili *et al.*, 1986a; Wilson *et al.*, 1988; McCargar *et al.*, 2001; Perkins *et al.*, 2001) and generally gelatine capsules were the most problematic, possibly due to the low density of the dosage form. There has been some discrepancy between the results of different studies (*in vitro vs. in vivo*) and it was concluded that the *in vitro* studies may not necessary correlate to *in vivo* results (McCargar *et al.*, 2001). A recent *in vivo* study showed that oval-shaped film-coated tablets adhered least to oesophagus due to the decreased surface area compared to capsules or uncoated tablets, for example, and it was concluded that size, shape and surface characteristics of the solid-dosage form can affect the lodging in the oesophagus (Newsblaze, 2006). Thus, the formulation of solid-dosage forms (especially size, shape and surface) has led to the initiative for several companies to produce tablet coatings, claiming their products to be easy-to-swallow formulations or with improved patience compliance (*e.g.* Banner Pharmacaps and Phoqus Ltd.) as well as providing a more recognisable product.

Coating of the solid-dosage form can affect adherence to oesophagus and addition of polymer coatings (other than conventional HPMC-coats) can also affect the disintegration and dissolution properties of the solid-dosage form; the additional coating may inhibit the disintegration and therefore delay the onset of the drug release. The aim of this chapter is to evaluate commercially available paracetamol-containing formulations with varying dissolution-enhancing technologies (*e.g.* addition of dissolution enhancing excipients) and also the effect of tablet coating on Panadol®-based products is investigated in relation to dissolution of the drug and inclusion of dissolution-enhancing excipients in the core formulation in order to see if the tablet coating can affect the release of the active ingredient despite of the excipients in the tablet core. Also commercially available ibuprofen-containing formulations are discussed in this chapter.

3.2 Materials and methods

Several commercially available uncoated and film-coated solid-dosage forms were studied; coating technologies and other characteristics of the solid-dosage forms are discussed, as well as the methodology used for their dissolution measurement and for analysis of the results.

3.2.1 Materials

Potassium dihydrogen phosphate and di-sodium hydrogen orthophosphate dihydrate were purchased from Sigma-Aldrich, UK. Hydrochloric acid S.G 1.18 (37%) and glacial acetic acid were obtained from Fisher Chemicals, UK. The water was double distilled in the laboratory

using Fisons Fi-Streem 4 litre bi distillation unit. Panadol®, Panadol® Actifast, Panadol® Extra, uncoated Panadol®, Gelatin-coated Panadol®, Gelatin-coated Panadol® Extra, Tabwrapped Panadol® and Tabwrapped BPI samples were provided by GlaxoSmithKline (GSK), Weybridge. Standard Panadol®, when no coating is defined, refers to conventionally film-coated Panadol® formulation (as purchased from retail outlet). Tylenol® samples (ortho McNeil) and Sav-On Osco® Gelcaps (Albertson) were purchased from pharmacy outlets in the appropriate countries. Other commercially available products were SuperDrug Paracetamol, SuperDrug Paracetamol Plus, Galpharm paracetamol, Nurofen® ibuprofen caplets, SuperDrug ibuprofen caplets and Galpharm ibuprofen tablets available in UK pharmacies.

3.2.1.1 Panadol® based products

Panadol® is a commercially available conventionally HPMC-coated paracetamol (500 mg) solid-dosage form caplet and uncoated Panadol® is the same core formulation but without any coating. The core formulation contains starch (disintegrant/binder), povidone (binder), potassium sorbate (preservative), talc (glidants) and stearic acid (lubricant). Other products based on Panadol® are Gelatin-coated Panadol® and Tabwrapped Panadol®. The conventional HPMC-coating contains hydroxypropyl methylcellulose (coating agent), triacetin (plasticiser), ethanol (solvent), propylene glycol (plasticiser), shellac (coating agent), brilliant blue FCF (colour), sodium lactate (flavour) and dimethylpolysiloxane (antifoaming agent).

Gelatin-coated Panadol® is pre-coated with HPMC (conventionally) and further coated with a gelatin-based formulation (Soflet® technology) by Banner Pharmacaps to produce more distinguishable products with use of two colours and printable coating to allow unique features (Banner Pharmacaps, 2004). Tabwrapped Panadol® utilises TABWRAP™ technology from BioProgress where XGel™ film (synthetic/semi-synthetic) is "shrink-wrapped" around the tablet without HPMC pre-coating. Tabwrapped Panadol® is coated in two halves, one blue, one clear with an aqueous acidic film (Figure 3.1). Gelatin-coated Panadol® and Tabwrapped Panadol ® cores are the same as Panadol® above.

Figure 3.1- Tabwrap™- coated Panadol®

Panadol® Actifast is also available conventionally HPMC-coated paracetamol (500 mg) solid-dosage form containing sodium bicarbonate as a dissolution-enhancing excipient. Other excipients in the core formulation are soluble starch (disintegrant/binder), povidone (binder), maize starch (lubricant), potassium sorbate (preservative), microcrystalline cellulose (disintegrant/binder/diluent) and magnesium stearate (lubricant). The tablet coating for Panadol Actifast® contains carnauba wax (coating agent), titanium dioxide (pigment), polydextrose (coating agent/binder), hydroxypropyl methylcelloluse (coating agent), triacetin (plasticiser) and polyethylene glycol (plasticiser). Tabwrapped BPI is coated in two halves, one blue, one clear film with neutral organic glue. Tabwrapped BPI core is based on the Actifast® formulation therefore it also contains bicarbonates. For the Tabwrap formulations the coating is a non-animal derived polymer (Bioprogress, 2003).

Panadol® Extra contains 500 mg paracetamol and 65 mg of caffeine as active ingredients and sodium croscarmellose as a superdisintegrant and dissolution enhancer as well as starch (disintegrant/binder), polyvinylpyrrolidone (disintegrant), potassium sorbate (preservative), talc (glidant) and stearic acid (lubricant). Panadol® Extra is also conventionally HPMC-coated with triacetin as plasticiser. Gelatin-coated Panadol® Extra is the Panadol® Extra further coated with gelatin utilising the same Soflet® technology by Banner Pharmacaps as outlined above.

3.2.1.2 Tylenol® based products

All Tylenol® products are manufactured by Ortho McNeil and contain 500 mg paracetamol. Both Tylenol® Gelcaps (capsule shape) and Geltabs (tablet shape) are gelatin dip-coated products (Berta, 1987) where the method allows the use of two colours and results in products with shiny and smooth surfaces. Tylenol® Rapid Release Gels, where the core is laser-treated to provide fast disintegration, are partially coated with gelatin (at the ends of the caplet) leaving the middle section (which may be coated with HPMC) with small openings allowing intimate contact between solution and the core (McNeil Consumer Healthcare, 1998 - 2006). All Tylenol® products contain benzyl alcohol (preservative), butylparaben (preservative), castor oil (lubricant), cellulose (binder/disintegrant/glidant), corn starch (binder/disintegrant/glidants/diluent), D&C Yellow #10 (colour), edetate calcium disodium (chelating agent), FD&C Blue #1 (colour), FD&C Blue #2 (colour), FD&C Red #40 (colour), gelatin (coating polymer), hypromellose (coating polymer), magnesium stearate (lubricant), methylparaben (preservative), propylparaben (preservative), sodium lauryl sulphate (lubricant), sodium propionate (preservative), sodium starch glycolate (disintegrant) and titanium dioxide (pigment).

3.2.1.3 Sav-On-Osco®

Sav-On-Osco® is produced by Albertson Inc. and it contains 500 mg paracetamol. It is a caplet shape coated with Press-Fit® technology from Capsugel® which is owned by Pfizer. It utilises a cold-shrink process producing a gelatin-coating with a two colour finish (Pfizer Inc., 2006). The core contains colloidal silicon dioxide (glidant), edible ink (colour), FD&C red (colour), gelatin (coating agent), hydroxypropyl cellulose (coating agent), HPMC (coating agent), polyethylene glycol (plasticiser), povidine (binder), pregelatinized starch (diluent/disintegrant/binder), sodium lauryl sulphate (lubricant), stearic acid (lubricant) and titanium dioxide (pigment).

3.2.1.4 SuperDrug products

SuperDrug paracetamol products (SuperDrug Paracetamol caplet and SuperDrug Paracetamol Plus caplet) both contain 500 mg paracetamol and 65 mg caffeine in the Plus formulation (Wrafton Laboratories Ltd.). The core formulation of SuperDrug Paracetamol caplet contains maize starch (lubricant), microcrystalline cellulose (disintegrant/binder/diluent), povidone (binder), sorbitol (diluent), sodium lauryl sulphate (lubricant), sodium starch glycolate (disintegrant) and magnesium stearate (lubricant) and does not contain any coating. Film-coated SuperDrug Paracetamol Plus contains povidone (binder), maize starch (lubricant), methylcellulose (disintegrant/binder), talc (glidant), calcium stearate (lubricant), hydroxypropyl methylcellulose (coating agent) and polyethylene glycol (plasticiser).

SuperDrug ibuprofen, film-coated Ibuprofen 200 mg tablet, was manufactured by Wrafton Laboratories Ltd., UK. The formulation consists of ibuprofen (active), colloidal anhydrous silica (absorbent/disintegrant), sodium starch glycolate (disintegrant), maize starch (lubricant), sodium lauryl sulphate (lubricant), sorbitol (diluent), microcrystalline cellulose (binder/diluent), talc (glidant), calcium stearate (lubricant), stearic acid (lubricant), methylhydroxypropylcellulose (coating agent) and polyethylene glycol (plasticiser).

3.2.1.5 Galpharm products

Galpharm Paracetamol caplets contain 500 mg of active drug (Galpharm International Ltd) and due to powdery appearance and from the ingredients list it can be concluded that the product is not coated. The core formulation contains additional pregelatinised maize starch (diluent/disintegrant/binder), sodium metabisulphite (antioxidant) and magnesium stearate (lubricant).

Galpharm Ibuprofen caplets contain 200 mg of active ingredient (Galpharm International Ltd.) and they are sugar-coated tablets. Additionally the formulation includes colloidal anhydrous silica (absorbent/disintegrant), maize starch (lubricant), sodium lauryl sulphate (lubricant), polyvinylpyrrolidone (disintegrant), microcrystalline cellulose (binder/diluent), alginic acid (binder/disintegrant), magnesium stearate (glidant), sodium starch glycolate (disintegrant), sodium carboxymethylcellulose (binder/disintegrant), talc (glidant), sucrose (coating agent) and titanium dioxide E171 (pigment).

3.2.1.6 Nurofen®

Nurofen® caplets are sugar-coated and contain 200 mg of active drug. The formulation consists of sucrose (coating agent), sodium citrate (buffer), talc (glidant), croscarmellose sodium (disintegrant), stearic acid (lubricant), titanium dioxide (pigment), acacia (binder), carmellose sodium (coating agent/binder disintegrant), sodium laurylsulphate (lubricant), macrogol (dissolution enhancer) and black ink (contains shellac, iron black oxide, soya lecithin, simeticone).

3.2.2 Methods

The drug release from the solid-dosage forms was determined by dissolution testing and all the samples were treated and analysed as described in sections 2.1 and 2.2.

3.2.2.1 Dissolution

Dissolution studies were carried out in Hansen Research (Chatsworth CA, USA) dissolution apparatus II. For paracetamol-containing products, the dissolution medium consisted of 900 ml of 0.05M HCl and for ibuprofen-containing products the dissolution medium was Sørensen's phosphate buffer pH 6.8. The temperature of the medium was set at 37.0 ± 0.5 °C, and the paddle speed was 30.0 ± 0.5 rpm for paracetamol products and 50.0 ± 0.5 rpm for ibuprofen products. The tablets were placed in the vessels, and the dissolution samples (2 ml) were withdrawn through 20 μm sintered polypropylene filters at pre-selected time intervals. Samples were treated and analysed by HPLC (section 2.1).

The rate of dissolution was calculated as the gradient of the linear portion of the dissolution curve (steady-state) and lag time was calculated using y=0 for the equation of the linear line for steady-state.

3.2.2.2 Tablet coating thickness measurement

Tablet coatings of the commercial solid-dosage forms were carefully removed with a scalpel and tweezers. The coatings were measured for their thickness with Electronic Digital Caliper (Linear Tools).

3.2.2.3 Statistical analysis

The dissolution data, % released, lag times and rate of dissolution, were compared statistically using analysis of variance (ANOVA) with Tukey's post-hoc test (95% confidence) (Statistical Package for Social Sciences (SPSS) for Windows). All the percentage data were transformed to an arcsin scale (Equation 3.1).

Equation 3.1 $$Sin\theta = \sqrt{\frac{\%}{100}}$$

3.2.2.4 The model independent f_2 analysis of the dissolution profiles

FDA recommends the usage of model independent determination of similarity of dissolution profiles (f_2) which is calculated according Equation 3.2, where n is the number of data points, R_t is the dissolution value of the reference at time t and T_t is the dissolution value of test at time t. The f_2 is unitless and a value of >50 indicates similarity of the two curves compared.

Equation 3.2 $$f2 = 50 \times \log \left\{ [1 + \frac{1}{n} \times \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100 \right\}$$

3.3 Results and discussion

3.3.1 Paracetamol dissolution in acidic pH

The dissolution medium for paracetamol formulations was 0.05M HCl with 30 rpm paddle speed as these conditions have been shown to discriminate between the formulations, and to correlate with *in vivo* release for paracetamol formulations (Rostami-Hodjegan *et al.*, 2002a). Dissolution of uncoated Panadol® was compared to Panadol®, Panadol® Extra and Panadol® Actifast which were all conventionally HPMC-coated with Extra and Actifast formulations containing dissolution-enhancing excipients such as croscarmellose sodium and sodium bicarbonate respectively (section 3.2.1.1). Actifast formulations dissolved rapidly in acidic

conditions reaching 80 % dissolution at 10 minutes (Figure 3.2). The formulation contained sodium bicarbonate which is widely used in effervescent tablets where reaction with water produces carbon dioxide leading to fast disintegration and alkaline pH (Rowe *et al.*, 2001), which may be the cause of fast dissolution of Actifast formulation (Grattan *et al.*, 2000; Rostami-Hodjegan *et al.*, 2002a; Rostami-Hodjegan *et al.*, 2002b; Kelly *et al.*, 2003; Shaw *et al.*, 2005). Although the Actifast formulation was conventionally HPMC-coated, the coating did not act as a barrier to dissolution which was also confirmed with the short lag time 0.70 ± 0.83 minutes. Panadol® Extra formulation contained croscarmellose sodium as a disintegration enhancing excipient and caffeine as an enhancer for effectiveness of paracetamol *in vivo*. The superdisintegrant, croscarmellose sodium, acts by increasing the water uptake through capillary action and hence allowing fast swelling of the superdisintegrant generally leading to enhanced dissolution of the formulation (FMC Biopolymer, 2005). The mean lag time for onset of dissolution of Panadol® Extra was less than that for Panadol® ($p>0.05$) therefore the inclusion of superdisintegrant croscarmellose sodium does not guarantee increased dissolution in paracetamol formulations. Croscarmellose sodium in an orally disintegrating paracetamol tablet led to enhanced disintegrating times (Abdelbary *et al.*, 2004). Croscarmellose sodium is included at high percentages in orally disintegrating tablets (8.6 % w/w) compared to normal capsule and tablet formulations and this may account for the differences (Rowe *et al.*, 2001).

Uncoated Panadol® and Panadol® contained the same core without any superdisintegrants/antacids with the Panadol® being coated with HPMC. There was an initial significant difference in percentage dissolved ($p<0.05$) between uncoated and HPMC-coated Panadol® (at 5 minutes) and the HPMC-coating may be inhibiting the onset of dissolution leading to increased lag time (3.76 ± 0.95 mins) for Panadol®. Despite the difference in dissolution at the early time points, there were no significant differences between uncoated Panadol® and Panadol® at later time points although f_2 analysis indicates that these two dissolution profiles were not similar (f_2=44.8) (Figure 3.2).

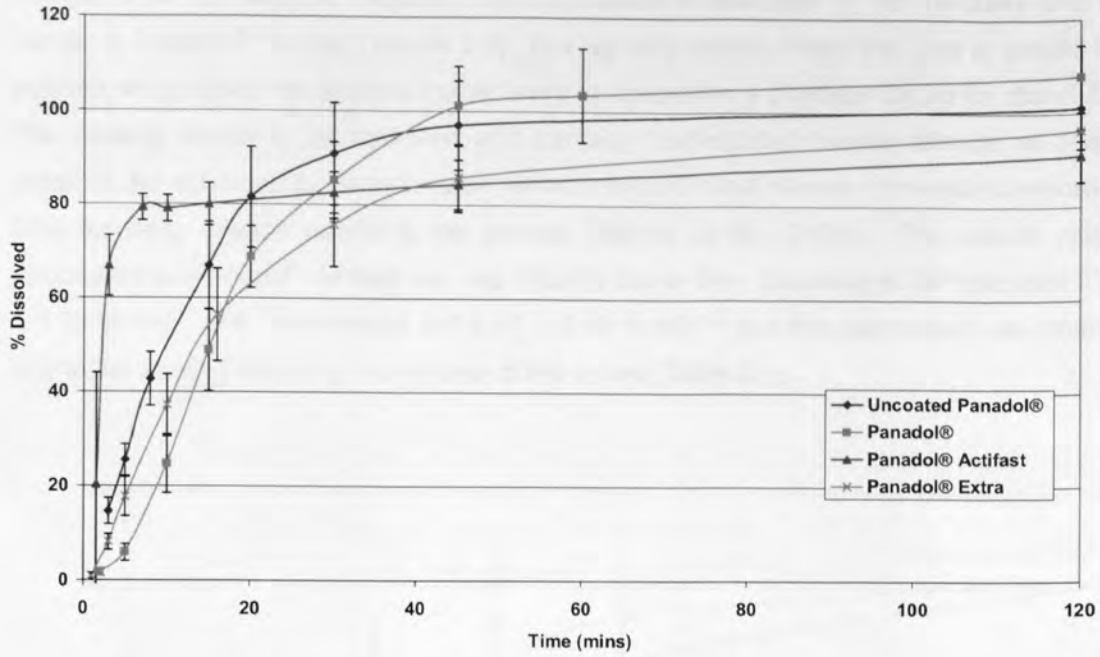


Figure 3.2- Dissolution profiles of Panadol® formulations *(0.05M HCl, 30 rpm, n=3-6; mean ± S.D.)*

The effects of additional coating were apparent from the dissolution profiles of the Gelatin-coated Panadol® and Tabwrapped Panadol® (Figure 3.3); the onset of drug release was retarded for both, leading significantly extended lag times (11.30 ± 1.25 and 19.11 ± 1.68 minutes respectively) compared to Panadol®, therefore the additional coating provides a further barrier to dissolution of the active ingredient.

For both Gelatin-coated Panadol® and Tabwrap Panadol®, the total mass increased due to the polymer coatings (approximately 22 % and 5 % w/w respectively), also the thickness of the coatings were measured and found to be 0.30 mm and 0.11 mm respectively. Due to the increased weight and dimensions of the Gelatin-coated Panadol®, it was expected that onset of dissolution may be retarded but this was not evident under the conditions employed. Lag times were shortest for Panadol® followed by Gelatin-coated Panadol®, then Tabwrap Panadol®. Gelatin dissolves readily at all physiological pHs at body temperature (37 °C) and so a lag time can be avoided. Also the manufacturing process for these coated formulations is different. It can be concluded that thickness of the coating is not the only factor affecting the onset of dissolution.

Both Tabwrapped BPI and Panadol® Actifast contain sodium bicarbonate in the core formulation which results in enhanced dissolution rates (Figure 3.4). The presence of sodium bicarbonate in the Tabwrapped BPI formulation decreased the lag time (4.74 ± 6.26 minutes)

compared to Tabwrapped Panadol® without sodium bicarbonate (> 19 minutes) and was similar to Panadol® Actifast (Figure 3.3). The lag time results when the core is coated with polymer which does not dissolve immediately or it provides a physical barrier for dissolution. The coating needs to be hydrated and partially disintegrated before release of drug is possible. An extended lag time is more relevant to controlled release formulations where the time for drug release needs to be defined (Manca *et al.*, 2003). The overall rate of dissolution for Panadol® Actifast was significantly faster than Tabwrapped BPI (Actifast 31.01 ± 8.16 % min^{-1} and Tabwrapped BPI 5.87 ± 0.88 % min^{-1}) and this decreased rate might be due to the coating inhibiting the release of the active (Table 3.1).

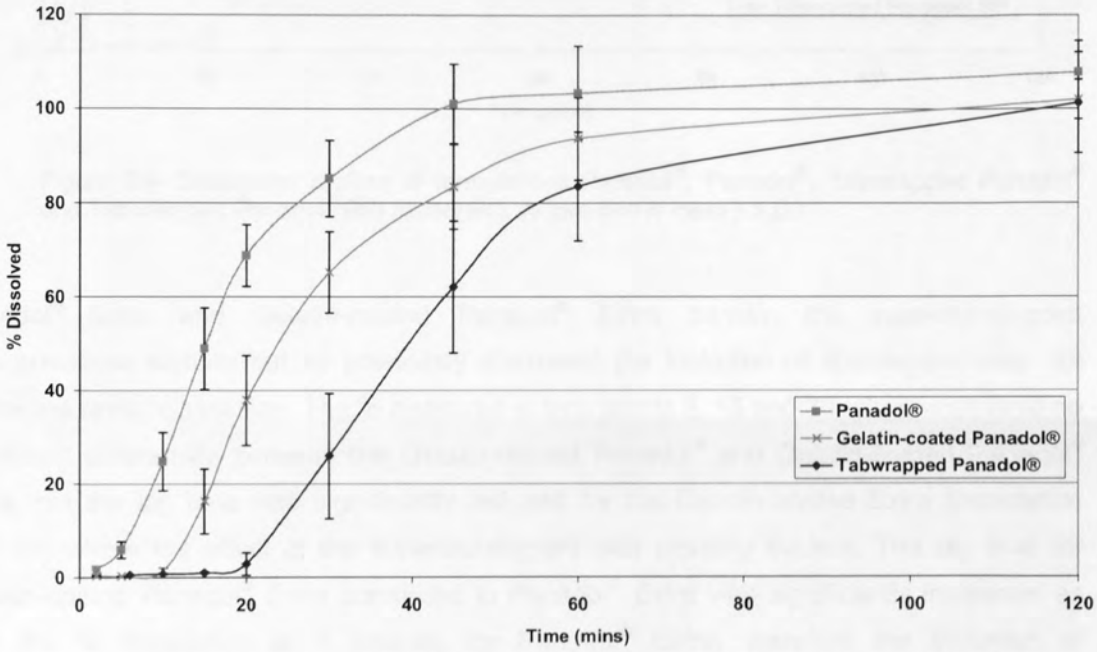


Figure 3.3- Dissolution profiles of formulations based on Panadol® core *(0.05M HCl, 30 rpm, n=6; mean ± S.D.)*

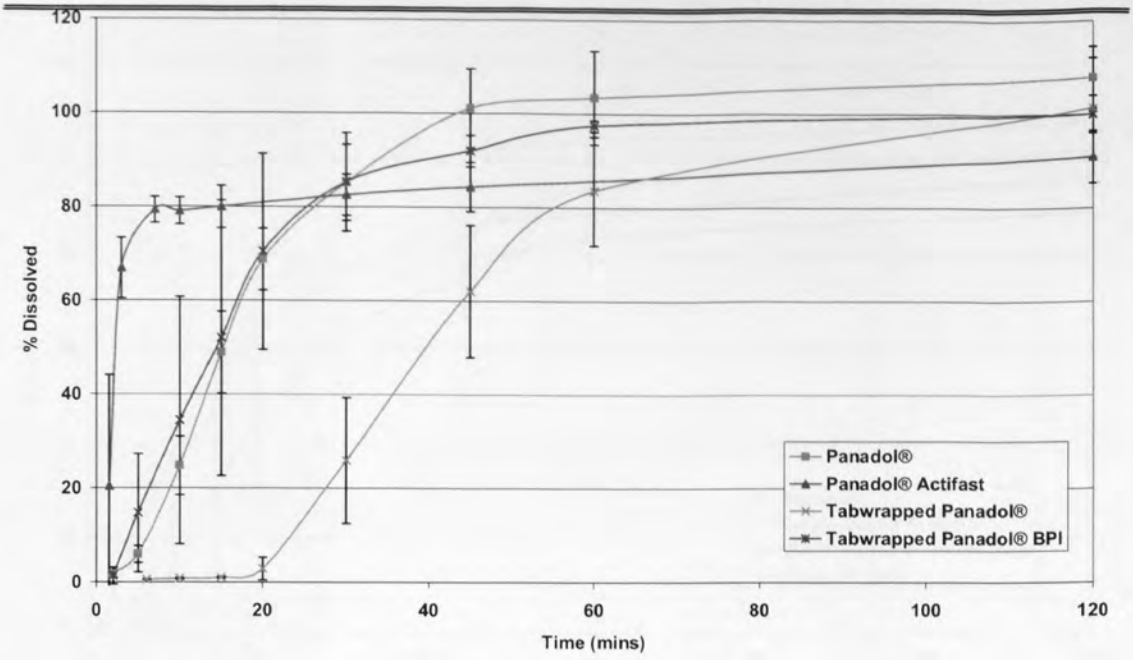


Figure 3.4- Dissolution profiles of formulations Panadol®, Panadol®, Tabwrapped Panadol® and Tabwrapped Panadol® BPI *(0.05M HCl, 30 rpm, n=3-6; mean ± S.D.)*

Panadol® Extra and Gelatin-coated Panadol® Extra contain the superdisintegrant croscarmellose sodium but as previously discussed the inclusion of disintegrant may not guarantee faster dissolution. The % dissolved at time points 5, 15 and 30 minutes showed no significant differences between the Gelatin-coated Panadol® and Gelatin-coated Panadol® Extra, but the lag time was significantly reduced for the Gelatin-coated Extra formulation ($p<0.05$) where the effect of the superdisintegrant was possibly evident. The lag time for Gelatin-coated Panadol® Extra compared to Panadol® Extra was significantly increased as was the % dissolution at 5 minutes for Panadol® Extra; therefore the inclusion of superdisintegrant does not override the effect of the gelatin-coating. Gelatin-coated Panadol® showed significantly increased lag times and % dissolution at 5 and 15 minutes compared to Panadol® Extra which may indicate that without the driving force from the core (*e.g.* swelling of superdisintegrant) the coating may limit the dissolution rate (Figure 3.5).

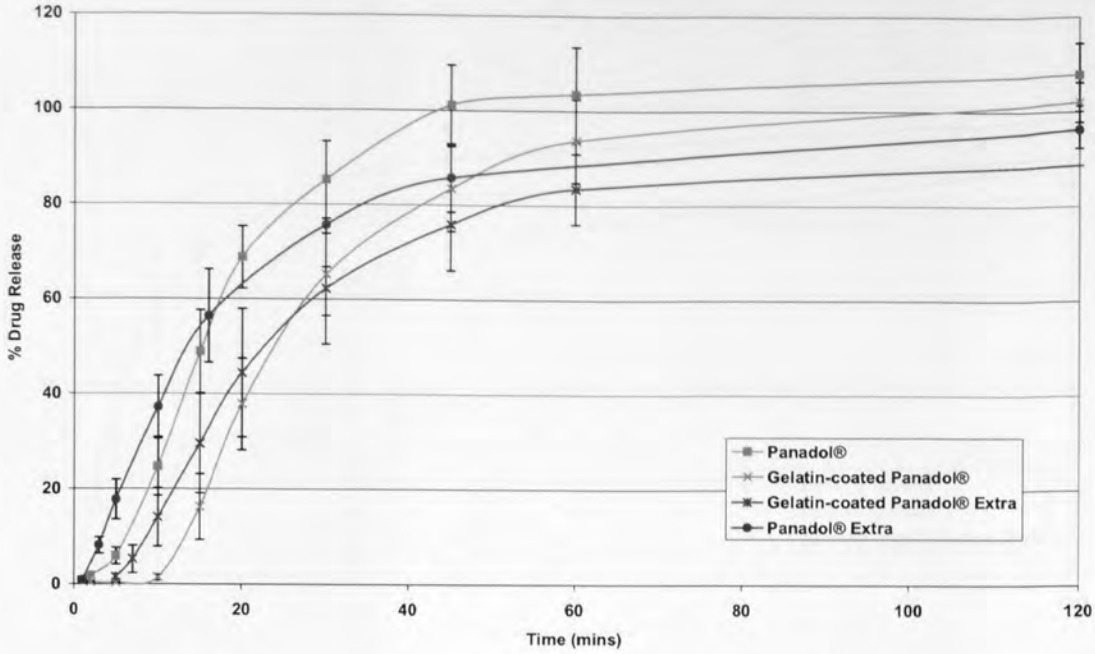


Figure 3.5- Dissolution profiles of formulations based on Panadol® core *(0.05M HCl, 30 rpm, n=6; mean ± S.D.)*

Tylenol® Geltabs and Gelcaps were both HPMC-coated, in addition to having a gelatin coat applied using a dip-coating method and although the shape of the solid-dosage forms was different, the dissolution profiles were not significantly different from each other (Figure 3.6). This was also supported by the overall similarity factor which was found to be f_2=55.2. Additional polymer coating extended the lag time as with other formulations (Figure 3.7). Drug release from Tylenol® Rapid Release Gels showed no lag ($p<0.05$) and there was a significant difference compared to Tylenol® Geltabs and Gelcaps at 5 minute time point but the rate of release was not significantly different compared to Geltab and Gelcap formulations nor was the % dissolved at later time points. Differences in initial behaviour may be due to the incomplete coating of the Tylenol® Rapid Release Gel and the treatment of the core by lasers, leading to a softer core and therefore quicker onset of disintegration and dissolution. Another formulation marketed as fast release is Panadol® Actifast and in acidic conditions, the rate of dissolution was significantly faster as was the dissolution at 5 minutes compared to Tylenol® Rapid Release Gels. Also the f_2 value between these two formulations was found to be 20.0, indicating that the dissolution profiles are not similar.

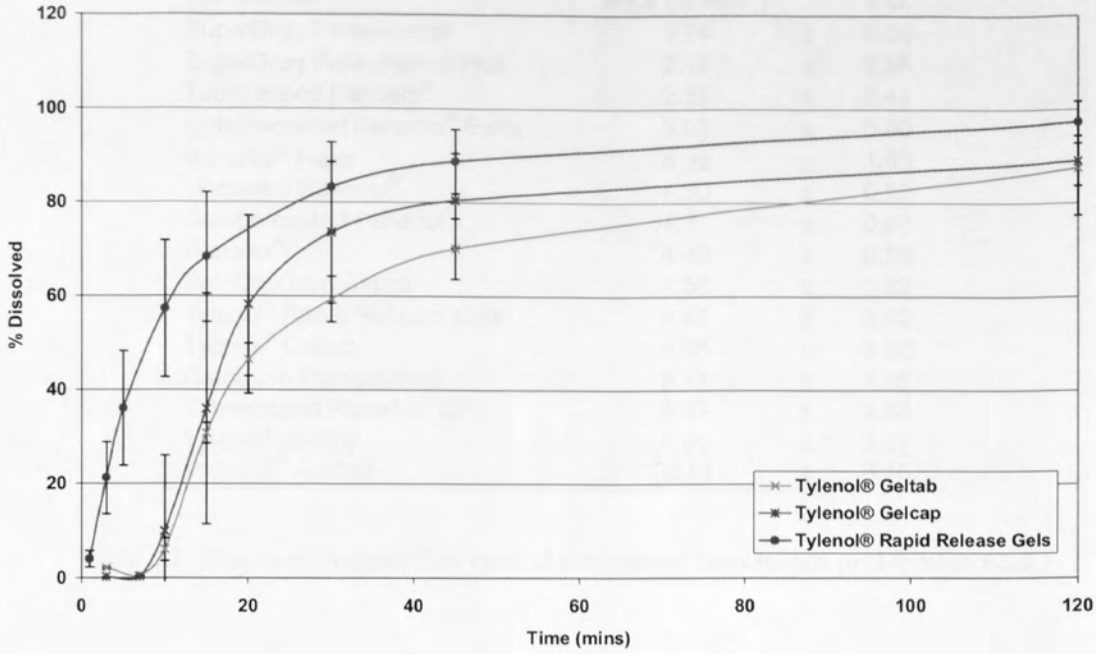


Figure 3.6- Dissolution profiles of Tylenol® formulations *(0.05M HCl, 30 rpm, n=6; mean ± S.D.)*

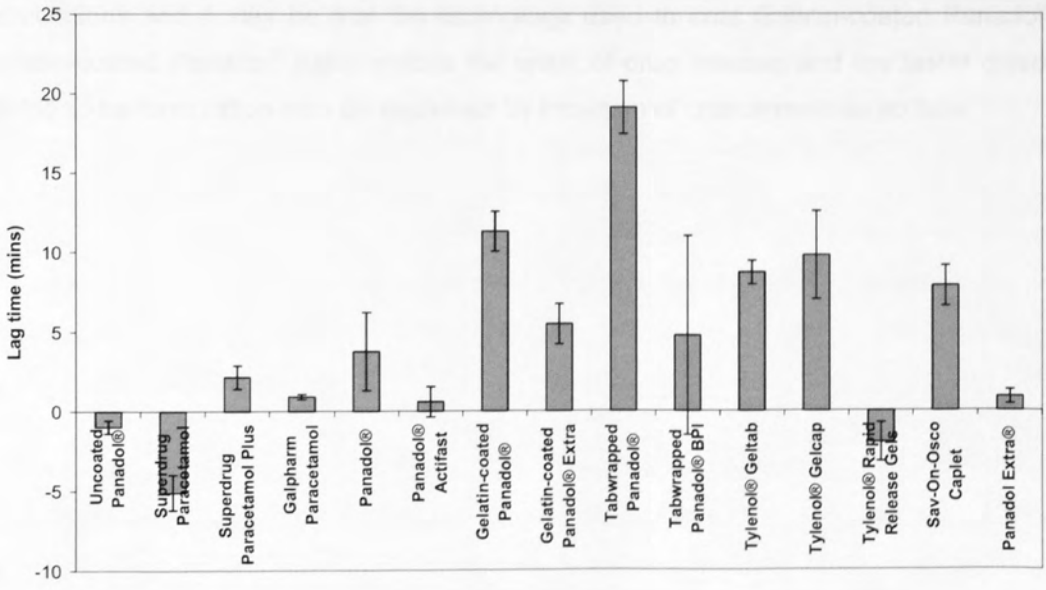


Figure 3.7- Lag time variations between the commercial formulations *(n=3-6; mean ± S.D.)*

Formulation	Rate (% min^{-1})		S.D.
SuperDrug Paracetamol	1.74	±	0.34
SuperDrug Paracetamol Plus	2.17	±	0.66
Tabwrapped Panadol®	2.37	±	0.44
Gelatin-coated Panadol® Extra	3.03	±	0.80
Panadol® Extra	4.29	±	1.03
Uncoated Panadol®	4.30	±	0.59
Gelatin-coated Panadol®	4.31	±	0.67
Panadol®	4.40	±	0.56
Sav-On-Osco Caplet	4.58	±	0.22
Tylenol® Rapid Release Gels	4.65	±	0.92
Tylenol® Geltab	4.95	±	0.82
Galpharm Paracetamol	5.11	±	1.08
Tabwrapped Panadol® BPI	5.87	±	0.88
Tylenol® Gelcap	6.99	±	2.17
Panadol® Actifast	30.01	±	8.16

Table 3.1- Steady-state dissolution rates of commercial formulations *(n=3-6; mean ± S.D.)*

Sav-On-Osco had a similar dissolution profile to Tylenol® Geltab and Gelcap and Gelatin-coated Panadol® Extra formulations, with similar lag times and rates of dissolution (no significant difference when compared to Sav-On-Osco) (Figure 3.8). This behaviour was expected as Sav-On-Osco is also coated with gelatin and does not contain superdisintegrants. Gelatin-coated Panadol® was an exception compared to these formulations and it may be that the technology used to coat Gelatin-coated Panadol® and Gelatin-coated Panadol® Extra inhibits the onset of drug release, and the faster dissolution for the Extra formulation may be explained by inclusion of croscarmellose sodium.

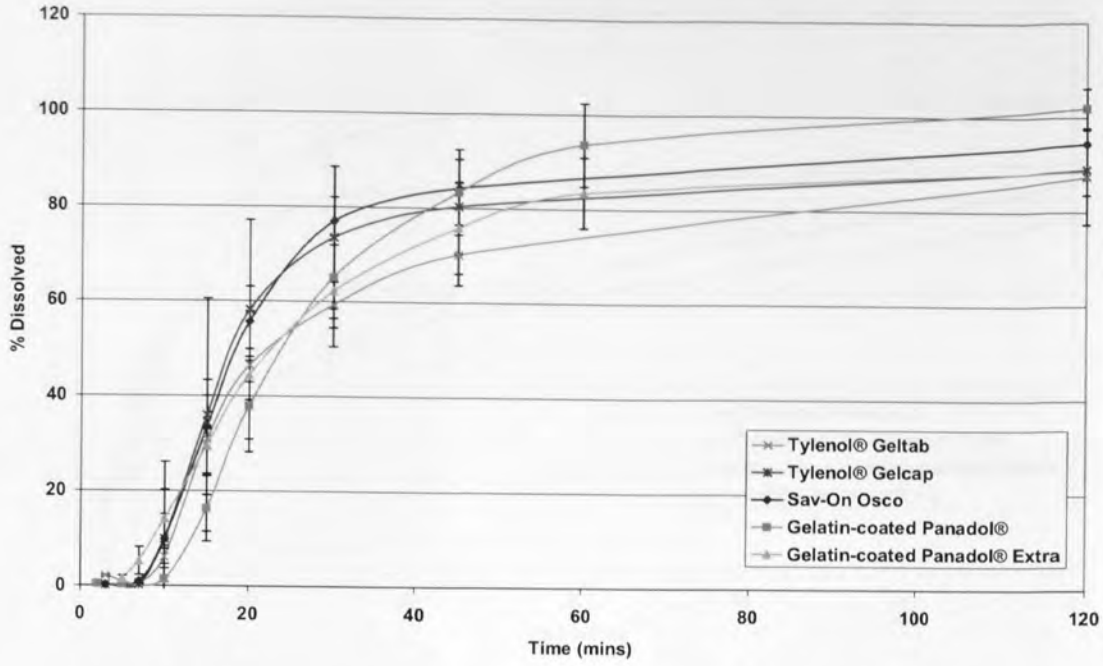


Figure 3.8- Dissolution profiles of Tylenol®, Gelatin-coated Panadol®/+Extra and Sav-On Osco formulations *(0.05M HCl, 30 rpm, n=6; mean ± S.D.)*

The dissolution of SuperDrug's own brand paracetamol formulations (SuperDrug Paracetamol and SuperDrug Paracetamol Plus) was also investigated. Although the lag time for these formulations was not long, their dissolution is slow compared to uncoated Panadol® and Panadol® ($p<0.05$) and the dissolution profile was different than the others' (SuperDrug Paracetamol vs. uncoated Panadol® f_2=27.4) (Figure 3.9). It may be that the product started to dissolve immediately for SuperDrug Paracetamol formulation (so called burst effect as resulted in a negative lag time using the calculation from the equation for steady-state rate) but the disintegrating properties of the core were not optimised for rapid dissolution, hence the disintegration might limit the dissolution therefore leading to slower rate of dissolution. A burst effect can be beneficial in IR formulations as it results in immediate onset of the drug release even though this may not be maintained as shown for SuperDrug Paracetamol (Figure 3.9). Typically the burst effect is less desired in the controlled release formulations as a burst can decrease the overall extent of drug release due to initial high concentrations of active ingredient which can also lead to toxic effects (Huang *et al.*, 2001). SuperDrug Paracetamol Plus contains an additional 65 mg of caffeine and the product was claimed to be fast-acting which may be due to caffeine possibly enhancing the analgesic effect *in vivo* (BNF, 2003) but there is no correlation with dissolution using 0.05M HCl with 30 rpm paddle speed.

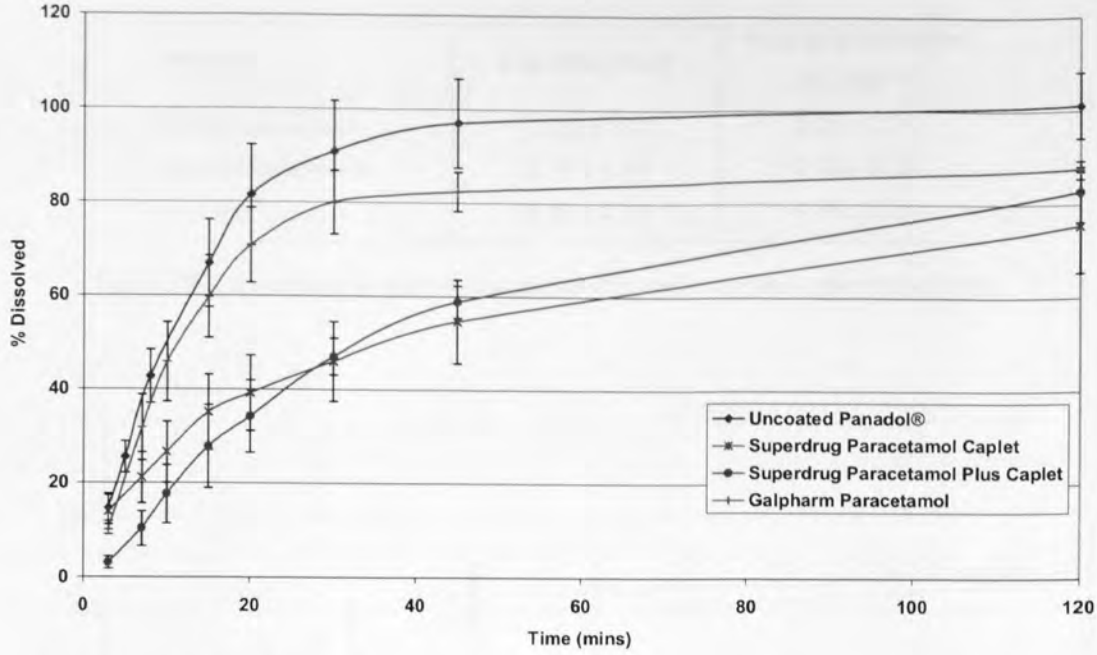


Figure 3.9- Dissolution profiles of SuperDrug and Galpharm paracetamol formulations *(0.05M HCl, 30 rpm, n=3-6; mean ± S.D.)*

3.3.2 Ibuprofen dissolution in pH 6.8 buffer

Dissolution of commercial ibuprofen-containing products was carried out to evaluate the difference between the formulations. The most obvious difference is between Galpharm ibuprofen and both Nurofen® and SuperDrug ibuprofen as the lag time is significantly longer for Galpharm caplets (Figure 3.10). SuperDrug ibuprofen is a film-coated solid-dosage form whereas Galpharm caplets and Nurofen® are sugar-coated. The applied film may affect the dissolution, especially at the start of the process when the coating can initially inhibit the onset of drug release. Sugar-coating on Galpharm caplets may be the reason for the significantly extended lag time 13.27 minutes when compared to SuperDrug and Nurofen® products, $p \leq 0.06$ (Table 3.2). Nurofen® is also sugar-coated but the inclusion of the superdisintegrant, crosscarmellose sodium, could aid the disintegration initially leading to shorter lag times. The rate of the dissolution is same for all formulations ($p>0.05$) indicating that the dissolution limiting step is the lag time. Although the Galpharm ibuprofen dissolution is significantly different to SuperDrug ibuprofen and Nurofen® dissolution only at 10 minutes ($p=0.02$), the similarity factor calculations reveal that Galpharm ibuprofen dissolution is not similar with Nurofen® and SuperDrug ibuprofen (f_2 = 32.05 and 32.16 respectively). Also dissolution profiles of Nurofen® *vs.* SuperDrug formulation are similar according to f_2 calculations (f_2 = 63.41).

Product	Lag time (min)	Rate of dissolution (% min^{-1})
Galpharm caplets	13.27 ± 1.41	4.05 ± 0.79
SuperDrug caplets	2.15 ± 1.65	3.45 ± 0.29
Nurofen®	6.10 ± 2.15	4.96 ± 0.71

Table 3.2- Lag times and rates of dissolution of commercial ibuprofen formulations

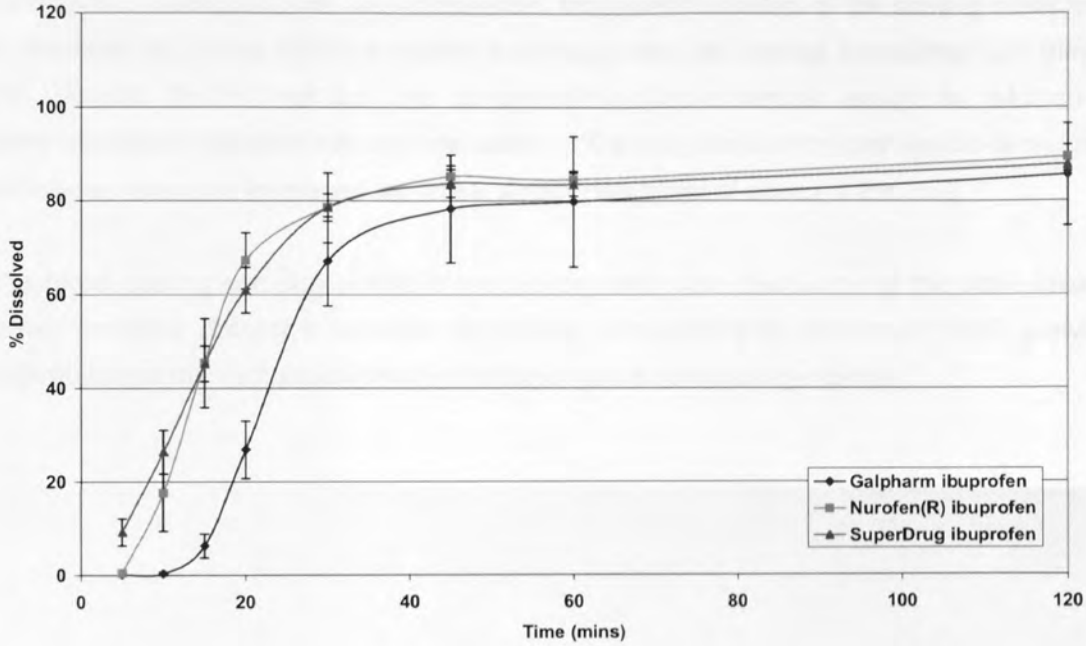


Figure 3.10- Dissolution profiles of Nurofen®, SuperDrug and Galpharm ibuprofen formulations *(pH 6.8, 50 rpm, n=3; mean ± S.D.)*

3.4 Conclusion

Although it initially appears that the proprietary brands had faster dissolution rates than the generic SuperDrug formulations, there was no significant difference between the rates.

On ranking, it was found that all uncoated or HPMC-coated formulations had the shortest lag times with exception of Tylenol Rapid Release which is partially coated but has been laser-treated to possibly soften the core. All polymer-coated formulations, other than conventionally HPMC-coated dosage forms seemed to have increased lag times but statistical analysis revealed them not to be significantly different compared to all formulations. The negative lag times indicated there was no lag and immediate drug release but depending on the core formulation the total drug release rate could still be low.

Although the additional polymer coatings did not have a large effect on the rate of paracetamol dissolution, they did have an effect on the lag times, especially for cores which did not contain any disintegration-enhancing excipients.

Ibuprofen-containing products showed differences in the dissolution which could be due to the applied coating.

It can be concluded that the dissolution of solid-dosage forms was affected by several factors such as the coating and the core formulation. Increased thickness of the coating could lead to extended lag times, also the coating technology and the coating formulation can play a role. Despite the fact that the core contains dissolution-enhancing excipients, addition of some coatings to facilitate security and safety of the drug formulation can lead to decreased dissolution rates and increased lag times, slowing the onset of action of the drug.

The tablet coating can play a role in the disintegration and dissolution of the solid-dosage forms, therefore chapter 4 explores the coating formulations as preformed films, allowing optimisation of the formulation prior to coating onto the solid-dosage form.

Chapter 4-

Studies on pre-formed films

4.1 Introduction

In order to investigate the potential of wrap-coating as an alternative method of tablet coating, it was considered essential to characterise film properties prior to coating (*i.e.* as pre-formed films). It was recognised that these films should dissolve rapidly, without delaying the onset of the drug release, but the films should be strong enough to facilitate handling and flexible enough to allow the moulding of the coating around tablet. Gelatin and cellulose-based polymers were chosen as the basis for the formulation due to their established history in the pharmaceutical and food industry.

Gelatin is widely used in pharmaceutical products, for example for preparation of films, ribbons and hard or soft gelatin capsules. It is a protein, physiologically inert, comprising a hygroscopic, amphoteric polymer, ranging from 300-4000 amino acids, having glycine, proline and 4-hydroxyproline as the most common units (glycine approximately 1 in 3). It can form heat-reversible gels, a true sol in water and is also soluble at any pH. In order to dissolve, gelatin needs to be wetted thoroughly, causing it to swell, possibly up to 5-10 times its own weight, before dissolving. It is produced from collagen, connective tissue found in mammalian skin and bones. Gelatin is denatured collagen, isolated usually from porcine or bovine skin/bones by acid or base extraction therefore resulting in two different types, A and B respectively. Gelatin is ideal for formulation of pharmaceutical films due to its glossy appearance, ability to hold dyes and neutral taste. It is readily soluble in biological fluids at body temperature and is a good film-forming material (Rama Rao *et al.*, 2003). Gelatin is also considered a non-toxic and non-irritant material in oral formulations (Price, 2001; Singh *et al.*, 2002) as well as inexpensive (Maurer, 1954), which promotes its use in pharmaceutical formulations. Gelatin has been mainly used in hard and soft capsules, but it has also been used to coat formulations *i.e.* gelatin-coated tablets. Due to the reasons outlined above, gelatin is the most widely used biopolymer in pharmaceutical and food industries.

Cellulose-based polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC) and hydroxyethylcellulose (HEC) are widely used in conventional immediate-release tablet coatings as well as in functional coatings. Typically the cellulose-based polymers are available in several grades varying in their viscosity and degree of substitution; higher viscosity polymers are used, for example, in extended-release formulations whereas low viscosity polymers are used for immediate-release formulations. Cellulose, generally obtained from cotton linters or wood pulp, is reacted with sodium hydroxide to produce alkali cellulose which is then reacted with propylene oxide, for example, to produce a hydroxypropyl side-chain. Some cellulose-based polymers are water-soluble

and good film formers as well as being considered safe, hence their extensive use in coating applications. The wide variety of cellulose-based polymers available with differing properties results in a large variety of applications within the pharmaceutical industry. HPMC has been combined with other excipients in films *e.g.* with titanium dioxide as an opacifier to aid photostability of nifedipine (Béchard *et al.*, 1992). Cellulose-based polymers are also used in matrices either alone or with other release-controlling polymers for the tablet cores; *e.g.*, ibuprofen was embedded in HPMC and carrageenan matrix in order to obtain linear release profiles (Nerurkar *et al.*, 2005).

As it was concluded in Chapter 3 that the tablet coating can play a role in the onset of the drug release therefore the aim of this chapter was to investigate the effects of excipients on the properties of the gelatin and cellulose films and to find suitable formulations to be taken forward to the coating studies. Typically tensile and puncture strength were measured as well as dissolution characteristics because the main application of the films in this study was to utilise them in the wrap-coating technology for solid dosage forms (Chapter 5) where the films need to be strong to withstand the vacuum force as well as fast dissolving due to studied drugs which are used as pain killers therefore fast onset of pharmacological effect is desired.

4.2 Materials and methods

This section describes the materials used in the experiments as well as specific methods used for analysis of the film formulations.

4.2.1 Materials

Gelatins A90-100, A300, B75, B225, glycerol, polyethylene glycols (200 and 400), DL-lactic acid, Tween 40, Tween 85, Brij35 (30%), docusate sodium, potassium bicarbonate, sodium bicarbonate, sodium carbonate, magnesium carbonate, potassium dihydrogen phosphate, disodium hydrogen orthophosphate, potassium persulphate, triacetin, potassium sorbate, propylene glycol, bicinchoninic acid and 4 % copper sulphate ($CuSO_4$) solution were purchased from Sigma-Aldrich, UK. Hydrochloric acid S.G 1.18 (37%) and glacial acetic acid were obtained from Fisher Chemicals, UK. Croscarmellose sodium, microcrystalline cellulose, crospovidone and sodium starch glycolate were kindly supplied by GlaxoSmithKline, Dungarven, Ireland. Different grades of hydroxypropyl methylcellulose were a gift from Colorcon, UK. Klucel® and Natrosol® grades were obtained from Aqualon, Hercules, UK. Water was double distilled in the laboratory using Fisons Fi-Streem 4 litre bi distillation unit.

4.2.2 Film preparation

Aqueous gelatin solution (5-15 % w/w) was heated to 40 ± 2 °C prior to addition of excipients. The excipients were added one at a time and mixed thoroughly for few minutes. Levels of plasticisers (PEG200, PEG400, glycerol, DL-lactic acid) were 1-6% (w/w), surfactants (Tween40, Tween85, Brij35(30%), docusate sodium) 1% (w/w), disintegrants (croscarmellose sodium, microcrystalline cellulose, crospovidone, sodium starch glycolate) 1% (w/w), carbonates (potassium bicarbonate, sodium bicarbonate, sodium carbonate, magnesium carbonate) 1-5% (w/w) and citric acid 1% (w/w). The exact details of the formulations are described in subsections of section 4.3. The resulting polymer solution was passed through a 100 mesh, 140 µm sieve and cast onto an acrylic plate using a Multicator 411 casting knife (Erichsen) with micrometer setting at 8 and dried at room temperature (RT) for 48 h. Dried films were then cut to an appropriate sample size and conditioned at 52 % relative humidity (RH) for 72 h according to the standard D882-02 (ASTM International, 2002).

The cellulose-based (HPMC, HPC, HEC, NaCMC) films were prepared by dissolving polymer (5-10 % w/w) in water overnight to allow complete dissolution of the polymer. The excipients (plasticisers propyleneglycol, DL-lactic acid, triacetin, PEG200, PEG1450, potassium sorbate, glycerol, triethanolamine from 1 to 7.5% w/w and surfactant Brij35 (30%) 1% w/w) were mixed into the polymer solution and the mixture was cast onto an acrylic plate using Multicator 411 casting knife (Erichsen) and dried at 60 ± 2 °C 24 h (Yoo *et al.*, 2006). Dried films were then cut to an appropriate sample size and conditioned at 52 % RH for 72 h according to the standard D882-02 (ASTM International, 2002).

The films were formed from solutions and when the wet films were dried the majority of the solvents had evaporated therefore a dry film consists of almost 100 % of polymers. In this thesis, the film formulations are described in according to solutions of which the film was cast.

4.2.3 Film thickness measurement

The films were cut to the appropriate sample size and thickness was measured at six positions using a Electronic Digital Caliper (Linear Tools). The mean thickness was used in all subsequent calculations.

4.2.4 Mechanical properties

The mechanical properties of the films were studied at RT, immediately after removing the samples from the 52 % humidity chamber. The method for tensile strength testing was based on the standard D882-02 (ASTM International, 2002).

Tensile properties were measured using Hounsfield Test Equipment with the appropriate load cell (5-5000 N). The films (n≥5) were cut to a standard size (13 x 2 cm^2) and the thickness of the films was measured. The cross-head speed was set to 50 mm min^{-1} and the length between the grips was 7.5 cm. The measurements were carried out until breakage of the film and the data were recorded on Hounsfield QMAT software. The tensile strength and % strain were determined by the software and elastic modulus was calculated from stress-strain curve (section 1.6.6.1).

Puncture strength was measured using a QTS 25 Texture Analyser (Stevens Mechtric, CNS Farnell). Pre-conditioned films (n≥3) were cut to standard dimensions (5 x 5 cm^2), thickness measured and the film was mounted between 2 plates having an exposed circular film area of 1.1442 x 10^{-4} m^2. The plates were tightened together with 4 screws and a 10 cm stainless steel probe with a hemispherical end (d=3 mm) was driven through the film at 10 mm min^{-1}. Peak load, area under first cycle and deformation at peak load were measured using QTS 25 Texture Analyser software and the puncture strength, strain and elastic modulus were calculated manually utilising data obtained from the software (section 1.6.6.1).

4.2.5 Dissolution studies for films

The thickness of pre-conditioned films (1 x 1 cm^2) was measured and the weight was recorded using an analytical balance (Sartorius Research). The films were placed between two wire mesh (100mesh, 140µm) plates prior to dissolution in 15 ml of Sørensen's phosphate buffer pH 5.8 or 0.05M HCl at 37 ± 0.5 °C. During dissolution the sample vessels were shaken at 120 strokes/minute. Samples (2 ml) were withdrawn at pre-determined time points, replaced with fresh buffer and the results were corrected for dilution according to Equation 4.1 where V_t is total volume of the dissolution medium, C is concentration at the time, V_s is sample volume and ΣC_p is the sum of previous concentrations. The samples were then analysed by BCA assay (section 4.2.5.1) for gelatin-only films and the viscosity of the medium was used to monitor dissolution of other films (Automated Microviscometer (Anton Paar), method described in section 4.2.5.2.

Equation 4.1 $$M_t = (V_t * C) + (V_s * \sum C_p)$$

The calibration curves for dissolution were constructed using standards of the same composition as film studied. The rate of dissolution (k_d) and lag time (t_{lag}) were calculated from the % dissolution-time curve.

4.2.5.1 BCA protein assay for gelatin-only films

A bicinchoninic acid (BCA) protein assay (Smith *et al.*, 1985) was used to analyse the concentration of gelatin in the dissolution studies. A standard calibration (50-800 µg/ml) was carried out at the time of the analysis and the standards were treated the same way as the samples. A working solution of BCA and 4 % $CuSO_4$ (50:1 ratio) was prepared, and 200 µl was added to 10 µl dissolution samples on a 96 well, flat bottom, microtitre plate (Fisher Scientific UK). The plates were incubated at 60 °C for an hour, and then absorbance was measured at 570nm with a MRX microplate reader (Dynex Technologies).

4.2.5.2 Microviscometry for excipient-containing films

The Automated Microviscometer (AMVn) (Anton Paar) can record small viscosity changes in the samples and therefore was utilised for the analysis of dissolution samples from gelatin films containing excipients that interfered with BCA assay and for cellulose films. The method is based on Stoke's law (Equation 4.2) where movement of a rolling ball is resisted or dragged when moved through a liquid and also the movement of the ball is influenced by gravity (Marriot 2002). This event is determined as in Equation 4.2 where η is viscosity, d ball diameter, v terminal velocity, g gravity, ρ_s sphere density and ρ_l liquid density. AMVn measures dynamic viscosity of liquid in the range of 0.3 – 2500 mPas viscosity range with accuracy for the time measurement is < 0.002 s.

Equation 4.2 $$\frac{\pi}{6} d^3 g(\rho_s - \rho_l) = 3\pi\eta dv$$

Samples obtained following dissolution of the films were filtered through 0.45 µm nylon syringe filter (Kinesis, UK) placed into a sealed 1.6-mm capillary tube containing a small steel ball; the procedure is based on the rolling ball principle, where the time taken the ball to roll a fixed distance is measured and converted to dynamic viscosity. The temperature during the analysis was set to 25 ± 0.05 °C and the measurement from each sample was repeated 4 times with 50° tilt. All measurements and calculations were monitored and performed on the Visiolab for AMVn software. The dynamic viscosities were converted % dissolution using a

calibration curve constructed using same film under investigation. The standard calibration was constructed carried out at each time of analysis in the range of 50 – 800 µg ml^{-1} and typically the linearity of the calibration curve was $R^2 = 0.995$ (Figure 4.1).

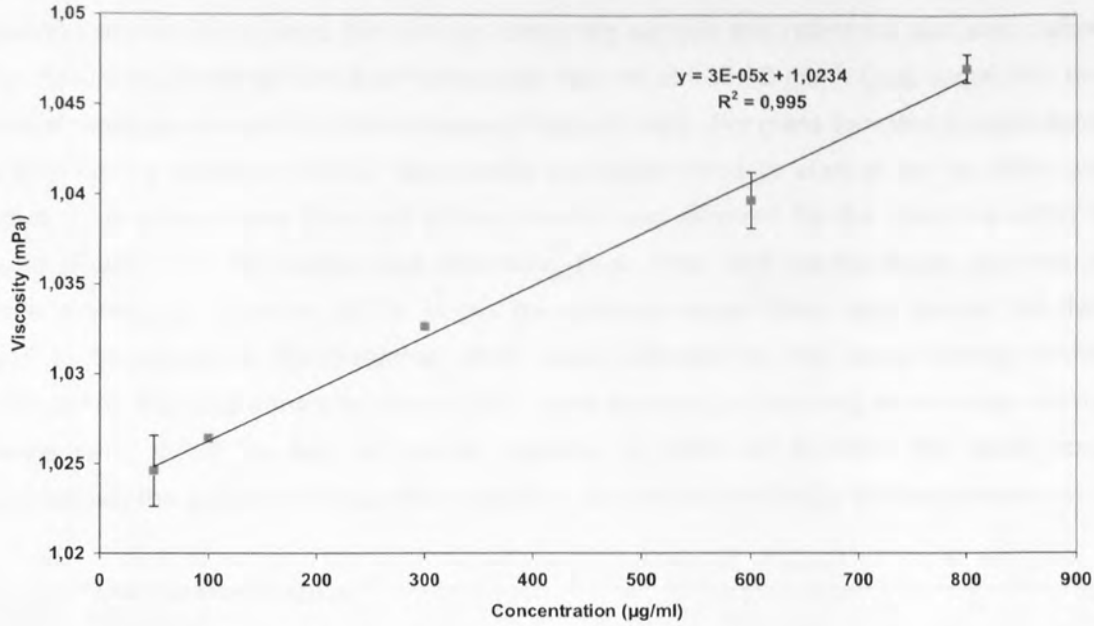


Figure 4.1- A typical calibration curve for polymer film dissolution *(example is calibration for film cast from 5% DL-lactic acid, 10% gelatin solution)*

4.2.6 Swelling

Pre-conditioned film was cut (1 x 1 cm^2), weighed and thickness measured. The film was then placed in 15 ml pH 5.8 buffer (or 0.05M HCl) and was removed at pre-determined time intervals. Surface water was removed with filter paper, and the weight of the film was recorded. The percentage swelling was calculated according to Equation 4.2 (Bigi *et al.*, 2002), where W_w is the wet weight and W_d is the initial dry weight. The percentage swelling *vs.* time curve was converted to % *vs.* square root time in order to obtain a linear curve for initial time points (Papadokostaki *et al.*, 1997; Tang *et al.*, 2002). The rate of swelling (K_s) was determined as a slope of the initial linear region of the curve.

Equation 4.2 $$W(\%) = \frac{(W_w - W_d)}{W_d} * 100$$

4.2.7 Thermal studies

The differential scanning calorimetry (DSC) was carried out using Pyris Diamond DSC connected to an Intracooler 2P-cooling accessory (Perkin-Elmer). The temperature range studied was typically from -50 °C to 200 °C, depending on the degradation temperature of the sample. The samples were weighed accurately on a Kern 770 analytical balance prior sealing into aluminium pans, the furnace containing sample and reference pan was purged with helium at 20 ml $min^{-1}$and the heating rate was set at 300 °C min^{-1}. Data acquisition and analysis were performed on Pyris Software (Perkin-Elmer). For glass transition temperatures (a step on the baseline of DSC trace) onset was determined as start of the transition and actual T_g is extrapolated from half of the specific heat required for the glass transition to occur (Figure 4.2). All analysis was performed three times and results shown as mean of three ± standard deviation (S.D.). Mainly the cellulose-based films were studied for their thermal transitions at temperatures which were relevant for the wrap-coating studies (Chapter 5). Possible transitions below 100°C were especially interesting as the wrap-coating temperature should be kept as low as possible in order not to affect the tablet core. Alternatively the exposure to high heat should be as fast as possible for the same reasons.

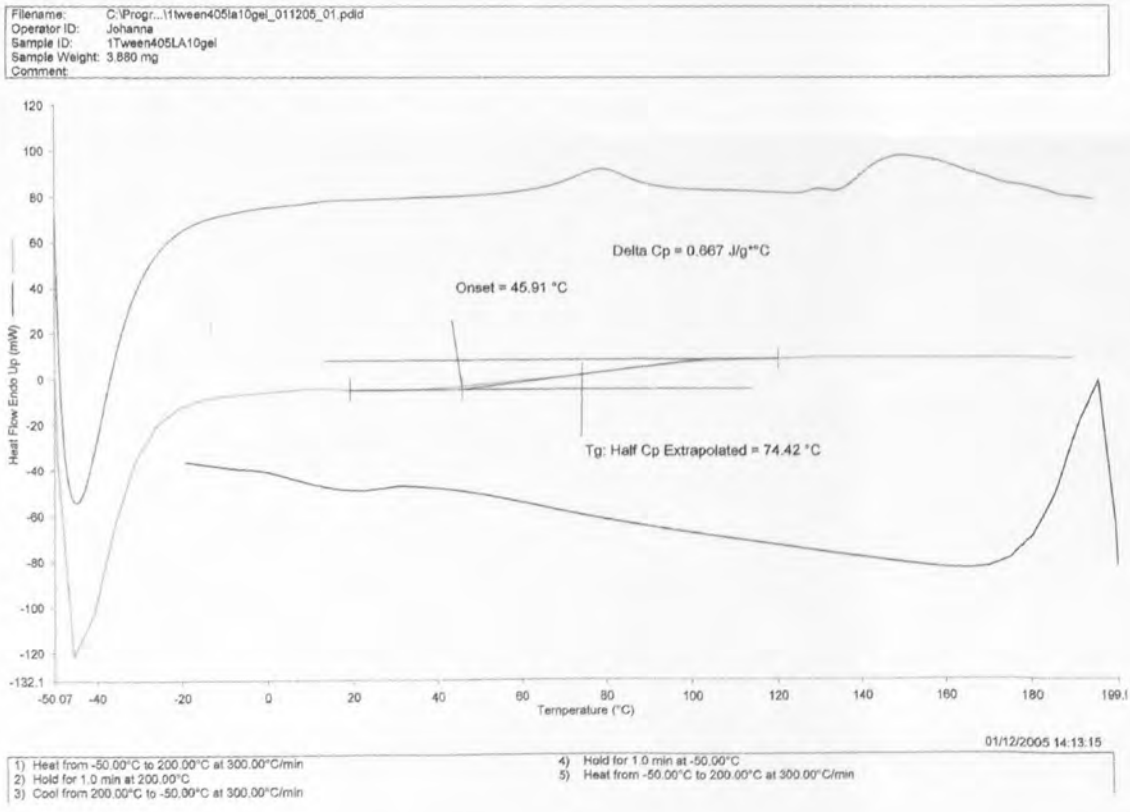


Figure 4.2- A typical DSC trace (top trace shows 1st heating, second trace the re-heating and the trace at the bottom shows cooling trace)

The thermogravimetric analysis (TGA) was carried out on Pyris 1 TGA thermogravimetric analyser (Perkin-Elmer). The sample (~ 6 mg) was heated in the open pan from 40-250 °C at 10 °C min^{-1} under a nitrogen purge, to monitor moisture content in samples as well as study the degradation of new samples. Data acquisition and analysis were performed on Pyris Software (Perkin-Elmer) where derivate of the % weight loss *vs.* temperature curve was taken which shows the transition points clearly (Figure 4.3). According to the areas the change in the weight loss can be calculated using the software. All analysis was performed three times and results shown as mean of three ± S.D..

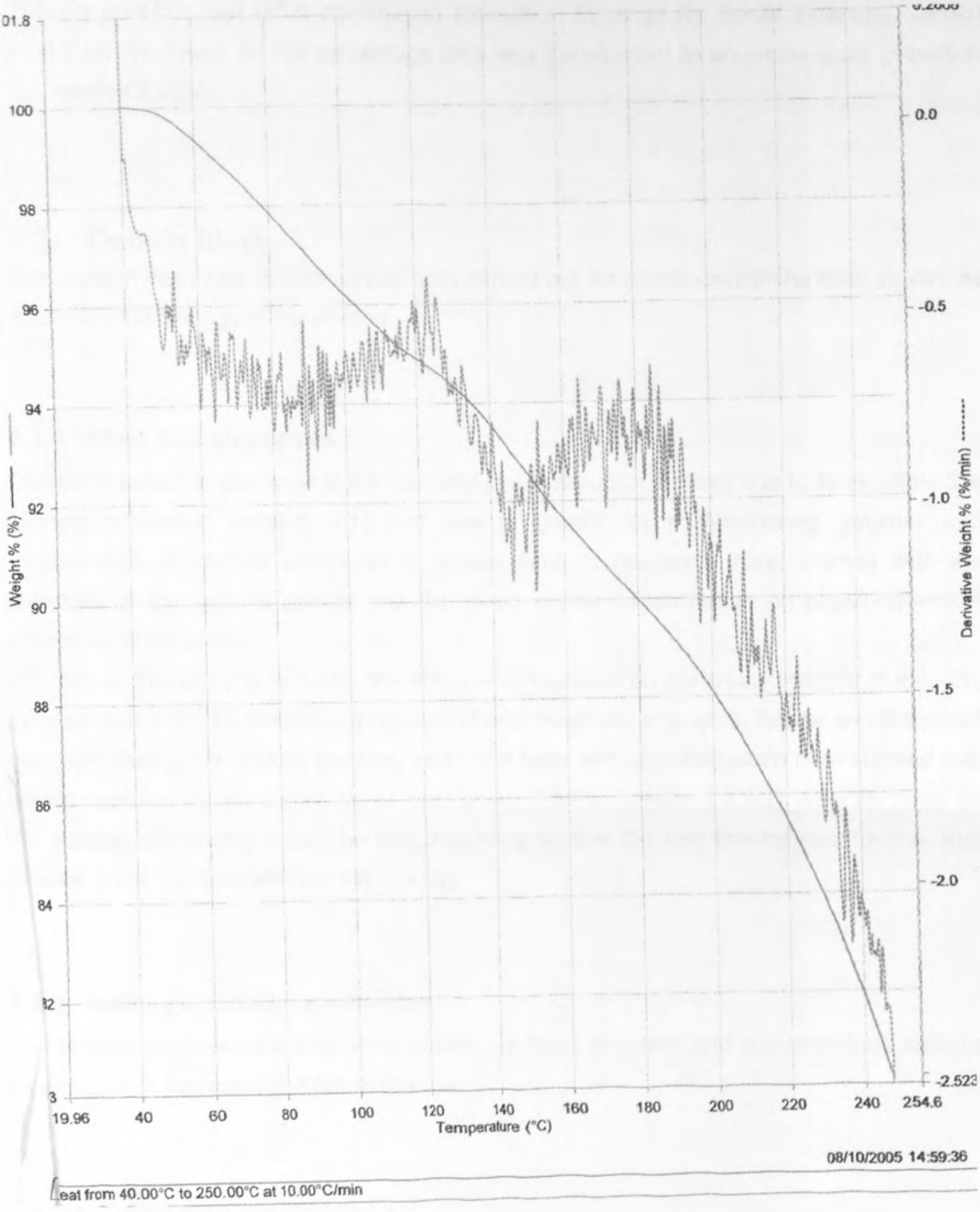


Figure 4.3- A typical TGA trace

4.2.8 Statistical analysis

The tensile and puncture characteristics, dissolution data, % released, lag times and rate of dissolution and swelling were compared statistically using analysis of variance (ANOVA) with

Tukey's post-hoc test (95% confidence) (Statistical Package for Social Sciences (SPSS) 12.0.1 for Windows). All the percentage data was transformed to an arcsin scale (Equation 3.1, section 3.2.2.3).

4.3 Gelatin films

This section describes all formulation work carried out for gelatin-containing films as well as discusses the findings of the studies.

4.3.1 Aims and objectives

Gelatin has been widely used in the food and pharmaceutical industry due to its excellent film forming properties (section 4.1) and use of gelatin as a film-forming polymer and incorporation of various excipients in gelatin films is discussed here, starting with the selection of the type of gelatin and the effect of the concentration on physicochemical properties of the films.

The aim of this study is to probe the effect of formulation on the characteristics of the film. For example a film for the coating process should be strong enough to handle and withstand the strain during the coating process, and initial tests with glycerol/gelatin films showed that elastic modulus values should be at least under 2 MPa (section 4.3.2.2). Also the films for the coating application should be fast dissolving so that the rate limiting step for the drug release is not the dissolution of the coating.

4.3.2 Initial gelatin-film evaluation

This section discusses the evaluation of different types of gelatin and concentrations suitable for gelatin-film formation and future studies.

4.3.2.1 Selection of gelatin type

Initially pure gelatin films were studied to identify which type of gelatin would be most suitable for future studies. Gelatin is available in four different forms varying in bloom strength and the procedure of manufacturing gelatin (section 4.1): A90-100, A300, B75 and B225. The puncture properties of the films (5 % w/w) were studied, and it was found that with A-type gelatin higher bloom strength films demonstrated higher strain values (Figure 4.4), there was no obvious trend in the puncture strength results. Also type-B gelatin with different bloom

strength did not result in different puncture strength or strain values. The effect of gelatin bloom type and strength, with and without cross-linking, has been studied by several groups (Rama Rao *et al.*, 2002; Bigi *et al.*, 2004; Ciper *et al.*, 2005) and as a general trend, the strength (MPa) and strain (%) of the gelatin films increases with increasing bloom strength. Also it was noted that higher bloom strength gelatin induces more cross-linking (Rama Rao *et al.*, 2002) and longer disintegration times (Ciper *et al.*, 2005). The lack of studies on the differences between the different types of gelatin may be due to availability of same bloom strength gelatin which would allow direct comparison. It has been reported that type B gelatin may be more prone to cross-linking (Levy *et al.*, 1987) but Rama Rao *et al.* (2002) did not find any difference in degree of cross-linking between the A- and B-type of gelatin.

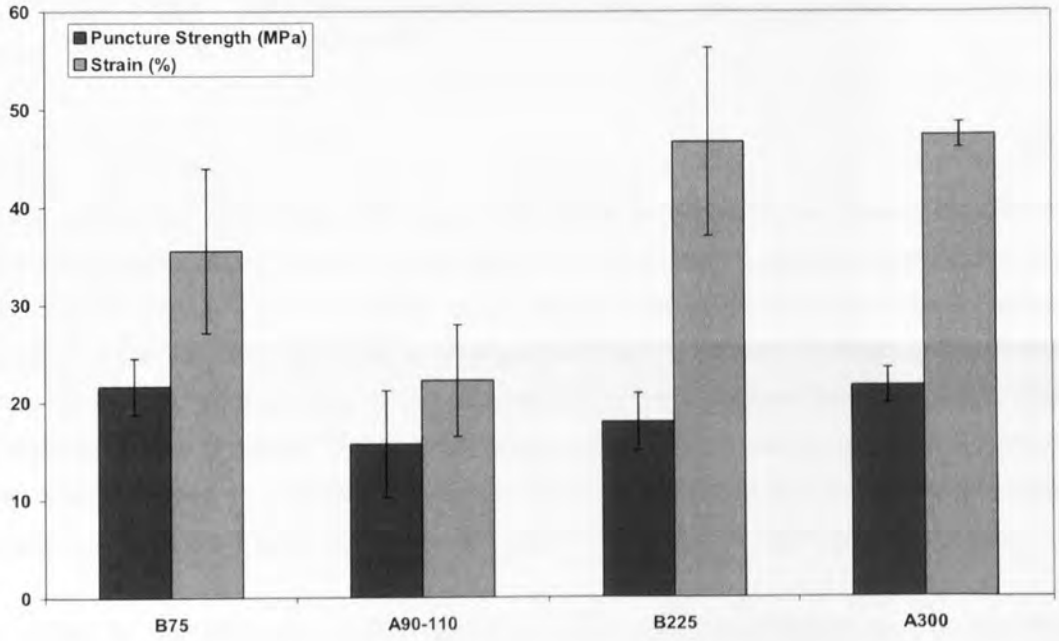


Figure 4.4- Puncture strength and strain of films cast from 5 % gelatin solutions *(mean ± S.D.; n=4-6)*

4.3.2.2 Effect of gelatin solution concentration on film properties

The effect of varying concentration of gelatin (B75) in the films was studied. It was noted that percentages over 15 formed either brittle films (*i.e.* impossible to peel off the plate intact) or the solutions were too viscous for casting and for even film formation. Although puncture strength, strain and elastic modulus were not significantly different between 5, 10 and 15 %

films an increasing trend in puncture strength and elastic modulus can be seen up to 10 % whereas lower values were obtained for 15 % formulation.

All gelatin-only films disintegrated rapidly in the Sørensen's phosphate buffer therefore swelling could not be measured. The dissolution rate and the lag time for these films were not significantly different ($p > 0.05$, Table 4.1).

%	σ_p (MPa)	ε_p (%)	EM_p (MPa)	K_d (% min^{-1})	t_{lag} (min)	K_s (% $min^{-0.5}$)
5	21.63 ± 2.87	35.55 ± 8.43	6.34 ± 0.95	16.15 ± 1.48	0.22 ± 0.36	-
10	24.08 ± 3.17	37.75 ± 10.59	6.81 ± 1.17	20.66 ± 9.25	0.87 ± 0.20	-
15	16.88 ± 1.34	36.49 ± 8.71	6.13 ± 1.12	27.16 ± 6.49	0.78 ± 0.36	-

Table 4.1- Mechanical properties, dissolution and swelling of gelatin films (B75) with varying concentration *(key: % concentration in solution (w/w); σ_p puncture strength; ε_p puncture strain; EM_p puncture elastic modulus; K_d rate of dissolution in pH 5.8; t_{lag} lag time; K_s rate of swelling in pH 5.8; -too fragile to measure; $n \geq 3$; mean ± S.D.)*

4.3.2.3 Conclusion

Gelatin types A90-100, A300, B75 and B225 were investigated as cast films and their puncture properties were studied. The higher bloom strengths demonstrated higher strain properties for gelatin type A-films and there was no obvious trend in the relative puncture strengths of the films. Higher bloom strengths have been reported to be more prone to cross-linking which may lead to even longer disintegration times (Rama Rao and Singh, 2002). Type A300 gelatin produced films with a slight yellow tinge whereas the type B produced clear films therefore it was decided to use the B75 gelatin in the future studies due to clearness of the film and less chance for the cross-linking having lower bloom strength.

The effect of concentration of B75 gelatin in films was also studied and no significant differences were found in the puncture properties although the puncture strength had decreased for 15 % (w/w) film which indicates the high concentration gelatin film to be more easily ruptured.

4.3.3 Effect of plasticisers

4.3.3.1 Introduction

Section 1.6.4.3 outlined briefly the functions of plasticisers. In pharmaceutical applications, plasticisers are typically used in tablet coating formulations or soft gelatin capsules. The aim of this study was to investigate the effect of glycerol, PEG200, PEG400 and DL-LA on the physicochemical properties of the gelatin films (dissolution, swelling, puncture properties, tensile properties and thermal properties), and to find suitable formulations of gelatin and plasticiser to be taken forward to the future studies as well as to find a suitable base formulation for coating studies with optimised dissolution properties and elastic behaviour.

4.3.3.2 Glycerol

The properties of polymer films can be altered by addition of suitable plasticisers; generally leading to more flexible films with increased strain/elongation and decreased strength and elastic modulus. Strength and strain alone may not describe the properties of the film therefore elastic modulus is calculated to describe the relationship between strength and strain as stiffness and rigidity of the film. Glycerol has been used as a plasticiser with gelatin (Arvanitoyannis *et al.*, 1997; Arvanitoyannis *et al.*, 1998b; Vanin *et al.*, 2005; Lukasik *et al.*, 2006a; Lukasik *et al.*, 2006b) but the reported studies have concentrated on examining the mechanical, water vapour permeability and thermal properties of films therefore dissolution, swelling, puncture and tensile strength studies were carried out to investigate the effect of glycerol in gelatin films.

As expected, a high proportion (5% w/w) of plasticiser in the formulation led to decreased strength and elastic modulus whereas the flexibility (elongation and strain) was increased; trend was exhibited for both tensile and puncture properties although it was more prominent in the tensile properties (Table 4.2). The 5/5 film formulation had too high plasticiser-polymer ratio as the film did not form once dried. There were no significant differences in the dissolution rates of all formulations ($p>0.05$) but the formulations prepared from 1 % (w/w) glycerol with 10 and 15 % (w/w) of gelatin showed significantly increased lag times compared to other formulations (Table 4.3). The formulations prepared from polymer solution containing gelatin with 5 % (w/w) glycerol possessed lower tensile and puncture strength with decreased elastic modulus values which demonstrated the plasticising effect of glycerol. The addition of plasticiser weakens the intermolecular forces between the polymer molecules (Hogan, 2000) by integrating in between polymer molecules which is possible due to small size of glycerol and possibility of H-bonding of glycerol to gelatin, making the film more flexible and soft which is demonstrated here with the mechanical properties as well as

dissolution properties; weaker films require less swelling prior disintegration and dissolution (Sungthongjeen *et al.*, 2004) which is evident with decreased lag times for the formulations containing 5 % (w/w) glycerol. The highest ratio (5/10) formulation had slower swelling rate (195.76 % $min^{-0.5}$) and shortest lag time (0.74 min) in accordance with the findings of Sungthongjeen and co-workers (2004).

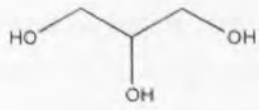


Figure 4.5- Molecular structure of glycerol (MW 92.06 g mol^{-1}, reproduced form Price, 2005)

Formulation	Tensile properties			Puncture properties		
Ratio	σ_t (MPa)	ε_t (%)	EM_t (MPa)	σ_p (MPa)	ε_p (%)	EM_p (MPa)
1/5	85.52±9.10	5.74±0.69	16.67±5.77	19.05±0.58	30.3±3.94	4.56±0.16
1/10	63.42±17.71	2.68±1.28	22.00±2.25	26.83±2.84	27.1±2.96	6.19±0.75
1/15	70.62±11.56	3.22±0.65	18.77±1.77	25.57±4.30	34.40±6.51	5.40±1.32
5/5	-	-	-	-	-	-
5/10	9.98±1.01	53.06±4.73	1.19±0.55	15.56±2.47	68.4±7.09	0.86±0.11
5/15	15.81±1.01	18.06±7.78	5.26±1.44	17.74±1.98	55.17±21.91	1.25±0.54

Table 4.2- Mechanical properties of glycerol/gelatin films *(key: formulation prepared from solution of glycerol to gelatin in % (w/w); σ_t tensile strength; ε_t tensile strain; EM_t tensile elastic modulus; σ_p puncture strength; ε_p puncture strain; EM_p puncture elastic modulus; - too sticky to handle; n≥3; mean ± S.D.)*

Formulation	K_d (% min^{-1})	t_{lag} (min)	K_s (% $min^{-0.5}$)
1/5	12.44 ± 1.96	-0.71 ± 0.45	326.33 ± 32.47
1/10	20.69 ± 5.15	2.70 ± 0.30	272.59 ± 19.09
1/15	19.56 ± 1.84	1.81 ± 0.88	244.49 ± 11.80
5/5	-	-	-
5/10	24.89 ± 5.98	0.74 ± 0.21	195.76 ± 6.64
5/15	19.81 ± 1.79	0.87 ± 0.57	246.61 ± 48.37

Table 4.3- Dissolution and swelling properties of glycerol/gelatin films *(key: formulation prepared from solution of glycerol to gelatin in % (w/w);K_d rate of dissolution in pH 5.8; t_{lag} lag time; K_s rate of swelling pH 5.8; - too sticky to handle; n≥3; mean ± S.D.)*

This study showed that 5/10 % ratio of glycerol to gelatin (w/w) produced most flexible film without being too stiff (elastic modulus value low compared to the other formulations here) as

well as favourable dissolution and swelling properties leading to a possibility of using it as a coating for the wrap method (section 5.3.3.1). Due to these results, polymer-plasticiser 5/10 ratio was used in subsequent studies to examine the effects of alternative plasticisers.

4.3.3.3 Polyethylene glycols

Polyethylene glycols (PEG) are widely used in pharmaceutical products *e.g.* as an ointment base, plasticiser, solvent, tablet lubricant (Price, 2001). PEGs are graded according to their molecular weight and PEG200-600 exist as liquids, although sometimes PEG600 can solidify at room temperature. The higher grade PEGs are generally used in solid-dosage forms as a lubricant but they are also used as dissolution-enhancing excipients for poorly soluble drugs *e.g.* PEG400 was used as a solvent and fill-liquid for ibuprofen-containing soft gelatin capsules (Felton *et al.*, 1996). The solid grades can also be used as tablet-coating polymers alone or with other polymers (Miralles *et al.*, 1982) and the lower-grade PEGs may increase water permeability and dissolution at low pH when used in coating formulations (Price, 2001). The molecular structure of PEG is shown in Figure 4.6.

Formulation	Tensile properties			Puncture properties		
5/10	σ_t (MPa)	ε_t (%)	EM_t (MPa)	σ_p (MPa)	ε_p (%)	EM_p (MPa)
Glycerol	9.98±1.01*	53.06±4.73*	1.19±0.55*	15.56±2.47	68.40±7.09	0.86±0.11
PEG200	18.82±2.25	67.70±4.23*	2.77±0.46*	18.35±2.23	68.80±11.01	1.08±0.22
PEG400	19.69±3.31	10.81±6.88*	5.55±1.19*	9.53±2.08*	27.13±5.74*	2.26±0.39*

Table 4.4- Mechanical properties of plasticiser/gelatin films *(key: formulation prepared from solution of plasticiser to gelatin in % (w/w); σ_t tensile strength; ε_t tensile strain; EM_t tensile elastic modulus; σ_p puncture strength; ε_p puncture strain; EM_p puncture elastic modulus; - too sticky to handle; * significantly different to other formulations in the table; n≥6; mean ± S.D.)*

Formulation	K_d (% min^{-1})	t_{lag} (min)	K_s (% $min^{-0.5}$)
glycerol	24.89 ± 5.98	0.74 ± 0.21	195.76 ± 6.64*
PEG200	18.87 ± 2.04	1.47 ± 0.21	118.60 ± 9.57*
PEG400	16.83 ± 6.04	1.57 ± 1.10	144.17 ± 5.65*

Table 4.5- Dissolution and swelling properties of plasticiser/gelatin films *(key: formulation prepared from solution of 5 % of plasticiser to 10 % gelatin (w/w);K_d rate of dissolution in pH 5.8; t_{lag} lag time; K_s rate of swelling in pH 5.8; - too sticky to handle; * significantly different to other formulations in the table; n≥3; mean ± S.D.)*

Inclusion of PEG200 in the gelatin film produced tougher but more flexible films compared to glycerol-containing counterparts (Table 4.4). As the molecular weight of the PEG increased, the tensile strength was not significantly different but the puncture strength of PEG400 was decreased. Puncture strength describes the resistance to breakage when something is forced through the sample (Radebaugh *et al.*, 1988) whereas the tensile strength is a

measurement of the strength required to pull the test piece apart thus they do not necessarily follow the same trends. The formulation containing PEG400 had a significantly lower tensile strain compared to PEG200 and glycerol formulation. It may be that the chain structure of PEG plays a role in the plasticising properties; the shorter chain in PEG200 may still be able to move in between the polymer chains resulting in more flexible films whereas the PEG400 may be too long with less hydrogen-bonding sites for interaction with gelatin therefore leading to a less flexible film. This phenomenon is also seen with the puncture strain results. Ciper and Bodmeier (2005) found that inclusion of hydrophilic excipients such as xylitol, sorbitol and PEG400 in gelatin film formulations led to increased disintegration times although it was mentioned that 5% (w/w) PEG400 formulations were too sticky to handle which was not the case in these studies.

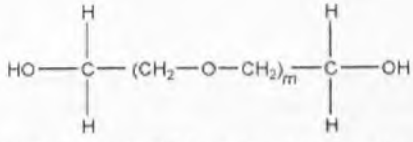


Figure 4.6- Molecular structure of PEG (where m is dependent on the grade of PEG, reproduced from Price, 2005)

Typically the PEG formulations produced tougher films which may lead to decreased dissolution rates and increased lag times which was the trend here for the mean values although differences are not significant. Weaker films require less swelling prior to disintegration and dissolution (Sungthongjeen *et al.*, 2004) and although the dissolution rates of the PEG formulations are lower, the swelling rates are also significantly lower. It may be that the PEG structure inhibits the swelling of gelatin without leading to faster dissolution.

A combination of glycerol with PEG200 and PEG400 was also investigated (Table 4.6), 1% PEG200 or PEG400 was added to 5 % glycerol/10 % gelatin solution. As expected the inclusion of additional plasticiser led to softer films, more elastic films and the effect of PEG200 was enhanced compared to films plasticised with PEGs alone. Although the dissolution rate was increased, the lag time was also increased suggesting a rapid dissolution once hydration had occurred.

Formulation	Tensile properties			Puncture properties		
	σ_t (MPa)	ε_t (%)	EM_t (MPa)	σ_p (MPa)	ε_p (%)	EM_p (MPa)
Glycerol	9.98±1.01	53.06±4.73	1.19±0.55	15.56±2.47	68.40±7.09	0.86±0.11
+PEG200	3.25±0.33	104.1±12.29	0.16±0.08	-	-	-
+PEG400	6.82±1.47	76.69±18.75	0.82±0.19	9.98±1.50	68.77±10.36	0.57±0.07

Table 4.6- Mechanical properties of the dual plasticised gelatin films *(key: prepared from solution of 5% (w/w) glycerol, 10 % (w/w) gelatin, with additional 1 % (w/w) PEG; σ_t tensile strength; ε_t tensile strain; EM_t tensile elastic modulus; σ_p puncture strength; ε_p puncture strain; EM_p puncture elastic modulus; - not done; n≥6; mean ± S.D.)*

Formulation	K_d (% min^{-1})	t_{lag} (min)	K_s (% $min^{-0.5}$)
Glycerol	24.89 ± 5.98	0.74 ± 0.21	195.76 ± 6.64
+PEG200	20.08 ± 2.09	0.12 ± 0.91	-
+PEG400	33.67 ± 11.51	1.24 ± 0.39	109.12 ± 3.90

Table 4.7- Dissolution and swelling properties of the dual plasticised gelatin films *(key: prepared from solution of 5% (w/w) glycerol, 10 % (w/w) gelatin, with additional 1 % (w/w) PEG; K_d rate of dissolution in pH 5.8; t_{lag} lag time; K_s rate of swelling in pH 5.8; - too sticky to handle; n≥3; mean ± S.D.)*

4.3.3.4 DL-lactic acid

DL-lactic acid (DL-LA) is used in injections and topical preparations as acidifier but not as a plasticiser (Lee, 2001). The effect of DL-LA as plasticiser was investigated here as it has been described as alternative plasticiser in the patent by Kessel *et al.*, 2002. Also structure of DL-LA with hydroxyl groups may allow the plasticising effect to be true.

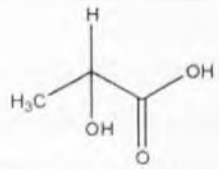


Figure 4.7- Molecular structure of lactic acid (MW 90.08 $gmol^{-1}$, reproduced from Lee, 2005)

At 5 % w/w the amount of DL-LA in the formulation with 10 % (w/w) gelatin solution was too high as the film was sticky and difficult to handle. However despite a small sample size due to these handling difficulties, the dissolution of the film was investigated. The dissolution rate was significantly increased compared to formulations containing PEG alone which shows that inclusion of DL-LA in the film may produce enhanced dissolution characteristics (K_d = 34.70 ± 7.34 % min^{-1}, t_{lag} = 0.16 ± 0.94 min). A lower concentration of DL-LA (2.5 % (w/w))

facilitated easier handling of the films and the dissolution rates (25.57 ± 7.36 min^{-1}) and lag times (0.84 ± 0.18 min) were not significantly different to those with higher concentrations. At lower levels, the inclusion of DL-LA results in significantly higher tensile strength but lower tensile strain therefore a reduced plasticising effect when compared to gelatin/glycerol film. The DL-LA provides some plasticity to the formulation if compared directly to the gelatin-only film (10 % (w/w)) as puncture strength decreases and strain increases.

The combined effects of DL-LA and PEG200 (2.5 % and 1 % w/w respectively) with 10 % (w/w) gelatin (in cast solution) were investigated; the effect was dramatic with significant decreases in the tensile and puncture strengths, and significant increases in the strain properties. Although mechanical properties were affected, there was no effect on dissolution (K_d 26.74 ± 2.49 % min^{-1}; lag_t 0.70 ± 0.48 min). It may be therefore possible to use these plasticisers in combination to manipulate the properties of polymeric films.

Formulation	Tensile properties			Puncture properties		
(w/w)	σ_t (MPa)	ε_t (%)	EM_t (MPa)	σ_p (MPa)	ε_p (%)	EM_p (MPa)
10 % Gelatin	-	-	-	24.08±3.17	37.75±10.59	6.81±1.17
Glycerol (5 %)	9.98±1.01	53.06±4.73	1.19±0.55	15.56±2.47	68.40±7.09	0.86±0.11
PEG200 (5 %)	18.82±2.25	67.70±4.23	2.77±0.46	18.35±2.23	68.80±11.01	1.08±0.22
PEG400 (5 %)	19.69±3.31	10.81±6.88	5.55±1.19	9.53±2.08	27.13±5.74	2.26±0.39
DL-LA (2.5 %)	16.88±1.17	7.90±2.27	5.79±0.67	19.03±1.70	54.44±6.34	1.11±0.08
DL-LA (2.5 %) + 1 % PEG200	5.37±0.98	47.32±10.52	0.80±0.12	6.00±1.53	81.07±15.75	0.35±0.03

Table 4.8- Mechanical properties of the plasticiser/gelatin films *(key: prepared from solution of 10 % gelatin + plasticiser; σ_t tensile strength; ε_t tensile strain; EM_t tensile elastic modulus; σ_p puncture strength; ε_p puncture strain; EM_p puncture elastic modulus; - not done; n≥6; mean ± S.D.)*

4.3.3.5 Conclusion for plasticiser containing films

All plasticisers investigated were compatible with gelatin resulting in even and clear films. The plasticising effect was evidenced by decreased strength of the films as well as decreased elastic modulus in comparison to gelatin-only films. The lag time was increased for PEG400-film when compared to other films but a direct correlation with mechanical properties was not found, although weaker films are perceived to dissolve faster than stronger films which require more energy to break the bonds between the polymer and plasticiser molecules.

Due to compatibility of all used plasticisers, it was concluded that three of them would be investigated in combination with other potential dissolution enhancing excipients. Glycerol- and DL-LA-containing films were showing favourable dissolution properties therefore these

films were used in further studies. Also as the inclusion of PEG200 resulted in increased elasticity in the film hence it may prove beneficial in coating applications (Chapter 5).

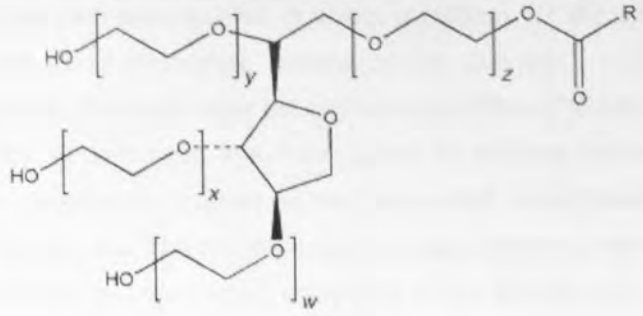
4.3.4 Effect of surfactants

4.3.4.1 Introduction

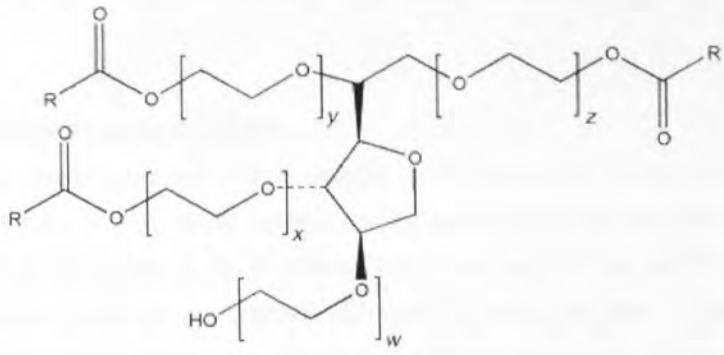
Surfactants are widely used in pharmaceutical products as wetting agents, solubilisation agents for poorly soluble drugs, to reduce surface tension of two phases and some surfactants can also act as plasticisers. In this project, non-ionic surfactants and an anionic surfactant were studied for inclusion in terms of effects on the mechanical and dissolution properties in film formulations.

4.3.4.2 Glycerol-based films

Addition of all surfactants (Tween 40, Tween 85, Brij35 (30%) and Docusate Na at 1 % w/w) enhanced the plasticising effect in combination with glycerol, evidenced in the decreased tensile strength and puncture strength (formulations **B-E**, Table 4.9). As plasticiser molecules move in between the polymer molecules the tension between polymer molecules is relaxed and the polymer molecules become more mobile. This usually leads to increased strain values as the films have become more flexible; this is evident for all the films except formulation **C**; the tensile strain for Tween 85-containing films is significantly less than other plasticised films (**A, B, D, E)**. Tween 85 is a triester (oleate) reducing the tension in the film leading softer films by moving in between polymer strands but it does not act as a binder for the polymer to tie them together leading more flexible films because of the lack of available hydrogen bonding sites. Tween 40 (used in formulation **B**) is a mono ester (*i.e.* smaller molecule with less fatty acid groups) leaving 3 hydroxyl groups available for bonding therefore inducing flexibility to the film (Figure 4.8). Although Brij35 in formulation **D** does not have many available bonding sites, it was used as aqueous solution therefore introducing additional water molecules into the film structure. Water can act as a plasticiser therefore it may explain why the Brij was such an effective plasticiser in this formulation (Arvanitoyannis *et al.*, 1998b). Dissolution of the films was not affected by addition of surfactants but the swelling rates were significantly lower compared to formulation **A** which may be due to the surfactant in the formulation.



Polyoxyethylene sorbitan monoester



Polyoxyethylene sorbitan triester

Figure 4.8- Basic structures of Tween monoester and triester (reproduced from Lawrence, 2005)

4.3.4.3 PEG200-based films

Only PEG200 was included in these studies as it provided more elasticity to the structure of the film which is desirable for the coating application and other properties were not significantly different between the different molecular weights used previously.

It may be that glycerol is more powerful plasticiser as discussed in the section 4.3.3.2, due to smaller molecular weight and size of the molecule with more possibilities of H-bonding with the polymer. Addition of surfactants to formulations containing PEG200, did not lower the tensile strength but the flexibility (tensile strain) was increased significantly for Docusate Na and Brij 35 films (formulations **J** and **I** respectively). Puncture properties were generally reduced with addition of surfactants in the formulations **G-J**, making the film more rigid. The rate of dissolution was increased with a decreased lag time, which was significant for **I** and **G**, containing Brij 35 and Tween 40 respectively. Film **I** in particular showed promising dissolution properties with rate of 56.10 % min^{-1} and was selected for the coating applications.

Both **G** and **I** formulations were also studied in acidic conditions for the dissolution; the lag times were negative indicating immediate release of the polymer (-1.26 and -0.29 min respectively) and the rate of dissolution was not significantly different to the dissolution at pH 5.8. Although the Tween 40-containing film (formulation **G**) showed favourable dissolution properties, the film had a tendency to shrink on the plate whilst drying therefore samples for tensile tests were not carried out. The moisture content was relatively high (10.63±0.60 %), which may be due to caused by hygroscopic excipients under the applied conditions (Price, 2001). Also other PEG200-containing films had high moisture content (>10%) which indicates that PEG200 may have absorbed moisture when conditioned in humidity chamber. Sometimes water can act as a plasticiser but the effect was not seen here (Figure 4.9).

4.3.4.4 DL-lactic acid-based films

Although 5 % DL-lactic acid with 10 % gelatin (formulation **K**) produced a film which was sticky and difficult to handle, films containing an additional 1 % of surfactant (Tween 40, Tween 85 and Brij 35; codes **M, N, O** respectively) resulted in films which easier to handle. Surfactants generally reduce the surface tension at interfaces and it may be that these reduced the tension within the film so that they were less sticky but still having the intended plasticising effect. There were no significant differences between the tensile strength of the formulations **M, N and O** but film **N** showed a low strain percentage, similar to Tween 85 in combination with glycerol and gelatin (**C**). Inclusion of Brij 35 had greater effect on tensile strain (**O**) compared to other DL-LA-surfactant-containing films resulting also in lower elastic modulus value (Table 4.9).

Dissolution parameters were not different from the polymer-plasticiser only film. The dissolution of formulations **M** and **O** was also studied in acidic conditions because their mechanical properties were promising with the desired flexibility; In acid, dissolution of film M was significantly faster (43.6 ± 5.83 % min^{-1}) with reduced a lag time (0.32 ± 0.25 min) compared to dissolution at pH 5.8. Thus, this film-base was selected for the coating studies (Chapter 5).

It was possible to produce films with 1 % Tween 40, Tween 85 or Brij 35 with 5 % DL-LA and 10 % gelatin, however this was not possible for Docusate Na. The film could not be removed from the plate intact: an indication that the plasticiser concentration was too high. It was therefore decided to use lower percentage of the plasticiser, reducing DL-LA content to 3 % (w/w). The addition of Docusate Na (formulation **P**) did not decrease the mechanical strength of the film nor did it increase the strain compared to 3 % (w/w) DL-LA alone with 10 % gelatin

(formulation **L**). The DL-LA-containing films are the only formulations where this effect of the Docusate Na was seen. The dissolution parameters were not any different from the other formulations in this series. It was not possible to measure swelling for these surfactant-containing DL-LA films as the films broke down immediately once immersed into the buffer. It is possible that the interaction between DL-LA and Docusate Na is weaker; Docusate sodium is incompatible with acids at low pH and this may have contributed to instability of the formulation (Malick., 2001)

4.3.4.5 Conclusion for surfactant containing films

Addition of surfactant to the gelatin film formulations with varying plasticisers resulted in an increase in the plasticising effect overall which was seen as decreased strength of the films (exception formulation **P**).

Film formulation **I** had a significantly higher dissolution rate (56.08 % min^{-1}) compared to all other gelatin/plasticiser/surfactant films with a greater tensile strain; this basic film formulation was therefore taken forward to the coating studies (Chapter 5). Also film formulation **M** had favourable dissolution properties (K_d > 30 % min^{-1}) and was easy to handle therefore was also selected for coating applications.

Solution of % (w/w) with 10% (w/w) gelatin film									Tensile properties			Puncture properties					
Formulation	Glycerol	PEG200	DL-LA	Tween40	Tween85	Brij35 30%	Docusate		σ_t (MPa)	ε_t (%)	EM_t (MPa)	σ_p (MPa)	ε_p (%)	EM_p (MPa)	K_d (% min^{-1})	t_{lag} (min)	K_s (% $min^{-0.5}$)
A	5	-	-	-	-	-	-		**9.98** ±1.01	**53.06** ±4.73	**1.19** ±0.55	**15.56** ±2.47	**68.4** ±7.09	**0.86** ±0.11	**24.89** ±5.98	**0.74** ±0.21	**195.76** ±6.64
B	5	-	-	1	-	-	-		**4.60** ±0.38	**93.55** ±17.18	**0.47** ±0.08	**5.20** ±0.91	**75.27** ±10.09	**0.42** ±0.13	**19.62** ±10.52	**1.89** ±2.68	+
C	5	-	-	-	1	-	-		**3.64** ±0.76	**28.92** ±13.67	**0.72** ±0.31	**4.10** ±0.99	**57.58** ±12.68	**0.53** ±0.14	**23.21** ±3.94	**1.34** ±0.54	**115.17** ±12.35
D	5	-	-	-	-	1	-		**6.27** ±0.25	**104.95** ±7.12	**0.58** ± 0.06	**6.11** ±0.28	**83.05** ±12.88	**0.39** ±0.05	**23.73** ±1.26	**1.01** ±0.49	**142.45** ±8.03
E	5	-	-	-	-	-	1		**3.43** ±0.44	**93.8** ±11.44	**0.31** ±0.05	**4.37** ±0.92	**77.96** ±6.07	**0.35** ±0.06	**14.37** ±4.19	**0.33** ±0.70	**93.65** ±4.32
F	-	5	-	-	-	-	-		**18.82** ±2.25	**67.70** ±4.23	**2.77** ±0.46	**18.35** ±2.23	**68.80** ±11.01	**1.08** ±0.22	**18.87** ±2.04	**1.47** ± 0.21	**118.60** ± 9.57
G	-	5	-	1	-	-	-		+	+	+	**8.994** ±0.59	**57.03** ±2.29	**0.60** ±0.16	**36.87** ±11.60	**0.60** ±0.48	**155.61** ±20.16
H	-	5	-	-	1	-	-		**16.83** ±3.20	**72.26** ±6.16	**3.03** ±0.65	**13.96** ±0.93	**49.06** ±6.35	**0.98** ±0.21	**27.81** ±7.93	**0.18** ±0.86	**132.05** ±11.61
I	-	5	-	-	-	1	-		**16.40** ±1.64	**106.41** ±8.36	**2.49** ±0.37	**13.45** ±2.42	**44.20** ±5.55	**0.75** ±0.19	**56.08** ±10.29	**0.85** ±0.22	**142.82** ±8.43
J	-	5	-	-	-	-	1		**14.83** ±2.51	**91.05** ±14.47	**2.17** ±0.24	**10.58** ±4.21	**58.78** ±4.22	**0.86** ±0.32	**20.24** ±1.62	**0.24** ±0.48	**118.02** ±13.27
K	-	-	5	-	-	-	-		+	+	+	+	+	+	**34.70** ± 7.34	**0.16** ± 0.94	+
L	-	-	3	-	-	-	-		**12.64** ±2.05	**32.20** ±12.80	**2.80** ±0.55	**12.95** ±0.56	**61.80** ±10.81	**0.69** ±0.12	**22.48** ±1.41	**0.91** ±0.13	+
M	-	-	5	1	-	-	-		**7.90** ±1.19	**66.79** ±11.47	**0.77** ±0.38	**13.14** ±2.06	**92.13** ±11.94	**0.57** ±0.15	**37.81** ±8.88	**0.68** ±0.30	+
N	-	-	5	-	1	-	-		**3.64** ±0.76	**28.92** ±13.67	**0.72** ±0.31	**4.10** ±0.99	**57.58** ±12.68	**0.53** ±0.14	**23.21** ±3.94	**1.34** ±0.54	**115.17** ±12.35
O	-	-	5	-	-	1	-		**6.27** ±0.25	**104.95** ±7.12	**0.58** ±0.06	**6.11** ±0.28	**83.05** ±12.88	**0.39** ±0.05	**23.73** ±1.26	**1.01** ±0.49	**142.45** ±8.03
P	-	-	3	-	-	-	1		**19.00** ±1.99	**21.10** ±7.50	**5.47** ±1.17	**27.30** ±6.74	**46.50** ±22.64	**1.84** ±0.20	**27.30** ±7.00	**0.57** ±1.14	+

Table 4.9- Results of mechanical, dissolution and swelling data for surfactant containing films (key: *σ_t tensile strength; ε_t tensile strain; EM_t tensile elastic modulus; σ_p puncture strength; ε_p puncture strain; EM_p puncture elastic modulus; K_d rate of dissolution in pH 5.8; t_{lag} lag time; K_s rate of swelling in pH 5.8; + not done; - does not contain; n≥3; mean ± S.D.)*

Formulation	Mean moisture content (%)
10% gelatin	13.29
A	3.92
B	6.23
C	6.46
D	4.07
E	5.89
F	11.17
G	10.64
H	11.27
I	11.52
J	10.63
K	5.53
L	8.38
M	6.22
N	6.04
O	5.10
P	8.70

Table 4.10- Results of thermogravimetric analysis of gelatin/plasticiser/surfactant pre-formed films (TGA)

4.3.5 Effect of disintegrants

4.3.5.1 Introduction

Generally disintegrants are included in tablet formulations to enhance the disintegrating properties of the core therefore leading to a faster dissolution due to increased surface area. Disintegrants work *via* a swelling mechanism; *e.g.* croscarmellose sodium can swell up to 8 times its size through capillary action hence leading to fast wetting and dissolution. The concentration of disintegrant in the tablet core formulation can be 0.5-15 % (w/w) depending on the type of disintegrant used and on the properties of the active ingredient.

4.3.5.2 Results and discussion

The effect of disintegrants on the dissolution of film formulations was investigated using 10 % gelatin (w/w) with 5 % glycerol (w/w) as the basic formulation solution for casting. The strength of the films was decreased for all disintegrant-containing formulations without significantly affecting the strain properties of the film (Table 4.11), except for the crospovidone-containing film where tensile and puncture strain were significantly decreased following its inclusion. Disintegrants may evenly distribute within the film but due to big size of the molecule, it interferes with the matrix structure leaving the film.

The dissolution properties were affected and swelling properties were also influenced (Table 4.12). Mean rate of dissolution in pH 5.8 was decreased as was the mean lag time for all disintegrant-containing formulations. This was an unexpected finding as it was initially believed that these disintegrants would allow swelling of the film matrix, but it may be the levels were too low to affect this change; higher levels of loading for disintegrants were difficult to obtain as uneven films resulted. Croscarmellose sodium has been reported to form coacervates with gelatin which could cause decrease in dissolution and also explain the lower swelling of the croscarmellose-containing formulation (Parsons, 2005).

Formulation (w/w)	Tensile properties			Puncture properties		
	σ_t (MPa)	ε_t (%)	EM_t (MPa)	σ_p (MPa)	ε_p (%)	EM_p (MPa)
Gelatin only	-	-	-	24.08±3.17	37.75±10.59	6.81±1.17
Gelatin + glycerol	9.98±1.01	53.06±4.73	1.19±0.55	15.56±2.47	68.40±7.09	0.86±0.11
+ 1 % Croscarmellose sodium	5.79±0.60	47.17±10.34	1.08±0.21	6.06±0.36	63.05±15.18	0.37±0.07
+ 1% Microcrystalline cellulose	4.46±0.56	48.83±10.76	0.92±0.23	5.07±0.40	61.65±11.89	1.30±1.46
+1 % Crospovidone	3.90±0.71	13.80±4.98	1.08±0.28	9.18±0.73	42.76±8.18	0.58±0.19
+ 1 % Sodium starch glycolate	5.96±1.80	41.52±20.56	1.15±0.16	7.92±0.96	57.92±10.72	0.42±0.06

Table 4.11- Mechanical properties of the disintegrant-containing films *(key: formulations prepared from solution of 10 % gelatin, 5 % glycerol compared to disintegrant containing formulation; σ_t tensile strength; ε_t tensile strain; EM_t tensile elastic modulus; σ_p puncture strength; ε_p puncture strain; EM_p puncture elastic modulus; n≥6; mean ± S.D.)*

Formulation	K_d (% min^{-1})	t_{lag} (min)	K_s (% $min^{-0.5}$)	Mean moisture content (%)
Gelatin only	20.66 ± 9.25	0.87 ± 0.20	-	13.29
Gelatin + glycerol	24.89 ± 5.98	0.74 ± 0.21	195.76 ± 6.64	3.92
+ 1 % Croscarmellose sodium	14.79±1.70	2.34±0.33	96.76±1.00	6.34
+ 1% Microcrystalline cellulose	15.68±1.73	1.94±0.32	96.62±5.35	5.95
+1 % Crospovidone	19.18±5.02	1.13±0.52	88.10±4.20	10.28
+ 1 % Sodium starch glycolate	14.79±3.86	2.17±0.66	97.89±5.88	8.75

Table 4.12- Dissolution and swelling properties of the disintegrant-containing films *(key: formulation prepared from solution of 10 % gelatin, 5 % glycerol compared to disintegrant containing formulation; K_d rate of dissolution in pH 5.8; t_{lag} lag time; K_s rate of swelling in pH 5.8; n≥3; mean ± S.D.)*

4.3.5.3 Conclusion for disintegrant containing films

Addition of traditional disintegrating agents and superdisintegrants into the film formulation did not result in enhancement of dissolution properties as expected. It could be that for disintegrants to be effective the levels should be much higher than 1 % which is not usually required for superdisintegrants. However, the strength of the films was decreased as was the flexibility, indicating that the disintegrants interfered with the structure of the film compared to plasticised gelatin films. The use of disintegrants in these film formulations did not result in any benefits therefore these excipients were not investigated further.

4.3.6 Effect of carbonates

4.3.6.1 Introduction

Some carbonates or bicarbonates have been known to have a disintegration-enhancing effect *e.g.* the use of sodium bicarbonate in effervescent tablets or in solid dosage forms *e.g.* Panadol® Actifast (Grattan, 2000). Typically the carbonate/bicarbonate reacts with water or acid to producing carbon dioxide and thus enhancing disintegration. Carbonates/bicarbonates are also used as antacids. Carbonates/bicarbonates have not been used in film formulations previously and the effect on mechanical, dissolution and swelling properties on gelatin/glycerol films was studied.

4.3.6.2 Results and discussion

Ideally it would have been beneficial to use the bicarbonates in the films due to the reaction with water or acids leading to fast disintegration. Potassium bicarbonate ($KHCO_3$) and sodium bicarbonate ($NaHCO_3$) were added at 1 and 5 % (w/w) in the gelatin/glycerol polymer solution but the films formed were uneven or did not peel off the support plate. Therefore either the bicarbonates did not dissolve (leading to solid deposits) or the bicarbonates reacted producing carbonates in the aqueous polymer solution although this generally happens at higher temperatures (Cable, 2001). Carbonates can have dissolution-enhancing properties so sodium carbonate (Na_2CO_3) and magnesium carbonate ($MgCO_3$) (1 % (w/w)) were added to polymer solutions with 10 % gelatin and 5 % glycerol (w/w). The Na_2CO_3 – containing film was very uneven whereas the $MgCO_3$-containing formulation produced an even, easy to handle film.

The tensile strength was significantly decreased following addition of $MgCO_3$ as was tensile strain compared to gelatin/glycerol films. Thus the film became weaker due to presence of

$MgCO_3$ but not tougher. The same trend is not followed for the puncture properties and the puncture strength is decreased significantly (ruptures easier) but the puncture strain is not different (Table 4.13).

The dissolution rate of $MgCO_3$-containing film was decreased and the lag time was significantly increased when compared to gelatin/glycerol or gelatin-only films. The film dissolution was also investigated in acidic conditions (0.05M HCl); the rate of dissolution was found to be 36.40 ± 4.97 % min^{-1} and the lag time 0.66 ± 0.06 min which were significantly different from dissolution at pH 5.8.

Formulation	Tensile properties			Puncture properties		
(w/w)	σ_t (MPa)	ε_t (%)	EM_t (MPa)	σ_p (MPa)	ε_p (%)	EM_p (MPa)
Gelatin only	-	-	-	24.08±3.17	37.75±10.59	6.81±1.17
Gelatin + glycerol	9.98±1.01	53.06±4.73	1.19±0.55	15.56±2.47	68.40±7.09	0.86±0.11
+ 1 % $MgCO_3$	2.98±0.54	37.71±7.23	0.57±0.17	6.18±0.60	73.55±8.36	0.38±0.03

Table 4.13- Mechanical properties of $MgCO_3$-containing film *(key: formulation prepared from solution of 10 % gelatin, 5 % glycerol compared to carbonate containing formulation; σ_t tensile strength; ε_t tensile strain; EM_t tensile elastic modulus; σ_p puncture strength; ε_p puncture strain; EM_p puncture elastic modulus; n≥6; mean ± S.D.)*

Formulation	K_d (% min^{-1})	t_{lag} (min)	K_s (% $min^{-0.5}$)	Mean % moisture
Gelatin only	20.66 ± 9.25	0.87 ± 0.20	-	13.29
Gelatin + glycerol	24.89 ± 5.98	0.74 ± 0.21	195.76 ± 6.64	3.92
+ 1 % $MgCO_3$	15.10±0.75	2.55±0.26	108.83±6.33	9.16

Table 4.14- Dissolution, swelling and thermal properties of carbonate-containing films *(key: formulation prepared from solution of 10 % gelatin, 5 % glycerol compared to carbonate containing formulation; K_d rate of dissolution in pH 5.8; t_{lag} lag time; K_s rate of swelling in pH 5.8; n≥3; mean ± S.D.)*

4.3.6.3 Conclusion for carbonate containing films

Inclusion of $MgCO_3$ in the formulation with gelatin and glycerol weakened the film significantly. The tensile strain was reduced compared to the gelatin/glycerol formulation but

the puncture strength was not significantly increased; it may be that this film is more resistant to rupture when something is driven through it rather than when it is stretched apart.

Due to the enhanced dissolution in acid and decreased dissolution in pH 5.8, the film base cast from solution containing 1 % $MgCO_3$, 5 % glycerol and 10 % gelatin was taken forward to the coating studies (Chapter 5).

4.3.7 Effect of citric acid

4.3.7.1 Introduction

The effect of DL-LA as plasticiser for gelatin was investigated (section 4.3.3.4) and it was concluded that DL-LA was a compatible plasticiser for gelatin resulting in films with faster dissolution. Due to success of DL-LA acting as plasticiser, it was proposed that other acids could induce the same effect. Citric acid was selected having three acidic groups (compared to DL-LA's one) which might allow further plasticising effects due to H-bonding. Bruce and his co-workers (2005) found plasticising effect of citric acid with Eudragit® S 100 polymer in hot-melt extruded 5-ASA-containing tablet formulations and it was discussed that high levels of citric acid with polymers for enteric / colonic applications can lead to decrease of micro-environmental pH. This can cause delayed release of drug in buffer medium due to ionic bond formation or hydrogen bonding formation due to acidity of the environment (Bruce *et al.*, 2005). Another study was carried out by Möller and his co-workers (2004) where citric acid had been used as a cross-linking agent for HPMC-containing films. The aim of this study was to evaluate the effect of citric acid on properties of gelatin-based films.

4.3.7.2 Results and discussion

Addition of citric acid (1 % w/w) to gelatin containing solution formed a film which was brittle and it was not possible to cut samples for testing. Citric acid inclusion in the gelatin glycerol (10/5) film increased the flexibility and stickiness of the film so much that tensile properties were difficult to measure. The puncture strength was significantly decreased indicating a weaker film but strain on the film was not different from gelatin only films (Table 4.15). Due to the stickiness of the highly plasticised 10/5/1 film, a 10/2.5/1 film was tested, where the reduction of the plasticiser content resulted in an increased tensile strength and tensile elastic modulus. Puncture properties show similar trends but the strain was not significantly decreased. Hence, addition of citric acid to the formulation may decrease the strength of the film but does not induce flexibility.

Solution formulation			Tensile properties			Puncture properties		
Gelatin	Glycerol	Citric acid	σ_t (MPa)	ε_t (%)	EM_t (MPa)	σ_p (MPa)	ε_p (%)	EM_p (MPa)
10	-	-	-	-	-	24.08±3.17	37.75±10.59	6.81±1.17
10	5	-	9.98±1.01	53.06±4.73	1.19±0.55	15.56±2.47	68.40±7.09	0.86±0.11
10	-	1	-	-	-	-	-	-
10	5	1	-	-	-	9.19±1.26	38.03±3.63	0.76±0.21
10	2.5	1	20.85±2.82	8.22±4.22	7.25±0.55	18.21±1.06	60.25±16.68	1.75±0.26

Table 4.15- Mechanical properties of the citric acid-containing films *(key: σ_t tensile strength; ε_t tensile strain; EM_t tensile elastic modulus; σ_p puncture strength; ε_p puncture strain; EM_p puncture elastic modulus; n≥6; mean ± S.D.)*

Citric acid has been used as a crosslinking agent in HPMC films where citric acid was proposed to react with free hydroxyl groups of HPMC (Coma *et al.*, 2003). There was no difference in dissolution rates between the citric acid-containing formulations and only the plasticised gelatin film had a significantly different lag time compared to the 10/2.5/1 formulation. The 10/2.5/1 dissolution rate was significantly slower compared to 10/5/1 film formulation and it may be that citric acid induces crosslinking effects when in combination with glycerol.

The rate of swelling was decreased following inclusion of citric acid; it is possible that crosslinking reduces the swelling as was found by Bigi *et al.* where gelatin was crosslinked with glutaraldehyde (2004).

Solution formulation			Dissolution properties			Thermal properties
Gelatin	Glycerol	Citric acid	K_d (% min^{-1})	t_{lag} (min)	K_s (% $min^{-0.5}$)	Mean % moisture
10	-	-	20.66 ± 9.25	0.87 ± 0.20	-	13.29
10	5	-	24.89 ± 5.98	0.74 ± 0.21	195.76 ± 6.64	3.92
10	-	1	31.18 ± 6.81	1.52 ± 0.35	-	10.91
10	5	1	16.75 ± 3.60	1.00 ± 0.07	137.64 ± 8.79	4.99
10	2.5	1	10.24 ± 2.32	2.06 ± 0.93	175.98 ± 3.43	5.52

Table 4.16- Dissolution, swelling and thermal properties of the citric acid-containing films *(key: K_d rate of dissolution in pH 5.8; t_{lag} lag time; K_s rate of swelling in pH 5.8; n≥3; mean ± S.D.)*

4.3.7.3 Conclusion for citric acid containing films

The aim of this study was to explore the effect of the citric acid in gelatin films and it was found that puncture strength was decreased indicating a plasticising effect of citric acid within gelatin films. Citric acid has also been used as a crosslinking agent and it is feasible that crosslinking occurred resulting in a decrease in dissolution rate for gelatin films containing both citric acid and glycerol.

Inclusion of citric acid may enhance the plasticising effects of the polymer film but there is a possibility that citric acid also enhances the crosslinking in gelatin which may be a disadvantage due to decreased dissolution rates resulting in a delayed onset of drug release.

4.3.8 Conclusion for gelatin film studies

Gelatin was chosen as a film-forming polymer due to its solubility at all physiological pHs and its ability to form films. Gelatin successfully formed films with the excipients studied and a variation in the film characteristics was seen for different formulations. Glycerol, PEGs and DL-LA were all compatible plasticisers with gelatin and also some of the surfactants studied enhanced the plasticising effect (except DL-LA with Docusate Na). Novel formulations **I** and **M** were selected to be taken forward to the coating studies due to their dissolution characteristics.

The addition of disintegrants did not promote dissolution as expected and $MgCO_3$ induced softness of the film with decreased dissolution and increased lag time. Because of its differential behaviour over a pH range, it was included as a tablet coating in the wrap-technology (Chapter 5).

Citric acid acted as a plasticiser and resulted in softer films. Weaker softer films may disintegrate faster because the energy needed for breaking apart is lower, but citric acid has been used as a cross-linking agent and it may be that this phenomenon is seen here with slower rate of dissolution.

Overall gelatin films produced even and successful films with varying characteristics depending on the excipients in the film formulation. Although gelatin has got excellent properties for film formulation and is still widely used in the pharmaceutical and food industry, there are concerns regarding its future use due to possible intra-species recycling and therefore contributing to the Bovine Spongiform Encephalopathy (BSE)- related safety measures (Hind, 2001).

4.4 Cellulosic films

4.4.1 Aims and objectives

Hydroxypropyl methylcellulose (HPMC) is widely used in pharmaceutical preparations due to its safety profile and low odour and taste. Due to the already wide use in pharmaceutical preparations as tablet binder, in film coating and as an excipient in extended release matrix formulations (Rowe *et al.*, 2001), HPMC was used to form films, plasticisers were added to the formulations and the mechanical and dissolution characteristics studied. The aim was to conclude if HPMC films would be suitable for the coating process (Chapter 5).

Also the film-forming characteristics and suitability for the coating process of other cellulose based polymers were studied (hydroxyl propylcellulose (HPC), hydroxyl ethylcellulose (HEC), sodium carboxymethylcellulose (Na CMC)) but the suitability for wrap-coating method is discussed further in Chapter 5.

4.4.2 Effect of plasticisers on HPMC films

4.4.2.1 Introduction

Typically conventional tablet coatings consist of HPMC with a plasticiser; HPMC is well studied and forms excellent non-tacky films for tablet coating which has contributed its popularity as a conventional film coating (Hogan, 1995). HPMC is available in various grades relating to its viscosity at particular conditions (viscosity of 2 % w/w aqueous solution at 20 °C) or the degree of substitution of methoxyl and hydroxypropoxyl groups in the side chain. Typically, low viscosity HPMC is water-soluble and is used as film former for tablet coatings whereas the higher viscosity grades retard dissolution and are therefore used as polymer matrix as for extended release formulations (Harwood, 2001).

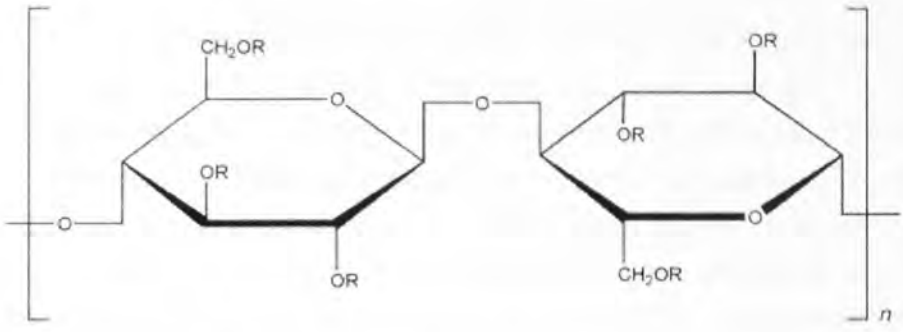


Figure 4.9- Molecular structure of HPMC where R is H, CH_3, or $CH_3CH(OH)CH_2$ (reproduced from Harwood 2005)

For coating applications, HPMC can be plasticised with a number of excipients such as PEGs, triacetin and glycerol (Johnson *et al.*, 1991; Béchard *et al.*, 1992; Sakellariou *et al.*, 1993; Heinamaki *et al.*, 1994; Ayranci *et al.*, 1997). Johnson *et al.* (1991) studied HPMC with PEG400 and triacetin where both induced a decrease in T_g and tensile modulus indicating a plasticising effect of the PEG400 and triacetin. Heinämäki *et al.* (1994) studied the effect of MW of PEG and its concentration on HPMC films, and noted that ≥ 20 % (w/w) plasticiser content resulted in softer and weaker films although % strain was not different from those with 10 % (w/w) plasticiser but still greater than HPMC alone. The % strain was at its maximum at 10-11 % which was still much lower than % strain values measured for gelatin films (section 4.3) indicating that HPMC forms much stiffer pre-formed films.

Alternative plasticisers (propylene glycol (PG), DL-lactic acid, PEG200, triacetin) were formulated together with a low MW HPMC and thermal and mechanical properties were measured along with dissolution. It was important to use a low grade polymer to avoid any

detrimental effects on dissolution. Swelling studies were also carried out but none of the HPMC-films investigated here were robust enough for the procedure.

4.4.2.2 Results and discussion

Initially films were cast with varying concentrations of HPMC (5-10 % w/w) in the polymer solution and two grades were used (3 cps and 5 cps) to study their effect on film properties. 5 % HPMC formulations resulted in migration on the plate due to the low viscosity of the polymer solution therefore the concentration was increased; Formulation **1** (Table 4.17) containing HPMC (3 cps) produced a workable films and therefore this was used as a base for the further film formulations.

Addition of propylene glycol (PG) in the cast solution resulted in significantly decreased the tensile strength and the elastic modulus of the plasticised films compared to HPMC alone pre-formed films (Table 4.17). The % strain was increased significantly for formulations **2** and **3** containing 2.5 % and 5 % PG respectively when compared to formulation **1**. The addition of 7.5 % PG led to significant changes in the puncture strength, % strain and elastic modulus for puncture compared to formulation **1**; the strength of the film decreased with increased strain which indicates that PG is a suitable plasticiser for HPMC. The puncture strain was increased ($p<0.05$) and elastic modulus was decreased ($p<0.05$) for formulation **4** compared to formulation **2** where the plasticiser content was increased from 2.5 % to 7.5% (w/w), supporting the evidence that HPMC is plasticised with PG. Although the plasticising effect is evident, the % strain for puncture and tensile properties were not increased greatly, possibly not enough for the use in the coating procedure where a degree of elasticity of the film prior heating is desired (section 1.6.1).

There were no significant differences between the rate of dissolution and lag times for formulations **1-4** although the general trend is that these HPMC films may have faster dissolution than plasticised gelatin films (Table 4.5). A direct comparison is not possible however because same plasticisers were not used and therefore there are more than one factor possibly affecting the dissolution as neither polymer nor plasticiser is the same.

DSC studies on the formulations **1-4** did not show conclusively the plasticizing effect of PG with HPMC; thermal transition for HPMC-only film was at 44.47 and 124.4 °C, still lower than for unformulated HPMC (180 °C) (Sakellariou *et al.*, 1985). The T_g for plasticised HPMC films were 44.0 °C, 59.7 °C and 48.0 °C for formulations **2**, **3** and **4** respectively (Table 4.16, Figure 4.6). TGA measurement of the water content was found to be 5.4 % and this made

identification of T_g using DSC difficult as the moisture peak can be very wide between 60 – 140 °C (Ford, 1999). This can be overcome by performing a scan where the sample is first heated over the temperature where transitions are visible but not to a degradation point, cooled and then re-heated. Due to relatively small transitions in polymers, it was suggested that use of greater sample mass would reduce the signal-to-noise ratio hence detection of the transition would be easier (Ford, 1999). An alternative way of overcome this problem is to use high speed-DSC (Hyper-DSC™) with fast scanning rates where the transitions happen much faster leading increased sensitivity hence easier to recognise but with no change in the T_g process (Perkin Elmer DSC-training, 2005). Similar methods were used for studies on polyvinylpyrrolidone (PVP) (Buckton *et al.*, 2006).

There is little known about the role of DL-LA as a plasticiser so its use with HPMC was also explored. It was noted that 7.5 % (w/w) of DL-LA was too high a concentration and the film formed was robust but after standardising at 52 % RH the film was too sticky and stretchy to handle. The DL-LA concentration was reduced to 5 % (w/w) which produced robust easy-to-handle films. Formulation **5** (DL-LA) had significantly different tensile properties from formulations **1** and **3**; the plasticising effect was more pronounced than PG-plasticised films (formulation **3**) with decreased strength and elastic modulus and increased % strain. The trends in the puncture properties differed from those of the tensile properties: the puncture strength for the DL-LA-containing film (formulation **5**) was significantly higher than in formulations **1** and **3** as was the % strain, indicating that addition of DL-LA produced tougher films with more resistance to rupture and higher limit to elongation. This combination of tensile and puncture properties may be beneficial in the coating process as the film would be suitably plasticised with high level of elasticity without brittleness, yet remaining robust enough withstand pulling around tablet under vacuum. The lag time for formulation **5** was decreased (*vs.* formulation **1**), $p<0.05$, whereas there was no difference in the rate of dissolution.

Triacetin has been reported to plasticise HPMC (Johnson *et al.*, 1991) and its suitability as plasticiser was investigated by measuring thermal and mechanical properties of the films. Initial screening studies indicted that 1 % (w/w) was a suitable concentration for the formulation **6** due to higher concentrations leading to film migration on the cast support. The mechanical properties of formulation **6** were not significantly different from the HPMC-only formulation (**1**), only the elastic modulus for tensile test was significantly lower which indicates an increased ductility of the film and therefore the triacetin in combination with HPMC can act as a plasticizer (table 4.17). The lack of change in properties, other than EM_t, may be due to low concentration of the plasticiser used. Also there was no significant

difference between the dissolution properties of formulations **1** and **6**. Even though the plasticising effect of triacetin is evident and has been shown also in the literature (Johnson *et al.*, 1991), the flexibility of the films was not affected. This may prove problematic if these films were used in the coating application.

PEGs have been cited as effective plasticisers in literature (Johnson *et al.*, 1991; Sakellariou *et al.*, 1993; Heinamaki *et al.*, 1994) and the aim of the studies was to define the effect of PEG200 and PEG1450 on the mechanical and thermal properties with the knowledge that PEGs should form compatible films with HPMC. A concentration of 2.5 % (w/w) was used for both PEGs and the films formed were even and easy-to-handle. After conditioning at 52 % RH the PEG1450-containing film had turned white and waxy. It is possible that although a successful film was produced initially, after drying the intermolecular network did not form due to fairly big size of PEG1450 molecule: formulation was unstable therefore discarded. The PEG200-containing film (formulation **7**) had a decreased tensile strength, elastic modulus and increased % strain. The puncture properties supported this conclusion. Again the plasticising effect is prominent but the strain properties may not be suitable for the coating application. The difference in elasticity between gelatin and HPMC is evident (Tables 4.9 and 4.17).

Potassium sorbate is normally employed as an antimicrobial preservative and has not been used previously as a plasticiser. Plasticisers can be defined as molecules which can move in between the polymer chains and therefore lower the tensile strength and T_g therefore the effect of potassium sorbate was studied here (Figure 4.17). The addition of potassium sorbate (5 % w/w) affected the mechanical properties significantly (exception % puncture strain); strength and elastic modulus significantly reduced as % tensile strain increased (formulation **8** *vs.* **1**). This suggests that potassium sorbate may have a plasticising effect on the HPMC film. Also the dissolution properties are significantly faster than films containing HPMC alone. Overall, the inclusion of potassium sorbate lowered the tensile strength and elasticity. A limitation with formulation **8** was the colour change from clear to white upon conditioning and its relatively low elasticity, restricting its suitability for coating purposes.

Figure 4.10- Molecular structure of potassium sorbate (MW150.22 g mol^{-1}, reproduced from Owen 2005)

% (w/w) with 10% (w/w) HPMC in solution						Tensile properties			Puncture properties			Dissolution properties		Thermal properties	
Formulation	PG	DL-LA	Triacetin	PEG200	Potassium sorbate	σ_t (MPa)	ε_t (%)	EM_t (MPa)	σ_p (MPa)	ε_p (%)	EM_p (MPa)	K_d (min^{-1})	t_{lag} (min)	T (°C)	Mean moisture loss (%)
1	-	-	-	-	-	**40.30** ±2.58	**3.20** ±0.40	**18.40** ±0.73	**4.83** ±2.03	**10.90** ±6.16	**3.68** ±1.20	**29.24** ±10.98	**0.81** ±0.04	**44.47** and 124.36	**5.35**
2	2.5	-	-	-	-	**28.70** ±2.48	**4.02** ±0.38	**9.78** ±1.29	**4.09** ±0.55	**10.40** ±1.01	**2.77** ±0.14	**34.90** ±7.33	**0.55** ±0.31	**43.95**	**4.08**
3	5	-	-	-	-	**28.30** ±1.90	**4.02** ±0.46	**10.70** ±1.73	**2.99** ±0.78	**13.70** ±1.61	**2.35** ±1.21	**35.69** ±5.64	**0.23** ±0.12	**59.69**	**3.85**
4	7.5	-	-	-	-	**18.40** ±8.60	**3.34** ±0.49	**4.56** ± 2.13	**1.88** ±0.40	**20.8** ±4.17	**0.21** ±0.15	**43.67** ±13.50	**0.58** ±0.31	**48.03**	**2.90**
5	-	5	-	-	-	**16.90** ±1.15	**4.97** ±0.24	**7.53** ±0.73	**8.66** ±0.83	**30.90** ±9.86	**1.99** ±0.31	**33.09** ±2.70	**0.05** ±0.10	**48.39** ±8.64	**5.69**
6	-	-	1	-	-	**37.10** ±6.18	**3.32** ±0.17	**14.80** ±1.03	**6.46** ±2.03	**19.8** ±5.51	**2.94** ±0.46	**24.58** ±13.39	**0.70** ±0.13	**60.25** ± 5.46	**2.12**
7	-	-	-	2.5	-	**9.50** ±0.53	**5.06** ±0.22	**4.02** ±0.22	**1.35** ±0.15	**6.89** ±3.11	**0.80** ±0.16	+	+	**22.24** ± 0.42	**4.27**
8	-	-	-	-	5	**6.25** ±0.84	**5.90** ±0.66	**3.38** ±0.55	**0.98** ±0.05	**10.2** ±3.57	**0.68** ±0.21	**48.18** ±1.54	**-0.07** ±0.07	**45.10**	**3.76**

Table 4.17- Mechanical and dissolution properties of HPMC films *(key for mechanical data: σ_t tensile strength; ε_t tensile strain; EM_t tensile elastic modulus; σ_p puncture strength; ε_p puncture strain; EM_p puncture elastic modulus; n≥6; mean ± S.D. ; key for dissolution data: K_d rate of dissolution in pH 5.8; t_{lag} lag time; T onset of transition temperature; + not done; n=3; mean ± S.D.)*

4.4.2.3 Conclusion for plasticisers

All chosen plasticisers did have an effect on HPMC films. The rate of dissolution for films studied was not affected. Plasticising properties were evident in the measured mechanical and thermal properties, the elasticity/flexibility of the films could not be increased (all results < 6 % tensile strain) thus it is possible that these HPMC-based films are not suitable as film coatings for wrap-method (Chapter 5) even if the flexibility is induced further when the film is heated.

Addition of surfactants to plasticised gelatin films resulted in enhanced plasticising effects in some cases with a lower strength but a higher strain. Brij 35 (30%) and Tween 40 were incorporated into formulations **1** and **3** to determine whether the effect was similar with HPMC films but it was not possible to cast acceptable films.

4.4.3 Depolymerisation of HPMC

4.4.3.1 Introduction

Due to lack of flexibility and elasticity in the HPMC films, it was proposed that the rigid structure of HPMC and lack of H-bonding sites for the plasticiser could contribute to the lack of flexibility in the HPMC films. Polymer degradation studies have been reported (Donescu *et al.*, 1980; Reddy *et al.*, 2004); Donescu *et al.* (1980) studied the degradation of hydroxyethylcellulose (HEC) where the oxidative reaction was monitored by viscometry and carried out in the presence of potassium persulphate in an aqueous medium at 70 °C. Reddy *et al.* (2004) degraded guar gum in presence of potassium persulphate by thermal degradation or microwaving the mixture; the degradation of guar gum resulted in tougher films with more elastic behaviour. This may be due to smaller polymer fractions therefore larger number of polymer molecules available for intramolecular interactions leading films to be less brittle.

The aim of the study was to degrade HPMC 3cp raw material by microwave degradation and investigate what effects this had on the mechanical properties of the films.

4.4.3.2 Method for degradation

The method was based on the work by Reddy *et al.* (2004). Potassium persulphate (0.3 g) was dissolved in double distilled water (60 ml) and this was mixed in with HPMC 3 cp (30 g) using a pestle and mortar to ensure an even mix. The mixture was heated for for 10 mins in a microwave oven at 120 Watts resulting in a white fluffy material. This was washed with

double distilled water (60 ml) and freeze-dried for 96 h in a Virtis Advantage freeze-dryer combined with Alcatel Pascal 2005SD vacuum pump. The resulting polymer was stored in a desiccator until use (Reddy *et al.*, 2004).

Degradation was confirmed by microviscometry and IR analysis. Aqueous solutions (1 % w/w) of HPMC 3 cp and depolymerised HPMC were prepared and analysed by microviscometry. The depolymerised HPMC solution had a viscosity of 1.5876 mPa.s whereas HPMC 3cp had higher viscosity of 1.7019 mPa.s which indicated that some depolymerisation had taken place. Successful depolymerisation reaction results in smaller polymer chains of the original polymer molecule therefore the molecular weight of the original polymer molecule is decreased which then directly affects the viscosity of the polymer solution having less sheer friction.

IR spectroscopy was carried out on an IR200 Spectrometer over the range of 3600-400 cm^{-1} to ensure that the degradation had happened and the results were displayed on OMNIC 7.0 software (both from Thermo Electron Corporation). A small amount of sample was kneaded with Nujol and the mixture was placed between sodium chloride (NaCl) discs. All IR traces showed stretching at 3436-3400 cm^{-1}, 1637-1635 cm^{-1} and 1072-1070 cm^{-1} corresponding O-H, C=O and C-O-C bonding respectively (Zaccaron *et al.*, 2005) and the traces were superimposable indicating that no major functional group transformations occurred during the degradation process *i.e.* chains were cut in the linkage part and not at the rings of HPMC.

4.4.3.3 Results and discussion

Film cast from 10 % (w/w) depolymerised HPMC solution (**9**) showed a significant decrease in tensile strength and elastic modulus for tensile test but the % tensile strain and puncture properties were not affected by the depolymerisation conditions (Table 4.18).

The addition of PEG200 decreased tensile strength and increased % strain in previous studies therefore it was selected to be included as an excipient with the depolymerised HPMC film. All tensile properties were significantly affected by the addition of PEG200 (**10**) which effectively plasticised depolymerised HPMC. There were no differences in puncture strain between formulations **9** and **10** but strength and elastic modulus for puncture indicated a softening of the plasticised depolymerised HPMC film. The elastic modulus for tensile and puncture testing of formulation **7** was significantly different from formulation **10**; it may be that the depolymerised and plasticised film is weaker.

There were no differences in the DSC and TGA results between these formulations.

% (w/w) in solution				Tensile properties			Puncture properties			Thermal properties	
Formulation	HPMC 3cp	Depol HPMC	PEG200	σ_t (MPa)	ε_t (%)	EM_t (MPa)	σ_p (MPa)	ε_p (%)	EM_p (MPa)	T_g (°C)	moisture loss (%)
1	**10**	-	-	**40.30** ±2.58	**3.20** ±0.40	**18.40** ±0.73	**4.83** ±2.03	**10.90** ±6.16	**3.68** ±1.20	**44.47** and 124.36	**5.35**
7	**10**	-	**2.5**	**9.50** ±0.53	**5.06** ±0.22	**4.02** ±0.22	**1.35** ±0.15	**6.89** ±3.11	**0.80** ±0.16	**22.24** ± 0.42	**4.27** ±0.08
9	-	**10**	-	**34.8** ±2.28	**2.86** ±0.13	**12.5** ±1.08	**2.91** ±0.43	**6.14** ±2.94	**4.07** ±0.50	**22.27** ± 0.78	**4.44** ±0.40
10	-	**10**	**2.5**	**7.99** ±1.07	**4.97** ±0.48	**2.34** ±0.75	**0.60** ±0.08	**8.25** ±2.23	**0.61** ±0.03	**22.17** ± 0.24	**4.33** ±0.08

Table 4.18 Mechanical properties of the HPMC 3 cp and depolymerised HPMC films *(key for mechanical data: σ_t tensile strength; ε_t tensile strain; EM_t tensile elastic modulus; σ_p puncture strength; ε_p puncture strain; EM_p puncture elastic modulus; T_g onset of transition;; n≥6; mean ± S.D.)*

4.4.3.4 Conclusion for depolymerisation

The depolymerisation of HPMC 3 cp did affect the mechanical properties of the films but not as predicted. The % strain values were still very low, indicating their unsuitability for the coating application.

4.4.4 Alternative polymers

4.4.4.1 Introduction

As a consequence of the low flexibility of HPMC films, the suitability of alternative polymers in the coating process was examined. Polymers for inclusion must be readily soluble in water and will dissolve rapidly at physiological pHs without extending lag times.

4.4.4.2 Results and discussion

Klucel® LF is a low viscosity grade of hydroxypropylcellulose (HPC) with a viscosity of 75-150 mPa.s (5% w/v). The low viscosity grades should produce flexible and adherent films with good barrier properties possibly without using a plasticiser (Hercules Inc., 2005). Although the excellent film forming properties of Klucel® LF without plasticising have been suggested, it was found here that the plasticiser was required for successful film formation. A 5 % (w/v) Klucel® LF solution was formulated with 2.5 % (w/w) plasticiser, propylene glycol (PG), producing stretchy but weak films which were too fragile for handling.

Alternative semi-synthetic polymer for HPMC is Natrosol® L PH which is hydroxyethylcellulose (HEC) with a typical viscosity of 75-150 mPa.s (5 % solution) and

molecular weight of approximately 90,000. This low viscosity grade is marketed for tablet coating as it provides improved flexibility compared to HPC, CMC and HPMC formulations (Hercules Inc., 2005). Natrosol® L PH film (5 % w/v) produced a film which was easy to peel but suitability for the coating process was not clear. The solution of 5 % (w/w) Natrosol® L PH was also formulated with DL-LA (3.75 % w/w) which was taken forward to wrap-coating studies (section 5.2.4).

Although a direct comparison of Klucel® and Natrosol® films to HPMC was not possible due to different percentages of polymer used in the formulation, it still is obvious from the results that Klucel® and Natrosol® produce weaker and more flexible films compared to HPMC which was expected. Formulation with DL-LA and Natrosol® showed the plasticising effect of DL-LA as the tensile strength significantly decreased and tensile strain increased (Table 4.19). The rate of dissolution for Klucel® and Natrosol® films was slow compared to HPMC films, but the addition of DL-LA to Natrosol® increased the rate significantly which may be due to weaker tensile properties of the plasticised film. Natrosol®-containing films have significantly longer lag times than HPMC films.

Solution Formulation	Tensile properties			Dissolution properties	
	σ_t (MPa)	ε_t (%)	EM_t (MPa)	K_d (% min^{-1})	t_{lag} (min)
10 % HPMC	40.30±2.58	3.20±0.40	18.40±0.73	29.24±10.98	0.81±0.04
5 % Klucel®	12.32±1.45	7.54±3.73	5.22±0.69	7.50±1.71	1.71±3.85
5 % Natrosol®	15.16±1.89	12.27±1.21	4.09±1.08	17.21±1.20	2.60±0.11
+ 3.75 % DL-LA	2.38±0.11	185.77±24.74	0.008±0.0003	33.56±2.62	2.67±0.10

Table 4.19 Mechanical and dissolution properties of the Klucel® and Natrosol® films *(key for mechanical data: σ_t tensile strength; ε_t tensile strain; EM_t tensile elastic modulus; n≥4; mean ± S.D. ; key for dissolution data: K_d rate of dissolution in pH 5.8; t_{lag} lag time; n=3; mean ± S.D.)*

4.4.4.3 Conclusion for alternative polymers

The film forming properties of alternative polymers and their suitability for the wrap-coating technology was assessed. Generally these polymers (HPC, HEC) produced much more elastic films than HPMC but the disadvantage of these formulations was that due to their stretchiness, they were also difficult to handle and often too weak.

It was found that Klucel® and Natrosol® (both 5 %) films were much less robust than HPMC but more flexible. Due to the lower polymer content, it was expected that these 5 % polymer films would possess superior dissolution characteristics, but this was not the case. It may be that Klucel® and Natrosol® are more resistant to water vapour and oxygen transmission than HPMC, that this affects the film dissolution. DL-LA successfully plasticised Natrosol® films and increased rate of dissolution compared to unplasticised film. This film was used as the only cellulose formulation possibly suitable for the wrap-coating technology.

4.4.5 Conclusion for cellulose studies

Cellulose-based polymers are used widely in pharmaceutical products, for example in the tablet core formulation or as a coating material. Typically a coating formulation consists of polymer and plasticiser which reduces the brittleness of the coating once dried.

It was found that many excipients promoted the plasticisation of HPMC-based films resulting in weaker films but typically the strain (flexibility) of the film was not greatly affected. This flexibility was required for the wrap-coating technology, thus, the HPMC-films were deemed not suitable for the application.

Alternative polymer, Natrosol®, was formulated with various levels of plasticiser and although these films possessed greater flexibility, they were not suitable for the wrap-coating application as they were not robust. Only the plasticised Natrosol® film was suitable for the coating studies and its use in the coating process will be discussed in Chapter 5.

Although all these polymers are widely used as coatings in the pharmaceutical industry, a wrap coating technology has different requirements (Chapter 5).

4.5 Conclusion

Prior studying the novel wrap-coating method it was recognised that the polymer films should be characterised and studied in order to find a formulation which can be coated and which as a coating does not significantly affect dissolution of the tablet core.

Initially gelatin films with different bloom strength were studied for their mechanical and dissolution characteristics in order to evaluate which bloom strength and gelatin concentration (in cast solution) would be most suitable for the further studies. The results did not show differences between the gelatin type and bloom strength therefore gelatin type B75 was chosen for the further studies as literature states that higher bloom strength is prone to

cross-linking and longer disintegration times (Rama Rao *et al.*, 2002; Ciper *et al.*, 2005) which are both undesirable characteristics for films which are required to dissolve fast. The gelatin film made of 15 % cast solution showed signs of brittleness as the tensile strength of the film was lower (17 MPa) compared to 10 % film (24 MPa) and also gelatin films cast from solutions containing over 15 % gelatin supported this phenomena as the films were not producing films which could be analysed. As gelatin is compatible with glycerol as plasticiser (Arvanitoyannis *et al.*, 1997; Arvanitoyannis *et al.*, 1998b; Vanin *et al.*, 2005; Lukasik *et al.*, 2006a; Lukasik *et al.*, 2006b), they were studied together as part of the pre-formed film work and it was found that the film cast from 5/10 % glycerol/gelation solution resulted in flexible and soft films. The puncture and tensile elastic modulus values were low (under 1.2 MPa) which typically indicate the film not to be stiff or rigid.

Gelatin was studied with plasticisers (glycerol, polyethylene glycols and DL-lactic acid) and all were found to be suitable plasticisers for gelatin as films were easy to handle and their mechanical strength was decreased when compared to gelatin only film which typically is an indication that plasticising effect has taken place. These formulations were also studied with surfactants (Tween40, Tween85, Brij35 30 % and Docusate sodium) which all resulted in further reduced strength values indicating further plasticising of gelatin. Films chosen for the further studies (I and M) had fast dissolution properties (over 30 % min^{-1}) which is required for the fast dissolving film coating, and puncture elastic modulus values < 1 MPa and tensile elastic modulus values < 2.5 MPa (Table 4.9). Also citric acid was proposed to be a good plasticiser for gelatin due to its molecular structure and ability to form H-bonds. The results showed that the inclusion of citric acid with gelatin only produced brittle films which could not be handled although 10 % gelatin film was easy to handle and analyse therefore no plasticising effect was seen when citric acid was formulated with gelatin. When gelatin was formulated with glycerol and citric acid, the puncture strength of the film was decreased from 16 MPa (gelatin/glycerol) to 9 MPa (gelatin/glycerol/citric acid) but puncture strain was not increased as decrease in strength and increase in strain is expected if further plasticising effect has taken place. The dissolution of the citric acid containing films was decreased which may indicate the cross-linking of citric acid with gelatin.

To get faster dissolving films, typical tablet core disintegrants and carbonates were formulated into the films with expectation that the films would be even faster dissolving than plasticiser/surfactants containing films. All disintegrant containing films had rate of dissolution under 20 % min^{-1} therefore the mechanism for the disintegration in the excipients may have been lost during the preparation of the film (*i.e.* making the cast solution) or the amount of the disintegrant in the formulation was not sufficiently high. Only magnesium carbonate

containing formulation produced acceptable film and the dissolution rate in acid was high (36 % min^{-1}) therefore it was chosen forward to the coating studies.

As alternative polymer for gelatin, cellulose-based polymers were studied as pre-formed films. Typically HPMC films had very low tensile strain properties (< 6 %) and generally high rates of dissolution where rate of dissolution is expected as HPMC is used as conventional film coating for tablets which require fast dissolution. Low tensile strain results indicate that these HPMC-films would not be suitable for the wrap-coating method as high elasticity is advantage in the utilisation of the wrap-coating method. Formulation containing HEC and DL-lactic acid was found to be flexible (tensile strain 186 %) and fast dissolving (rate of dissolution 34 % min^{-1}). This HEC/DL-lactic acid film was taken forward to the coating studies but it may be that the formulation could be too weak with only tensile strength of 2 MPa.

Overall gelatin films were easier to work with and produced many formulations with large variety of properties where few were chosen forward to the wrap-coating studies. Although HEC-DL-lactic acid proved to be promising as tablet coating according to pre-formed film characteristics, it can be concluded that cellulose-based films are not as workable in this application as gelatin-based films.

Chapter 5-

Novel coated solid-dosage forms

5.1 Introduction

Pharmaceutical science and formulation is continually evolving and therefore there is an impetus to develop new techniques to improve current processes to make them more efficient or exploring new processes to extend knowledge. The majority of the solid dosage forms are coated either by film-coating or sugar-coating (Chapter 1) which are carried out in conventional manners *i.e.* utilising pan coating or fluid bed technology. This element of pharmaceutical technology may have room for improvement where the coating process could be more effective with faster and efficient processes. An alternative coating process, wrap-coating technology, is explored in this chapter.

Polymer coatings (other than conventional HPMC-coatings) were shown to affect the release of the paracetamol in acidic conditions and also the dissolution of ibuprofen was thought to be affected by the applied coating as well as the core formulation (Chapter 3). Chapter 4 described a variety of the film formulations and their characteristics which were then evaluated in terms of their suitability for the wrap-coating process. It was previously identified for the wrap-coating trials that the film should be fast dissolving so that the coating would not inhibit the dissolution of the active ingredient. Also it was identified that flexibility of the film is essential together with a degree of strength in order to allow the film to wrap around the tablet core without breaking. Therefore the elastic modulus value should be sufficiently low to facilitate stretchiness of the film, *e.g.* approximately under 0.2 MPa can be strong enough with suitable flexibility as elastic modulus describes the stiffness and rigidity of the film.
The aim of this chapter was to utilise film formulations (identified in Chapter 4) in the wrap-coating technology and probe the effect of the coating on the dissolution of active ingredient.

5.2 Wrap-coating process development

There is little information available in the scientific literature regarding the process of wrap-coating and there was no commercially available machinery for the coating process. One aim of the project, therefore, was to design equipment suitable for the purpose.

5.2.1 Coating equipment

The tablet coating machine was built at Si-Plan Electronics Research Ltd, Stratford-upon-Avon, U.K. The equipment consists of a temperature controller (1), vacuum-forming station with infra-red heating (or heated plate) located above the tablet base and film (2), temperature probe, vacuum control (3) and cutting station (4) (Figure 5.1). It was designed to house 36 capsule-shaped tablets of 17.5 x 7.30 mm. In addition to the equipment itself, electrical supply (230VAC 50Hz) and clean, dry, oil-free, filtered, 4-8 bar compressed air

were required. A Factair (KY-16-TF-18)-compressor was used with 6 bar pressure which was high enough for controlling the film during the coating process (section 5.2.2)

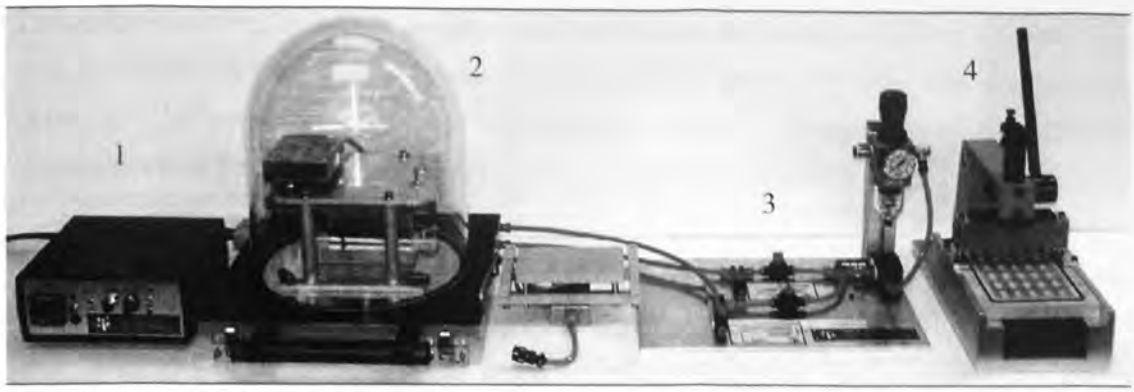


Figure 5.1- Picture of the coating machine *(temperature controller (1), vacuum-forming station (2), vacuum control (3) and cutting station (4).*

5.2.2 Coating process

The tablets were positioned on a base unit with a bed for each unit to hold it in position. The base unit containing tablets was placed inside the vacuum-forming station and the film was positioned on the frame on top of the tablet bed so that the film did not touch the tablets. The vacuum-forming station was sealed by placing a glass bell-jar over the vacuum-forming station and the infra-red heating plate was turned on. The temperature close to the films was increased at a steady rate and once the temperature started to rise and the film visually started to flex, the vacuum was applied. The vacuum then pulled the film around the tablets coating the exposed surface. The base unit containing coated tablets was transferred to the cutting station where the film was cut so that it covered half of the tablets. The same procedure was repeated on the other side of the capsule-shaped tablet.

5.2.3 Formulations

The methods used for manufacture and characterisation of the films are described in the section 4.2. In Chapter 4, the pre-formed films were discussed and a number of potential film formulations for the coating process were identified according to their dissolution and mechanical behaviour. Gelatin-containing formulations were modified to be more suitable for the coating process *i.e.* the film used for the coating needs to be flexible (at RT or at elevated temperatures) so that it can be pulled around the tablets without breaking but it should be also strong so that it can be handled prior the coating process. Differences between pre-formed films and formulations suitable for the coating procedure were that the films prepared for the coating became sticky on conditioning so that they were impossible to analyse, therefore no conditioning was carried out in these studies. Due to this difference in the

procedure, it is not possible to directly compare the results of pre-formed films *vs.* final coating formulations.

Cellulose-containing films were prepared and handled as described in section 4.2. Polymeric glue was required for cellulose-based film formulations where the glue was sprayed with spray gun on the tablet core prior to coating in order to promote sticking of the film formulation onto the tablet core.

The formulations used for the coating process are described in Tables 5.1 and 5.2. There was a possibility that tablet cores would be exposed to high temperatures because the heating element of the coating equipment is located just above the film and therefore the cores have to be resilient to the temperatures needed for the coating process.

5.2.4 Results and discussion (pre-formed films only)

In general, according to the results and observations described in Chapter 4, it was assumed that the gelatin-based films would be amenable to the wrap-coating process due to the ease of handling of the films and their mechanical and thermal properties. The gelatin-based pre-formed film, formulation **M** (Chapter 4), was identified as a promising film for the wrap-coating process due to its fast dissolution at pH 5.8 and its relatively high tensile and puncture strain suggesting it was tough enough to be used in the coating process. Although formulation **M** was promising, it still had to be modified in order to render it suitable for the wrap-coating process *i.e.* the film needed to be stretchier for the coating process: different ratios of DL-LA and glycerol were formulated and formulation **G1** was found to suitable (Table 5.1). Adding glycerol and lowering the proportion of DL-LA in the formulation (**G1**) led to lowered tensile strength and increased tensile strain ($p<0.001$). Also, although the puncture strength decreased ($p<0.001$), the puncture strain was not affected ($p=0.34$). Elastic modulus was ≤ 0.2 MPa for the films which were successfully implemented in the coating process (Table 5.1). The dissolution rate and lag time in pH 5.8 were not different for formulations **G1** and **M** ($p>0.4$).

Formulation **G2** was also modified in order to produce a film which could be used in the wrap-coating technology: more glycerol was added in addition to a small quantity (0.01% w/w) of Brij 35 (30%). The increase in plasticiser content and addition of surfactant led to significantly increased tensile strain and decreased puncture strength ($p<0.001$). Also the elastic modulus was reduced which may indicate suitability for the wrap-coating *i.e.* it needs to be elastic which is indicated by low elastic modulus values. Unfortunately the decreased

dissolution rate of the $MgCO_3$–containing film at pH 5.8 was lost with the modification of the pre-formed-film (Table 5.1 and section 4.3.6).

In accordance to studies in Chapter 4, Tween 40 was proposed to be responsible for enhancing dissolution of formulation **G1**, and $MgCO_3$ for decreasing the dissolution in formulation **G2** therefore both formulations were prepared without these excipients. These altered formulations **G1a** and **G2a** were also studied as potential coating formulations. As pre-formed films these formulations (**G1a** and **G2a**) had similar properties to **G1** and **G2** (Table 5.1).

Film **I** had a relatively fast dissolution (K_0=56.1 % min^{-1}, Table 5.2) but was not successful in the wrap-coating process, even after heating to 85 °C. The film became stiff and cloudy upon heating indicating instability of the film at high temperatures and this was not reversible upon cooling. Glycerol is compatible with gelatin and has been shown to produce flexible films (section 4.3.3.2) therefore glycerol was added to the formulation. Adjustment of the formulation to facilitate coating resulted in the removal of the Brij 35 (30%) surfactant, as desired properties for the film were obtained by varying the ratio of polymer to plasticiser content and further on addition of DL-LA as an additional plasticiser to the formulation. Finally the **G3** formulation was obtained which dissolved quickly and had a significantly reduced tensile elastic modulus compared to **G1** and **G2** ($p<0.001$), and also increased strain, considered to be desirable characteristics for the coating procedure.

As an alternative to gelatin-based films, cellulosic films were studied (Chapter 4). Further on to studies in Chapter 4, a 5 % (w/v) Klucel® LF film was plasticised with 2.5 % (w/w) propylene glycol (PG) producing stretchy but weak films. This film formulation was promising due to elasticity of the film but was not wrapping around tablet when utilised in the coating process thus higher PG content was examined as well as various other plasticisers (*e.g.* glycerol, triethanolamine and PEG 200). Increasing the PG content to 3.5 % (w/w) with 5 % (w/v) Klucel® LF produced a flexible film and once used in the coating process the film did pull around the tablets but the surface looked as the film had melted on the tablet losing the glossiness desired for the tablet coating. Addition of glycerol (2.5% w/w) as a plasticiser to 5 % (w/v) Klucel® LF led to flexible but very weak films which could not be removed from the casting plate. It was not possible to form HPC films using PEG 200 as the plasticiser because the films formed were over plasticised resulting in a sticky mass on the casting plate.

Plasticisers (1 % glycerol and 2 % PG) were used in combination with 5 % Klucel® LF to introduce flexibility from glycerol and strength from PG. As expected, the film was very flexible but again not robust enough for the coating process. Thus, 1 % HPMC (3 cps) was added to allow easier handling of the film which was obtained but it was impossible to tell if the wrap-coating was covering the sides of the tablet once the film was pulled down over the tablet core due to transparent nature of the film. The wet film thickness was increased (*i.e.* from 8 to 12 micrometer setting) to produce slightly thicker films and to determine whether the film, once coated, was covering the sides of the tablets. It was noted that the thicker film acted similarly when the film was pulled around the tablet and it was concluded that the coating did not cover the sides but the top of the tablet only. As a possible strain-enhancing excipient, Tween 40 (possibly acting as a plasticiser), was added to the glycerol and PG containing formulation at low levels (0.04 % w/w); this lead to a weaker film as expected but so much so that the peeling off the cast support was impossible and if the surfactant content was increased an unstable film formulation was produced.

The use of triethanolamine (TEA), 1 % w/w, with Klucel® LF (5 %) produced flexible but weak films; 0.5 % w/w HPMC (3 cps) was included to add strength to the film which led to an easier to handle film but when applied for the coating process the film was not pulled around the tablet enough to cover the sides and led to form an discontinuous coating. For some gelatin-based films, addition of a surfactant led to increased strain properties for the films, hence it acted as a plasticiser. One percent w/w Brij35 (30 %) was added to the formulation but this led to crystals within the film indicating an incompatibility between the excipients or that some of the excipients had precipitated out in the film.

Sodium carboxymethylcellulose, Blanose® 7LF PH, with a typical viscosity of 25-50 mPa.s (2 % w/v solution) can be used as a film-former providing high gloss and low transmission of oxygen and water vapour which is desirable for coating characteristics (Johnson *et al.*, 1989). Although low elasticity and strain properties were reported (Hercules Inc., 2005), the inclusion of plasticisers (Johnson *et al.*, 1989) may increase elasticity. A 5 % (w/v) Blanose® 7 LF PH film was brittle as expected and neither triacetin nor PEG200 were effective plasticisers.

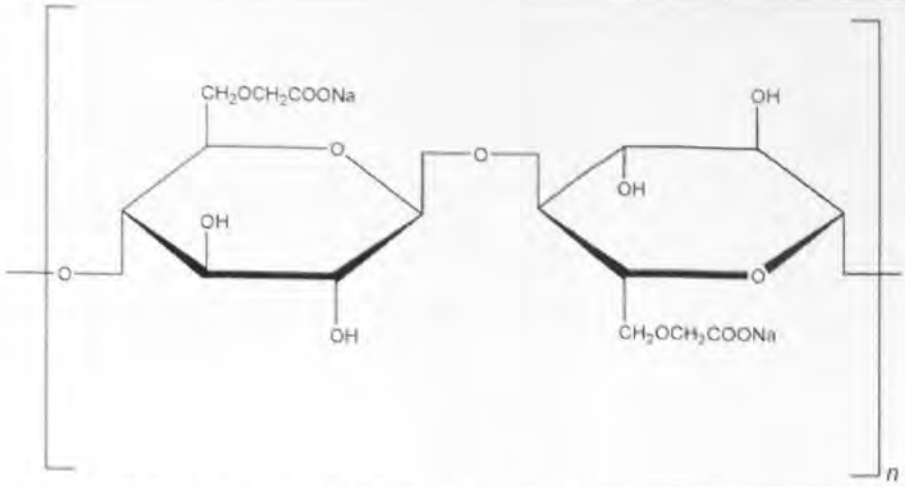


Figure 5.2- Molecular structure of sodium carboxymethylcellulose (reproduced from Parsons 2005)

Natrosol® L PH which is hydroxyethylcellulose (low viscosity grade) which is marketed for tablet coating as it provides increased flexibility compared to HPC, CMC and HPMC formulations (Hercules Inc. 2005). Natrosol® L PH film (5 % w/v) produced a film which was easy to peel but did not possess the flexibility required for the coating process. Addition of glycerol (1 % w/w) induced flexibility but not enough to wrap around the tablet. Further increases in glycerol content (2 % w/w) resulted in films that proved too difficult to handle. The 5 % (w/w) Natrosol® L PH was also plasticised with DL-LA (3.75 % w/w) which was a successful formulation for wrap-coating technology. Due to flexibility of the plasticised Natrosol® L PH films and Klucel® LF producing easy peel and clear films with a tendency to stretch in the coating process, a film combining the polymers was prepared. An equal ratio of Natrosol® L PH and Klucel® LF (totalling 5 %) with 2 % glycerol showed some flexibility in the coating process but still was not wrapping around the tablet as required. Also TEA (2 % w/w) in the combination film induced an elasticity in the film but the film was again difficult to handle. Various other combinations Natrosol® L PH, Klucel® LF, HPMC with plasticisers were formulated but the resulting films were not reproducible.

Hydroxyethylcellulose softens at 135 – 140°C (Harwood, 2005) therefore the heating mechanism of the wrap-coating machine may not aid the adhesion of the film to the tablet core surface. This was noted during trials, therefore a polymeric solution (5 % HPC in EtOH (50 %) was sprayed lightly on the tablet cores prior the wrap-coating process. Addition of DL-LA to Natrosol® enabled flexibility of the pre-formed film that increased with decreasing tensile strength and elastic modulus. Also the rate of dissolution at pH 5.8 was increased which may be due to a mechanically weaker film therefore requiring less energy for disintegration and finally dissolution. The lag time did not change with the increased rate of dissolution.

Solution of % (w/w) with 10% (w/w) gelatin						Tensile properties			Puncture properties			Dissolution properties (pH 5.8)			Dissolution properties (0.05 M HCl)		
Formulation	Glycerol	DL-LA	Tween40	$MgCO_3$	Brij35 30%	σ_t (MPa)	ε_t (%)	EM_t (MPa)	σ_p (MPa)	ε_p (%)	EM_p (MPa)	K_d (% min^{-1})	t_{lag} (min)	K_s (% $min^{-0.5}$)	K_d (% min^{-1})	t_{lag} (min)	K_s ($min^{-0.5}$)
G1	3.5	3.5	1	-	-	**5.32** ±0.30	**161.77** ±14.14	**0.22** ±0.01	**4.65** ±0.16	**99.18** ±5.99	**0.16** ±0.06	**33.39** ±1.28	**0.62** ±0.11	+	**37.28** ±1.08	**0.44** ±0.36	+
G1a	3.5	3.5	-	-	-	**4.89** ±0.25	**167.45** ±7.22	**0.19** ±0.004	**3.81** ±0.02	**88.69** ±4.23	**0.17** ±0.05	**35.33** ±11.15	**-0.34** ±1.54	+	**29.79** ±9.55	**0.47** ±0.36	+
G2	8	-	-	1	0.01	**2.89** ±0.21	**123.43** ±10.04	**0.14** ±0.01	**2.94** ±0.35	**93.64** ±13.52	**0.17** ±0.03	**42.31** ±32.56	**-0.72** ±1.87	+	**37.35** ±8.96	**0.18** ±0.25	+
G2a	8	-	-	-	0.01	**2.35** ±0.63	**121.60** ±19.96	**0.11** ±0.01	**2.96** ±0.37	**100.78** ±4.73	**0.10** ±0.04	**30.93** ±9.36	**0.54** ±0.16	+	**24.41** ±2.58	**0.48** ±0.46	+
Formulations described in Chapter 4																	
Solution of % (w/w) with 10% (w/w) gelatin																	
M		5	1	-	-	**7.90** ±1.19	**66.79** ±11.47	**0.77** ±0.38	**13.14** ±2.06	**92.13** ±11.94	**0.57** ±0.15	**37.81** ±8.88	**0.68** ±0.30	+	**43.62** ±5.83	**0.32** ±0.25	+
	5	-	-	1	-	**2.98** ±0.54	**37.71** ±7.23	**0.57** ±0.17	**6.18** ±0.60	**73.55** ±8.36	**0.38** ±0.03	**15.10** ±0.75	**2.55** ±0.26	**108.83** ±6.33	**36.36** ±4.97	**0.66** ±0.06	+

Table 5.1- Results of mechanical, dissolution and swelling data for coating formulations as pre-formed films (key: *σ_t tensile strength; ε_t tensile strain; EM_t tensile elastic modulus; σ_p puncture strength; ε_p puncture strain; EM_p puncture elastic modulus; K_d rate of dissolution; t_{lag} lag time; K_s rate of swelling; + not done; - does not contain; n≥3; mean ± S.D.)*

Formulation	Gelatin	Glycerol	DL-LA	PEG 200	Brij35 30%	Tensile properties			Puncture properties			Dissolution properties (pH 5.8)			Dissolution properties (0.05M HCl)		
						σ_t (MPa)	ε_t (%)	EM_t (MPa)	σ_p (MPa)	ε_p (%)	EM_p (MPa)	K_d (% min^{-1})	t_{lag} (min)	K_s (% $min^{-0.5}$)	K_d (% min^{-1})	t_{lag} (min)	K_s (% $min^{-0.5}$)
G3	**11**	**1.5**	**1.6**	**4**	-	**2.73** ±0.40	**149.60** ±14.28	**0.02** ±0.003	**1.86** ±0.11	**114.48** ±11.05	**0.07** ±0.01	**40.79** ±7.85	**0.09** ±0.63	+	**44.45** ±5.38	**0.67** ±0.13	+
Formulations described in Chapter 4:																	
I	**10**	-	-	**5**	**1**	**16.40** ±1.64	**106.41** ±8.36	**2.49** ±0.37	**13.45** ±2.42	**44.20** ±5.55	**0.75** ±0.19	**56.08** ±10.29	**0.85** ±0.22	**142.82** ±8.43	**32.22** ±9.67	**-0.29** ±1.29	+

Table 5.2- Results of mechanical, dissolution and swelling data for alternative gelatin-based pre-formed film formulations used in the coating process (key: σ_t *tensile strength;* ε_t *tensile strain;* EM_t *tensile elastic modulus;* σ_p *puncture strength;* ε_p *puncture strain;* EM_p *puncture elastic modulus;* K_d *rate of dissolution;* t_{lag} *lag time;* K_s *rate of swelling; + not done; - does not contain; n≥3; mean ± S.D.)*

Formulation		Tensile properties			Dissolution properties (pH 5.8)		Dissolution properties (0.05M HCl)	
		σ_t (MPa)	ε_t (%)	EM_t (MPa)	K_d (% min^{-1})	t_{lag} (min)	K_d (% min^{-1})	t_{lag} (min)
C1	5 % Natrosol®	15.16±1.89	12.27±1.21	4.09±1.08	17.21±1.20	2.60±0.11	42.74±4.35	0.50±0.43
	+ 3.75 % DL-LA	2.38±0.11	185.77±24.74	0.008±0.0003	33.56±2.62	2.67±0.10	34.22±7.72	0.71±0.29

Table 5.3- Mechanical and dissolution properties of the Klucel® and Natrosol® films *(key for mechanical data:* σ_t *tensile strength;* ε_t *tensile strain;* EM_t *tensile elastic modulus; n≥4; mean ± S.D. ; key for dissolution data:* K_d *rate of dissolution;* t_{lag} *lag time; n=3; mean ± S.D.)*

5.2.5 Conclusion for pre-formed films

Although the dissolution and mechanical properties of the films meet the criteria defined for the wrap-coating technology (*i.e.* fast dissolving and low EM), it may still be required to modify the formulations further in order to enable a successful coating process. Comparison of the pre-formed films described in Chapter 4 *versus* the modified formulations described here show that the tensile or puncture strain of the pre-formed film needs to be high (> 120 % tensile strain and > 88 % puncture strain here) with a low elastic modulus (≤ 0.2 MPa) which indicates low stiffness and rigidity of the film. It was found here that although the formulations were modified to be suitable for the wrap-coating process, the initial dissolution properties of the pre-formed film were not different from original formulations identified in Chapter 4 (exception the loss of low dissolution rate of $MgCO_3$-containing film in pH 5.8). Required mechanical properties combined with desired dissolution characteristics, are essential for a successful formulation.

All new formulations described in section 5.1.4 can be considered as suitable for the wrap-coating process hence these formulations were taken forward to the coating process. The following section describes the utilisation of these formulations as wrap-coatings on paracetamol-containing tablet cores.

5.3 Dissolution of paracetamol-based products

5.3.1 Introduction

In Chapter 4, various film formulations were discussed and some of them were taken forward to the wrap-coating studies as potential fast dissolving coatings as well as according to their possible suitability for the wrap-coating process. In the previous section the possible films were discussed in relation to the coating process and with formulation alterations some films were identified as good film coating candidates for this wrap-coating process. The ability to evaluate the exact film properties prior the coating is major advantage over the conventional tablet coating methods such as pan coating. Obara and McGinity (1994) studied casting method *vs.* spraying method on preparation of pre-formed films and they found that the method affected the mechanical properties of the films. The coating process in the pan coating method is therefore not easily mimicked outside the actual coating process so that identical film could be produced and analysed. Here the selected film formulations discussed in Chapter 4 are utilised as tablet coating formulations. The release of active ingredients, paracetamol and ibuprofen, is studied here from the wrap-coated dosage forms and the effect of the coating on dissolution of the core is probed.

5.3.2 Materials and methods

5.3.2.1 Materials

Paracetamol, maize starch (disintegrant), pregelatinised starch (binder), povidone (binder), talc (glidant), stearic acid (lubricant), microcrystalline cellulose and magnesium stearate were supplied by GlaxoSmithKline, Dungarven, Ireland. Sodium bicarbonate (disintegrant) and potassium sorbate (preservative) were obtained from Sigma-Aldrich, UK. Pepsin, sodium chloride, potassium dihydrogen phosphate and di-sodium hydrogen orthophosphate dihydrate were purchased from Sigma-Aldrich, UK. Hydrochloric acid S.G 1.18 (37%) and glacial acetic acid were obtained from Fisher Chemicals, UK. The water was double distilled in the laboratory using Fisons Fi-Streem 4 litre bi distillation unit. Panadol® and uncoated Panadol® were kindly supplied by GlaxoSmithKline, Weybridge, UK.

5.3.2.2 Solubility

Paracetamol solubility was measured in three solutions: 0.05M HCl, Sørensen's phosphate buffer pH 5.8 and pH 6.8. Paracetamol was added to the solution until no more dissolved. The saturated solutions (n=3 for each condition) were left overnight into a shaking water bath (80 strokes per minute, RT), the saturated solution was checked visually and the pH adjusted to the starting pH with NaOH or HCl and if required, more paracetamol was added. The solubility of paracetamol was found to be 15.62 ± 0.31 mg ml^{-1} in 0.05M HCl, 15.59 ± 2.07 mg ml^{-1} in pH 5.8 and 14.69 ± 0.03 mg ml^{-1} in pH 6.8 therefore sink conditions in all dissolution media were fulfilled.

5.3.2.3 Granulation

Excipients for wet granulation (formulations in Table 5.4) were accurately weighed on an Acculab balance (Sartorius Group ALC-80.4) or Mettler PC4000 (Mettler Instrumente AG). Excipients were sieved (710 µm sieve) and then mixed mechanically for 10 minutes. Double distilled water was added to the powder mix until the end point was reached, which was visually determined by absence of free powder. The wet granulation mass was sieved (1 mm sieve), dried overnight at 45 °C and sieved again through 1 mm sieve. The granules were stored in a sealed container until further use.

5.3.2.4 Compression

The granules were mixed with extra granular excipients in a mechanical mixer for 5 minutes. The tableting mass was compressed with a Manesty E2 Press using a capsule-shaped die

with a break-line on one side of the tablet (I-Holland, UK). Tablets were compressed to result in a crushing strength of 177.4 ± 32.9 N, measured with a Schleuniger-4M Tablet Hardness tester. The same tablet shape and size was used for all core formulations and the fill-depth was set according to the appropriate strength of the tablet therefore the drug content between different core formulations was not constant. In order to compare different core formulations in the same figure, the dissolution profiles were adjusted so the plateau of the profile was assumed to be corresponding to complete dissolution of the drug and the profiles were normalised to 100%.

5.3.2.5 Wrap-coating

The wrap-coating procedure is described in detail in section 5.2.

5.3.2.6 Dip-coating

Tablets were picked up, six at the time, with a device which consisted of separate suction cups connected to an air compressor which the allowed the tablets to be picked up simultaneously ready for the dipping process. Tablets were dipped into a polymer solution for one second one side at a time and then dried for 20 minutes in an air stream. The procedure was then repeated for the other side. Dip-coated tablets were then stored in an amber glass jar with a desiccator until use.

5.3.2.7 Dissolution

The dissolution of the tablets was carried out as described in section 3.2.2.1. Additionally some dissolution was carried out in Sørensen's phosphate buffer pH 5.8 or 0.05M HCl with temperature of the medium at 37.0 ± 0.5 °C and a paddle speed of 50.0 ± 0.5 rpm.

5.3.2.8 Statistical analysis

Section 3.2.2.3 describes the statistical analysis used to assess the significance of the results.

5.3.3 Results and discussion for gelatin-based coatings

5.3.3.1 Effect of wrap-coating on dissolution

Initial wrap-coating trials were carried out on a gelatin-based formulation consisting of 5% glycerol (w/w) as plasticiser with 10 % gelatin (w/w); formulation **A** in Chapter 4. This gelatin-glycerol-film was wrap-coated on conventionally coated Panadol® (HPMC-coated) and on uncoated Panadol® cores. The need for the film formulation was identified once initial trials for wrap-coated tablets were dissolved. The dissolution in acidic conditions was same for both wrap-coated formulations and Panadol® ($p>0.05$) (Figure 5.3).

The same formulations were dissolved at pH 5.8, 50 rpm (Figure 5.4), and the rate of dissolution of Panadol® was significantly faster compared to the wrap-coated formulations up to 15 minutes ($p<0.05$). An obvious lag effect for the wrap-coated formulations can be seen in the initial stages of the dissolution (Figure 5.4) which could be caused by the additional coating on the tablet core. The dissolution rate for gelatin-glycerol (10-5 % w/w) pre-formed films (Chapter 4) is faster in acidic conditions *vs.* pH 5.8 ($p<0.05$) but the lag times are not different ($p>0.05$). It could be the slower dissolution at pH 5.8 is the cause of the lag time in the wrap-coated formulations. Paracetamol products are typically used for acute pain therefore any delay in dissolution is not desirable, hence the need for a faster dissolving film coating was identified.

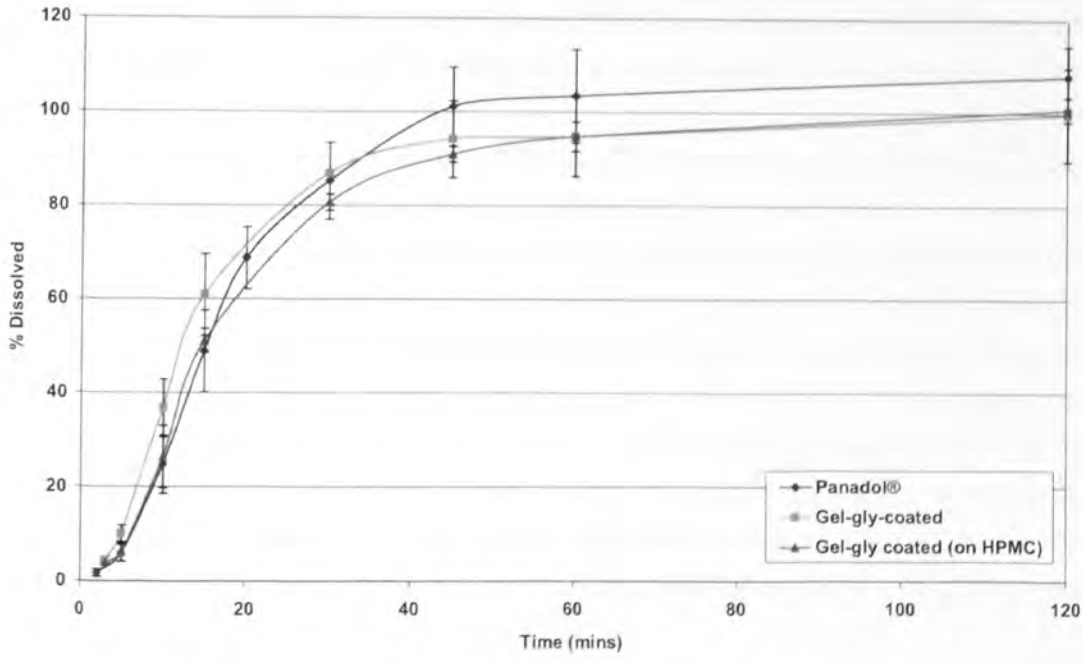


Figure 5.3- Paracetamol dissolution from conventional HPMC coated Panadol®, gelatin/glycerol (formulation for cast solution 10/5 % w/w) wrap-coated on uncoated Panadol® cores and on HPMC-coated Panadol® cores *(0.05M HCl, 30 rpm, n≥3, mean±S.D.)*

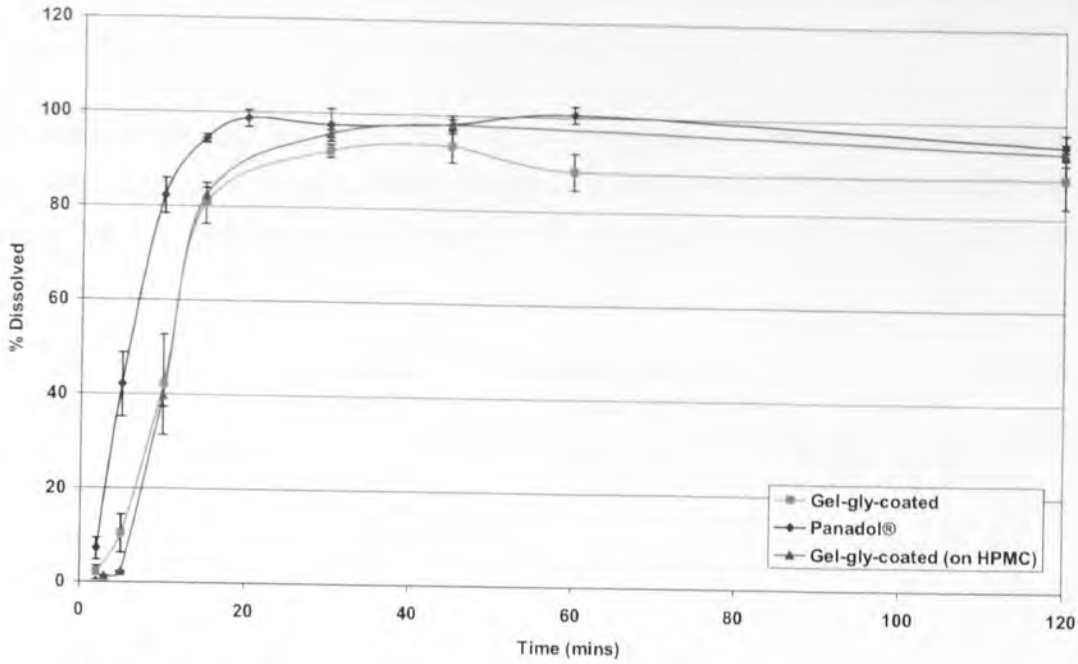


Figure 5.4- Paracetamol dissolution from conventional HPMC coated Panadol®, gelatin/glycerol (formulation for cast solution 10/5 % w/w) wrap-coated on uncoated Panadol® cores and on HPMC-coated Panadol® cores *(pH5.8, 50 rpm, n≥3, mean±S.D.)*

Possible film formulations for wrap-coating process were discussed in section 5.2.4. Suitable film formulations were chosen and adjusted according to their dissolution and mechanical properties. Three gelatin-based formulations (**G1**, **G2** and **G3**) were wrap-coated onto uncoated Panadol® cores and their dissolution was compared to conventionally HPMC-coated Panadol® and uncoated Panadol® cores (Figure 5.5). At the 5 minute time point, dissolution of the uncoated Panadol® is significantly faster than all other formulations ($p<0.001$). Dissolution of pre-formed films, **G1**, **G2** and **G3**, was not different in acid ($p>0.05$) but used as coating formulations dissolution of the **G2**-coated core is significantly slower than **G1**- and **G3**-coated formulations in acidic conditions (30 rpm). At 15 minutes, Panadol® is significantly ($p>0.05$) slower than uncoated Panadol®, **G1**- and **G3**-coated formulations, and dissolution of Panadol® and **G2**-coated formulations was similar (Figure 5.5). Although in the pre-formed film studies (Chapter 4), there was no strong correlation between the thickness of the film *vs.* lag time in dissolution, it may be that the weight gain plays a role in the paracetamol core dissolution. The weight gain in **G2**-coated formulations was at least 1.85 % higher than **G1**- or **G3**-coated (Table 5.4) therefore the weight increase due to coating could contribute to the slower dissolution in this instance.

Gelatin-coated formulations (**G1**, **G2** and **G3**) were also dissolved in acid with higher paddle speed (50 rpm) in order to see if the same trend can still be seen as for 30 rpm dissolution.

Same lag effect for **G2**-coated formulation can be seen as it is significantly slower at 3 and 5 minutes ($p<0.05$) although all formulations reach 100 % dissolution in less than 20 minutes (Figure 5.6).

At 5 minutes, Panadol® and uncoated Panadol® are significantly faster than the wrap-coated formulations ($p<0.05$). The lag effect and the resulting slower dissolution for **G2**-coated formulation is evident also in pH 5.8 (up to 15 minutes significantly slower $p<0.05$) (Figure 5.7).

Formulation	Weight increase (%)
G1	6.24 ± 0.83
G2	9.45 ± 1.10
G3	7.60 ± 1.44

Table 5.4- Weight increase from the wrap-coating process *(n≥9; mean ± S.D.)*

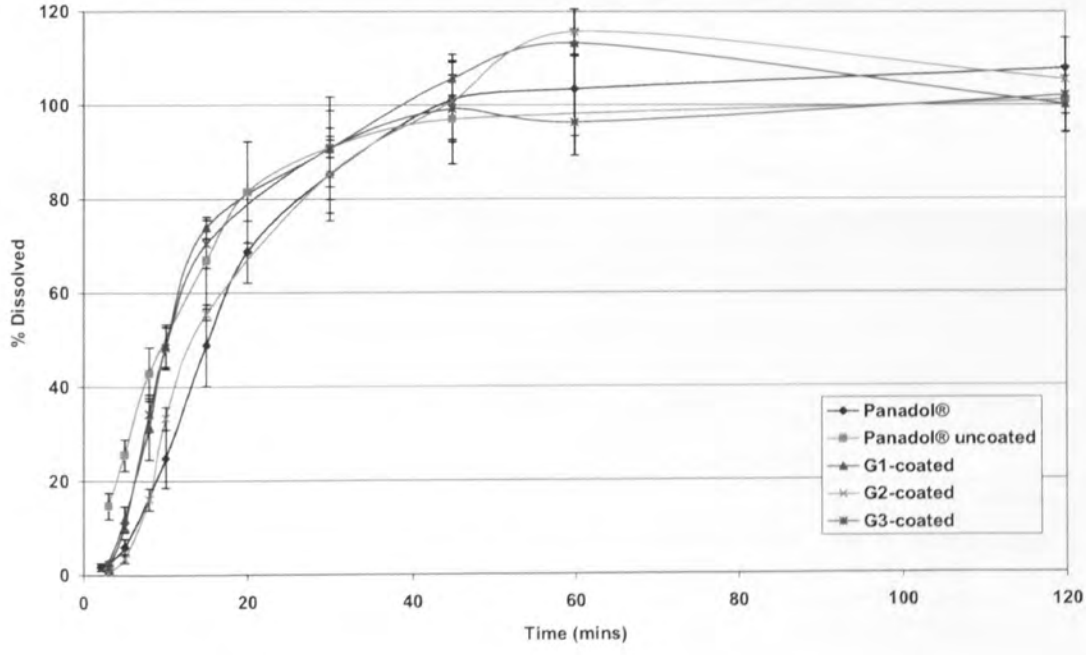


Figure 5.5- Paracetamol dissolution from conventional HPMC coated Panadol®, uncoated Panadol®, G1, G2 and G3 wrap-coated on uncoated Panadol® cores *(0.05M HCl, 30 rpm, n≥3, mean±S.D.)*

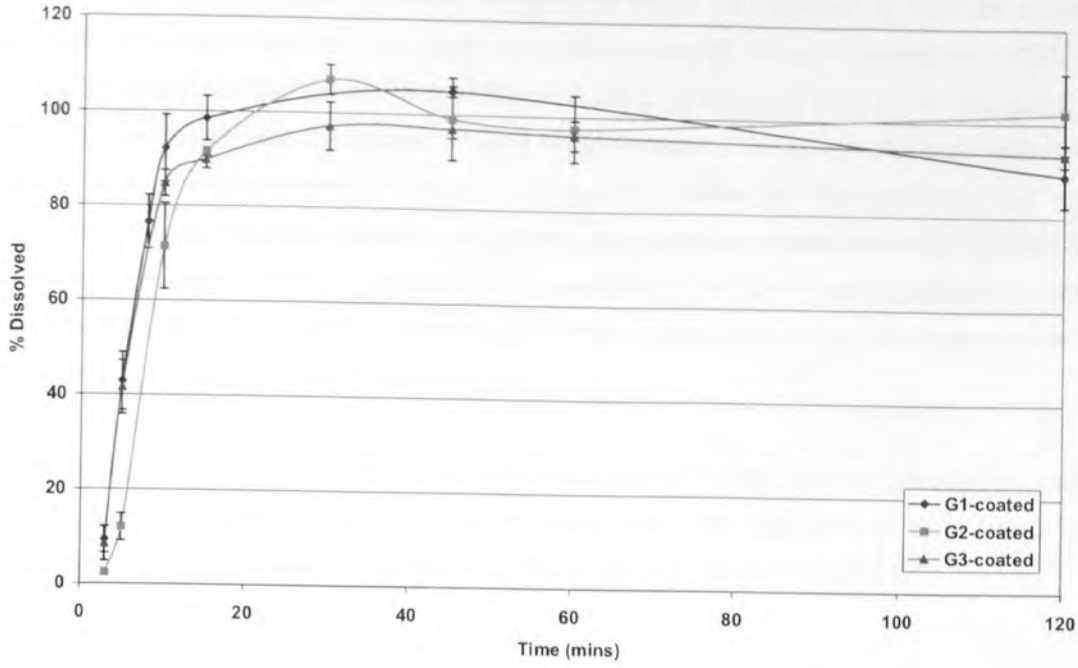


Figure 5.6- Paracetamol dissolution from G1, G2 and G3 wrap-coated on uncoated Panadol® cores *(0.05M HCl, 50 rpm, n=3, mean±S.D.)*

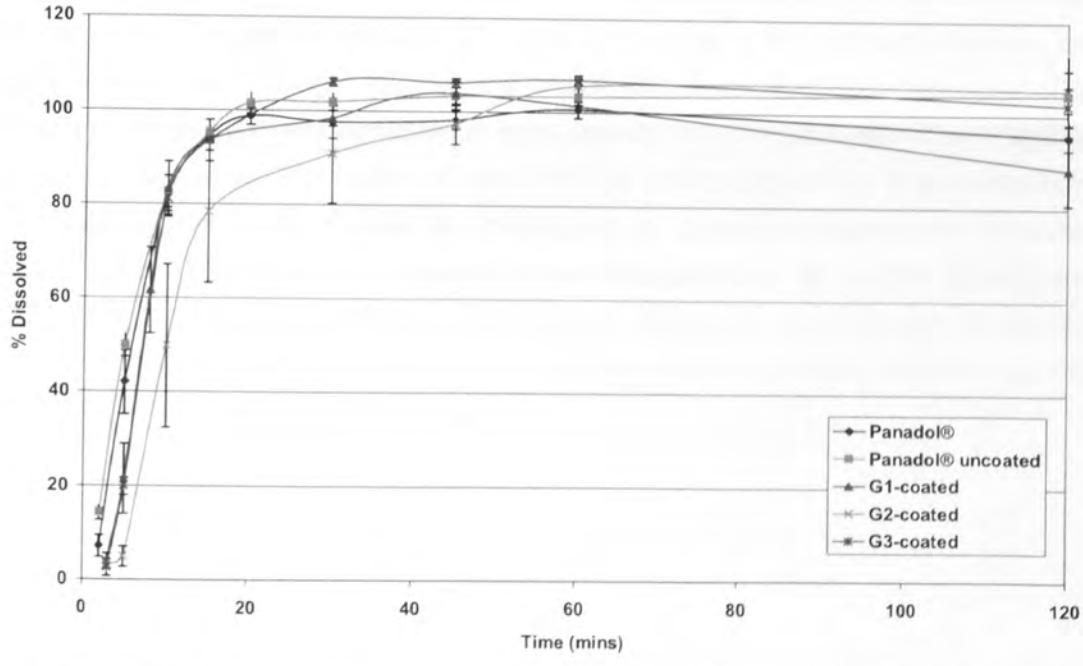


Figure 5.7- Paracetamol dissolution from conventional HPMC coated Panadol®, uncoated Panadol®, G1, G2 and G3 wrap-coated on uncoated Panadol® cores *(pH 5.8, 50 rpm, n≥3, mean±S.D.)*

Due to nature of the wrap-coating process, it was tried if an active ingredient could be formulated in the dry film coating. Paracetamol and metoclopramide can be administered simultaneously but so far these are in separate dosage forms therefore metoclopramide was

included in the **G1**-formulation in order to see if it would be possible to coat an active containing film on paracetamol core. From the surface area of the paracetamol core (366.4 mm^2) together with knowledge of the cast film size (38 x 13 cm) and drug content (0.332 g / cast), it was estimated that the applied coating should contain 2.3 mg of metoclopramide per tablet. Metoclopramide-containing film was successfully coated on Panadol®-core but the dose is still very low therefore possibly only potent drugs can be considered to be included in the coating formulation without affecting the properties of the film. Metoclopramide is also light sensitive drug hence the coating should contain a pigment or the "metoclopramide"-coated product should be packed appropriately.

As conclusion of the dissolution of wrap-coated paracetamol cores, the film formulations can be designed to be fast dissolving and not inhibiting the initial drug release from the solid dosage form. Also it is possible to utilise the coatings as drug delivery systems.

5.3.3.2 Effect of coating formulation on dissolution

The effect of surfactants or carbonates on dissolution of pre-formed films (in pH 5.8 or 0.05M HCl) was evident (sections 4.3.4 and 4.3.6) therefore films were also formulated without the excipients which were thought to exert the largest effects on dissolution behaviour. The formulations **G1** and **G2** were compared to same formulations without Tween 40 and $MgCO_3$ respectively (pre-formed film studies in section 5.2.4) and no differences in characteristics were observed. Formulations were still investigated as coated formulations on uncoated Panadol® but no differences were observed at early time points for **G1** *vs.* **G1a** formulations in dissolution of paracetamol (Figures 5.8 and 5.9). Dissolution at 3, 15 and 45 minutes (0.05M HCl, 30 rpm, Figure 5.10) was slower for **G1a**-formulation ($p<0.05$), this trend was not seen in the pre-formed film studies (section 5.2.4).

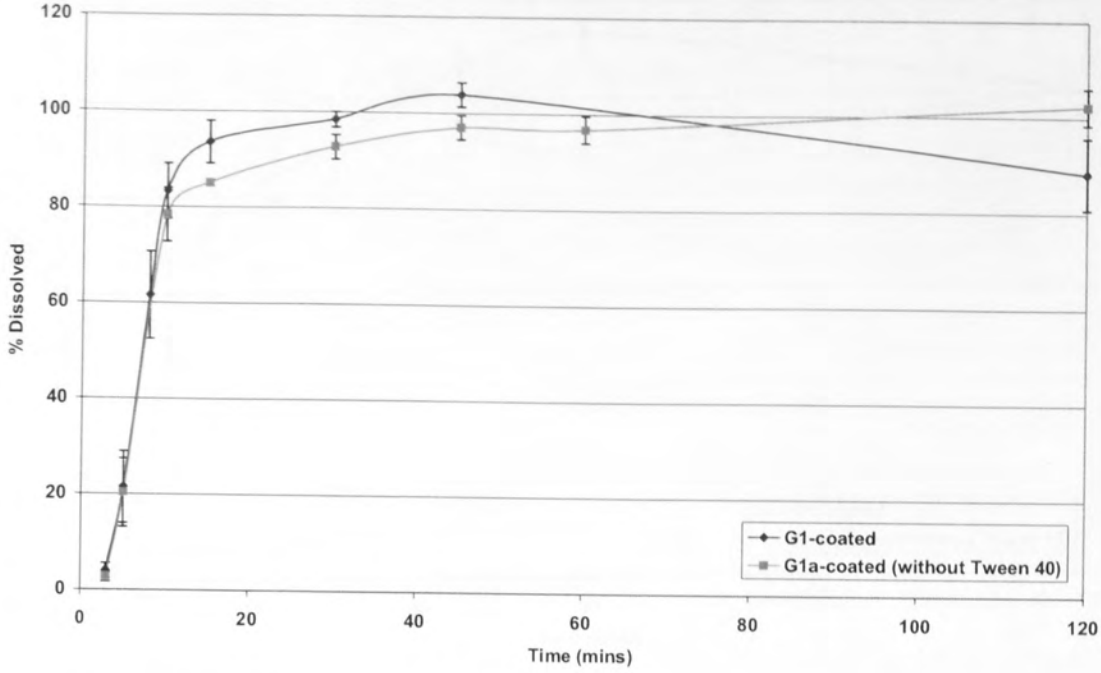


Figure 5.8- Paracetamol dissolution of G1 and G1a without Tween 40 formulation wrap-coated on uncoated Panadol® cores *(pH 5.8, 50 rpm, n=3, mean±S.D.)*

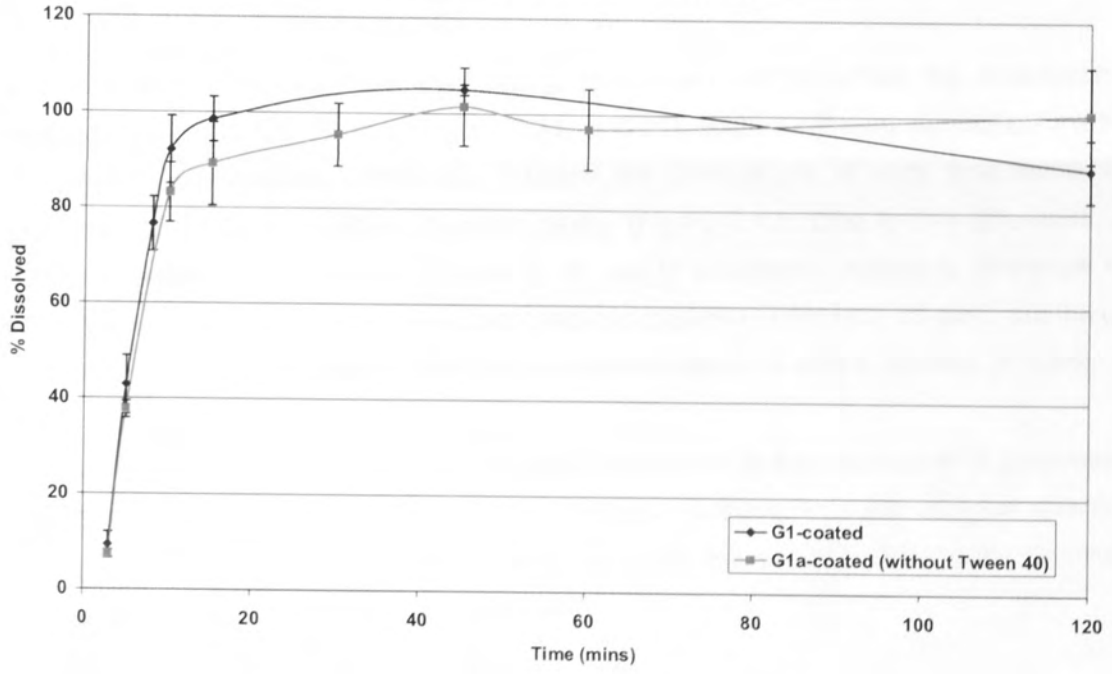


Figure 5.9- Paracetamol dissolution of G1 and G1a without Tween 40 formulation wrap-coated on uncoated Panadol® cores *(0.05M HCl, 50 rpm, n=3, mean±S.D.)*

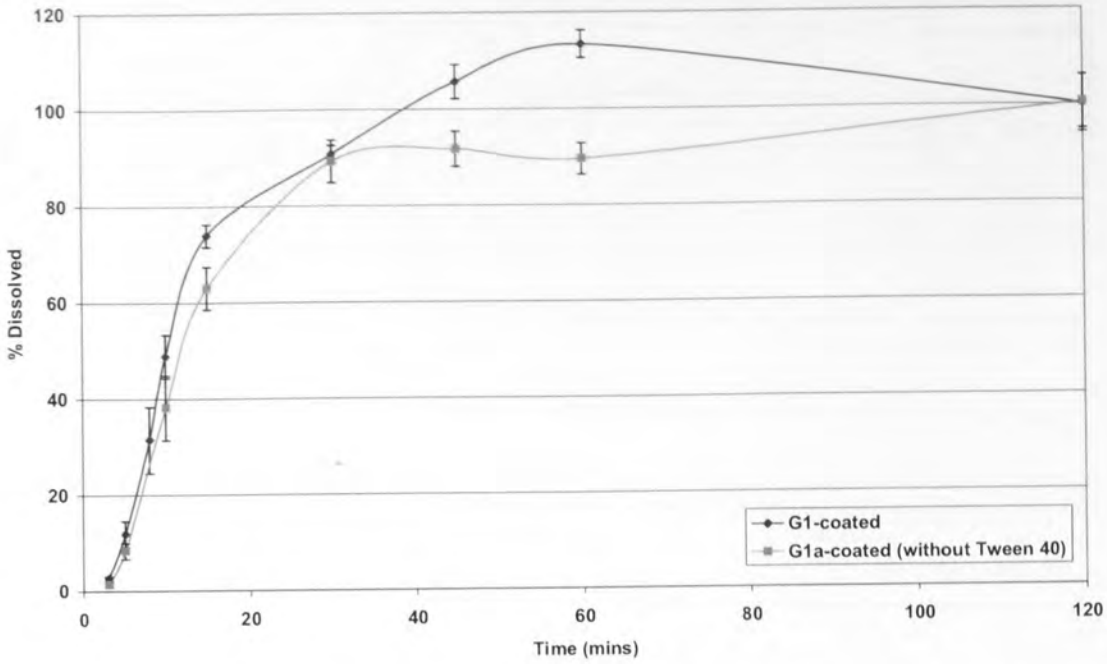


Figure 5.10- Paracetamol dissolution of G1 and G1a without Tween 40 formulation wrap-coated on uncoated Panadol® cores *(0.05M HCl, 30 rpm, n=3, mean±S.D.)*

The exclusion of $MgCO_3$ from the coating formulation did not affect the dissolution of paracetamol at pH 5.8, 50 rpm (Figure 5.11, $p>0.05$). With a different dissolution medium (0.05M HCl, 50 rpm) the differences between the formulations at early time points was significant; the **G2a** formulation dissolved faster (Figure 5.12). Due to this difference, the paddle speed was reduced from 50 rpm to 30 rpm to determine whether is difference was still evident. Figure 5.13 shows the paracetamol dissolution (0.05M HCl, 30 rpm), but the only difference in dissolution between the two coated formulations is after 5 minutes ($p<0.05$).

According to these results there are no great differences in the dissolution of paracetamol even though the tablet coating formulation changes. All these films are very fast dissolving hence small differences in the pre-formed-film characteristics is not affecting the dissolution of an active ingredient from solid dosage form.

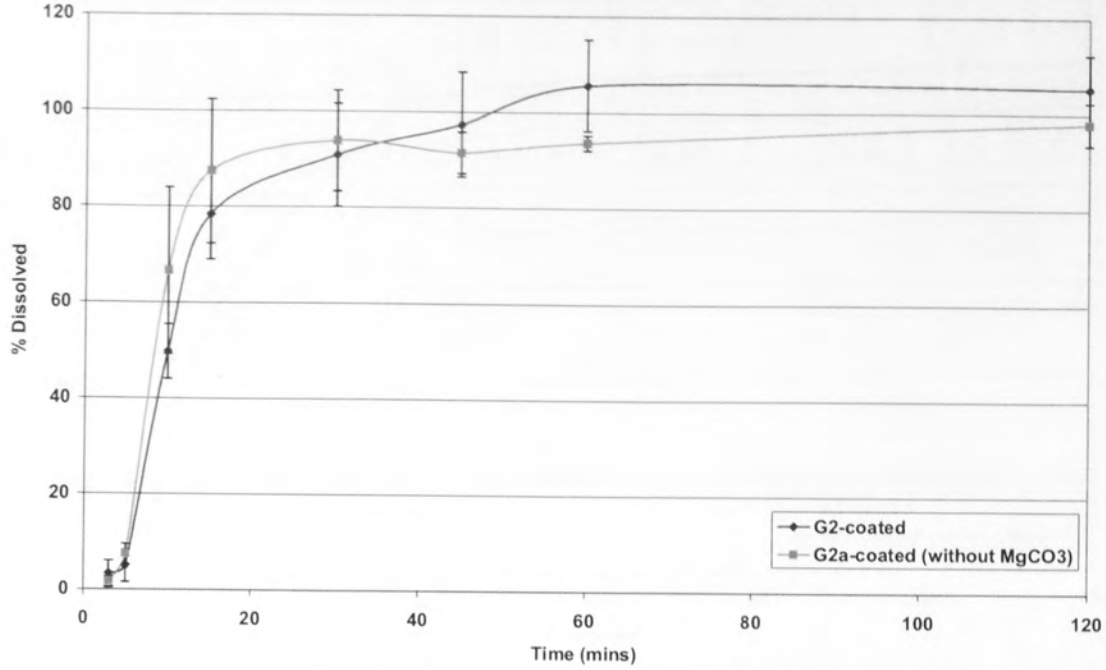


Figure 5.11- Paracetamol dissolution of G2 and G2a without $MgCO_3$ formulation wrap-coated on uncoated Panadol® cores *(pH 5.8, 50 rpm, n=3, mean±S.D.)*

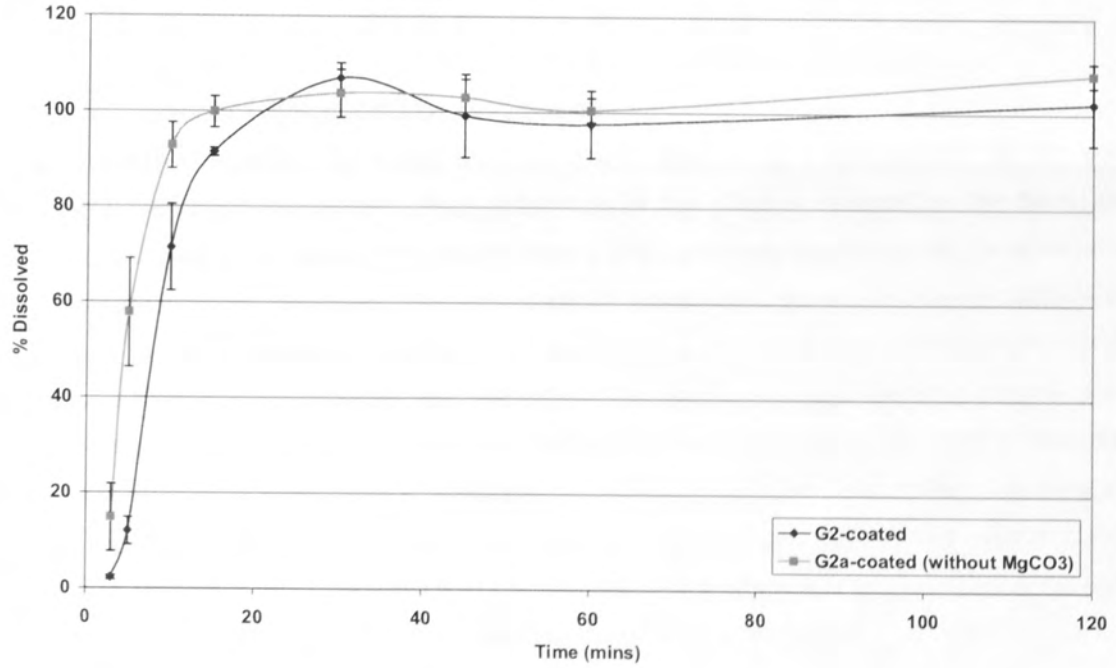


Figure 5.12- Paracetamol dissolution of G2 and G2a without $MgCO_3$ formulation wrap-coated on uncoated Panadol® cores *(0.05M HCl, 50 rpm, n=3, mean±S.D.)*

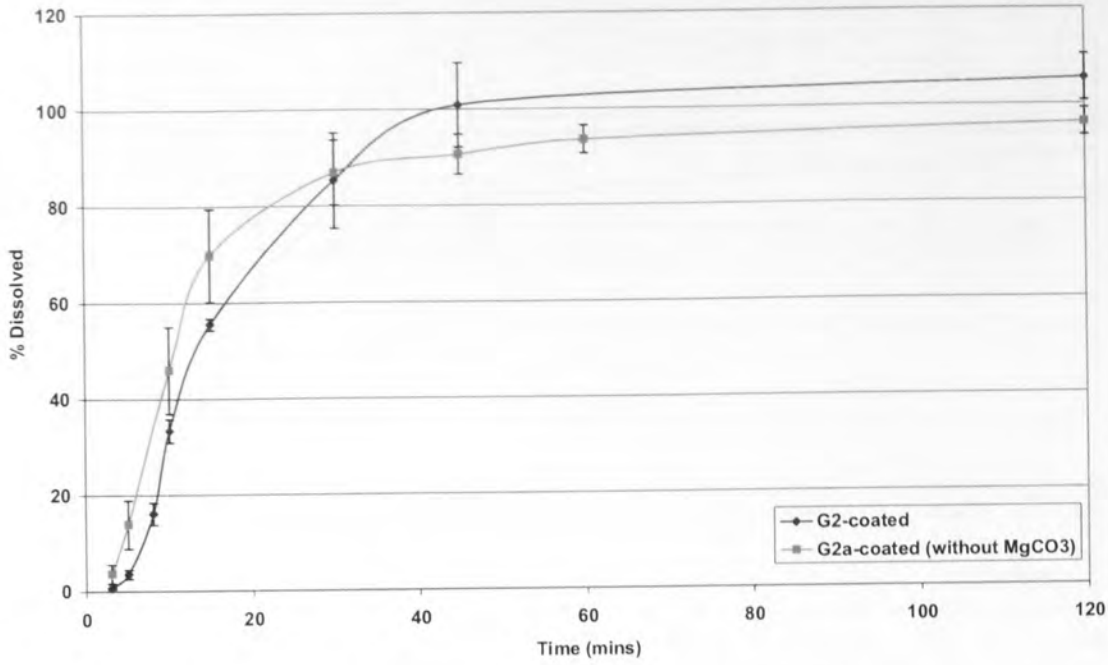


Figure 5.13- Paracetamol dissolution of G2 and G2a without $MgCO_3$ formulation wrap-coated on uncoated Panadol® cores *(0.05M HCl, 30 rpm, n=3, mean±S.D.)*

5.3.3.3 Effect of dip-coating on dissolution

The effect of dip-coating on tablet dissolution was studied as a comparison for the wrap-coating technology. Initially the effect of layering of the polymer solution on the tablet core was studied where the tablet cores were dipped into a polymer solution once, for another set the dip-coating was done twice. For a third set of tablet cores the dip-coating procedure was repeated as many times as possible. Four applications were found to be maximum number of dip coatings that could be applied and dried. The lag for coated cores was evident due to the HPMC-coating on paracetamol cores; the additional gelatin dip-coating did not decrease the initial release of paracetamol. Although the coated cores dissolved similarly at early time points, later on (30 minute time point) the core with a single application of the gelatin-glycerol solution was significantly slower ($p>0.05$) (Figure 5.14). Therefore it was concluded that a single dip coating was sufficient to discriminate between formulations.

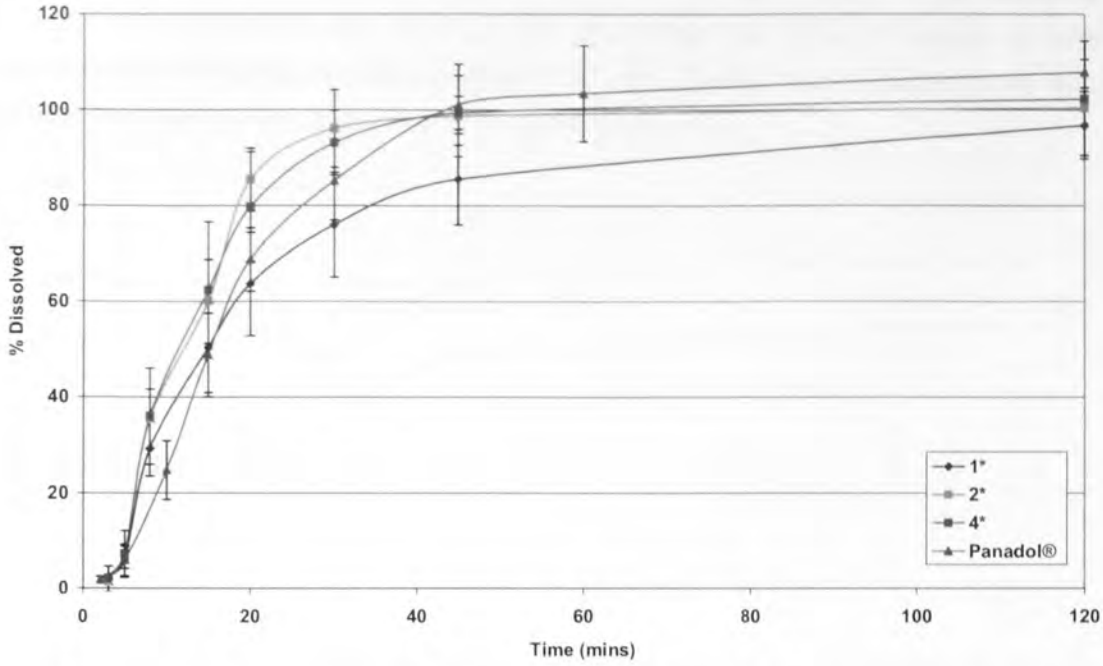


Figure 5.14- Paracetamol dissolution of dip-coated Panadol® cores versus Panadol® (5% glycerol, 10% gelatin (w/w) polymer solution, 1* dipped once, 2* dipped twice, 4* dipped four times, *0.05M HCl, 30 rpm, n≥3, mean±S.D.)*

The wrap-coating formulations **G1** and **G2** were also applied as dip-coatings onto Panadol® cores (which contained HPMC-coating); in acidic conditions (30 rpm) the **G1**-formulation visually seems slowest and is significantly slower compared to Panadol® at 5, 30 and 45 minutes (Figure 5.15). The high variability associated with dissolution from **G1** coated formulations meant that the results for **G1** and **G2** were not significantly different.

Figure 5.16 shows the effect of the dip-coating process *vs.* wrap-coating process on paracetamol dissolution for formulation **G1**; dip-coated core was slower at all time points up to 45 minutes ($p<0.05$). This effect may be due to "double-coating" on dip-coated formulations because the dip-coating is applied on HPMC-coated cores whereas the wrap-coating can be applied onto an uncoated core. Also the polymer solution on dip-coating procedure can produce stronger film layer as the polymeric molecules can coalesce together during drying and also attach to the HPMC-coating underneath (Chapter 1). In the wrap-coating method, the film is pulled around the tablet and is attached by overlapping areas on the sides of the tablet core. It may be that dissolution can start immediately once the medium penetrates the film and can then progress underneath the coating resulting in faster wetting of the core. Dissolution from the **G2** wrap-coated formulation was slower (section 5.3.3.1) compared to **G1** and **G3**. In the dip-coating procedure the effect on dissolution from formulation **G1** and **G2** was not clear. There was no difference between the dissolution of **G2** wrap-coated or **G2** dip-coated cores (Figure 5.17).

Direct comparison of dip-coated formulations and wrap-coated formulations is challenging as in order not to affect the core structure, the dip-coating had to be performed on HPMC-coated core which results in double-coating of the core. Overall it can be said that the coating method can affect the end behaviour of the solid dosage form.

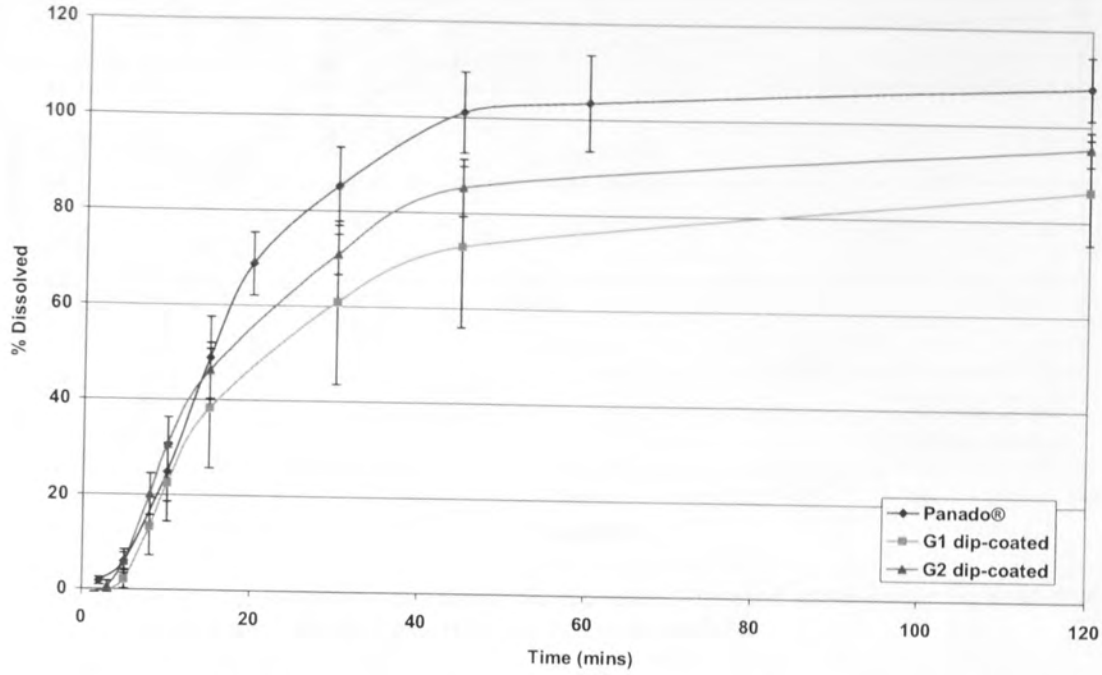


Figure 5.15- Paracetamol dissolution of dip-coated Panadol® cores versus Panadol® (dip-coating polymer solutions G1 and G2, *0.05M HCl, 30 rpm, n≥3, mean±S.D.)*

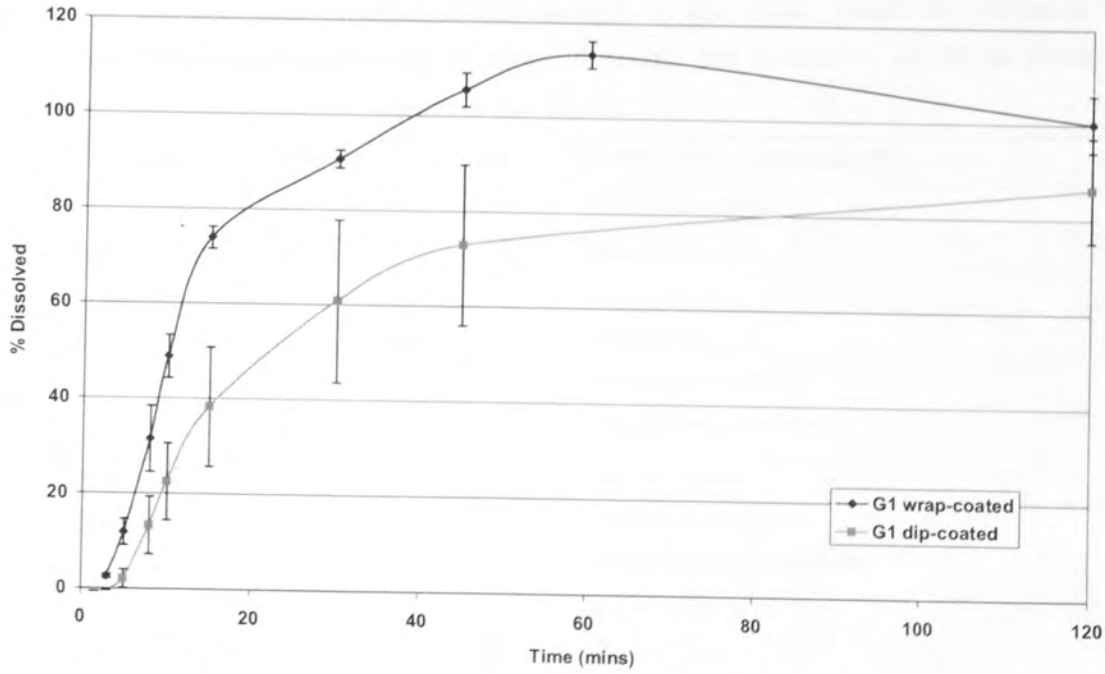


Figure 5.16- Paracetamol dissolution of G1 dip-coated Panadol® cores *versus* G1 wrap-coated uncoated Panadol® cores *(0.05M HCl, 30 rpm, n=3, mean±S.D.)*

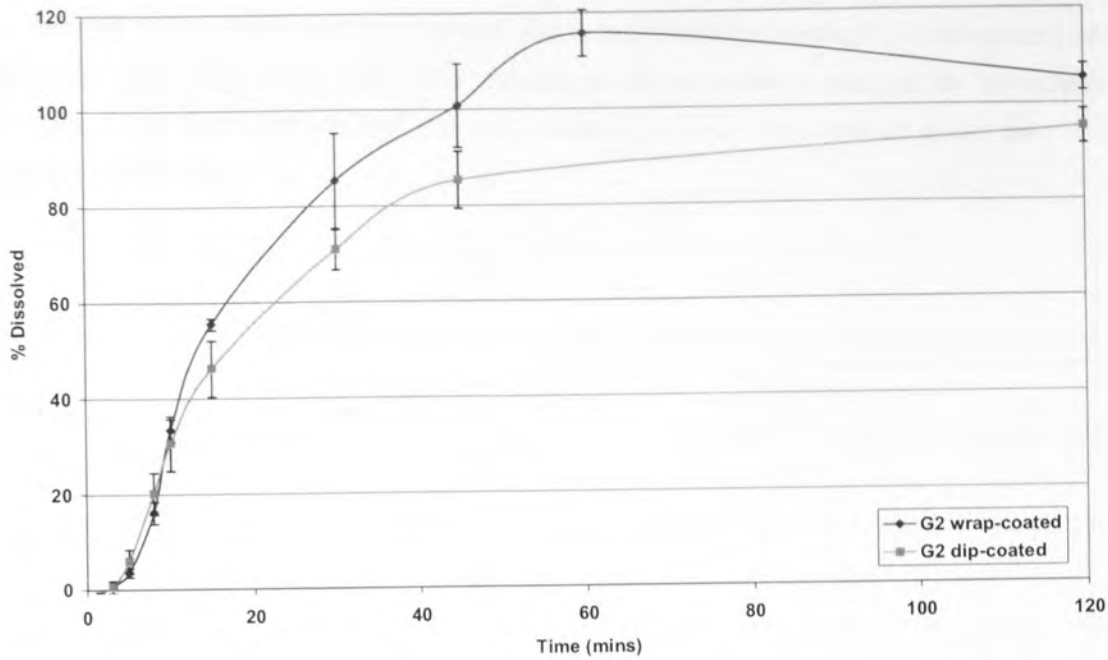


Figure 5.17- Paracetamol dissolution of G2 dip-coated Panadol® cores *versus* G2 wrap-coated uncoated Panadol® cores *(0.05M HCl, 30 rpm, n=3, mean±S.D.)*

5.3.3.4 Effect of core formulation on dissolution

Paracetamol-containing formulations (Table 5.5) were compressed to ensure similar crushing strengths; the aim was to ensure that strength of the tablet would not influence the dissolution of formulations and the factors influencing the dissolution would be either the excipients within the core formulation or the applied coating.

Formulation 1 ingredients	Formulation 2 ingredients
Wet granulation:	Wet granulation:
Paracetamol	Paracetamol
Pregelatinised starch	Maize starch
Povidone	Povidone
Potassium sorbate	Potassium sorbate
	Pregelatinised starch
Tablet mass:	Tablet mass:
Maize starch	Sodium bicarbonate
Talc	Microcrystalline cellulose
Stearic acid	Magnesium stearate
Water	Water

Table 5.5- Excipient list for paracetamol-containing formulations

Dissolution of the core formulations 1 and 2 showed significant differences over all time points except at 10 and 120 minutes. Formulation 2 contains sodium bicarbonate which generates carbon dioxide with on contact with water therefore leading to disintegration of the tablet (Cable, 2001) and hence the dissolution is enhanced compared to formulation 1 (Figure 5.18). Both formulations are fast dissolving without evidence of a lag prior to the onset of dissolution.

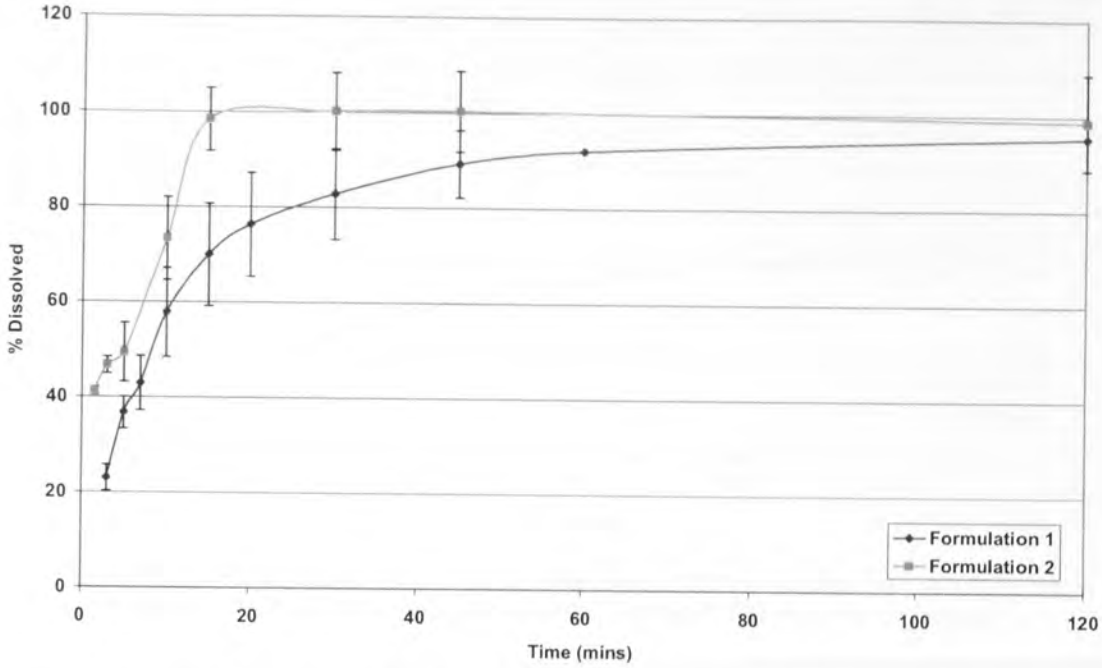


Figure 5.18- Paracetamol dissolution of uncoated paracetamol-containing core formulations 1 (no bicarbonate) and 2 (contains carbonate). *(0.05M HCl, 30 rpm, n=6, mean±S.D.)*

The pro-dissolution effect of sodium bicarbonate was reported previously where dissolution of bicarbonate-containing tablet cores was not affected by paddle-speed (10, 20, 30 and 40 rpm) whereas all profiles for conventional paracetamol formulations were dissimilar (Rostami-Hodjegan et al. 2002). A similar study was carried out for formulations 1 and 2 where both of the formulations were coated with the film-formulation **G2** (section 5.2.5). The same trend can be seen for the coated formulations (Figure 5.19 and 5.20), *i.e.* inclusion of sodium bicarbonate (formulation 2) overrides the effect of the coating producing no differences between the applied paddle speeds. At early time points (1.5 and 3 minutes) for formulation 1 the paddle speed did not play a significant role in the dissolution ($p>0.05$). Dissolution at 50 rpm was significantly faster already at 8 minutes and all profiles for core-formulation 1 were significantly different at 15 minutes ($p<0.001$). Varying paddle speed showed the same trend here as in the study carried out by Rostami-Hodjegan *et al.* (2002) indicating that tablet core formulation plays important role in the dissolution process but the

coating can also play a role *e.g.* coated formulations can induce a significant lag effect ($p<0.001$) for the release of the active ingredient compared to an uncoated formulation 1 (Figure 5.21).

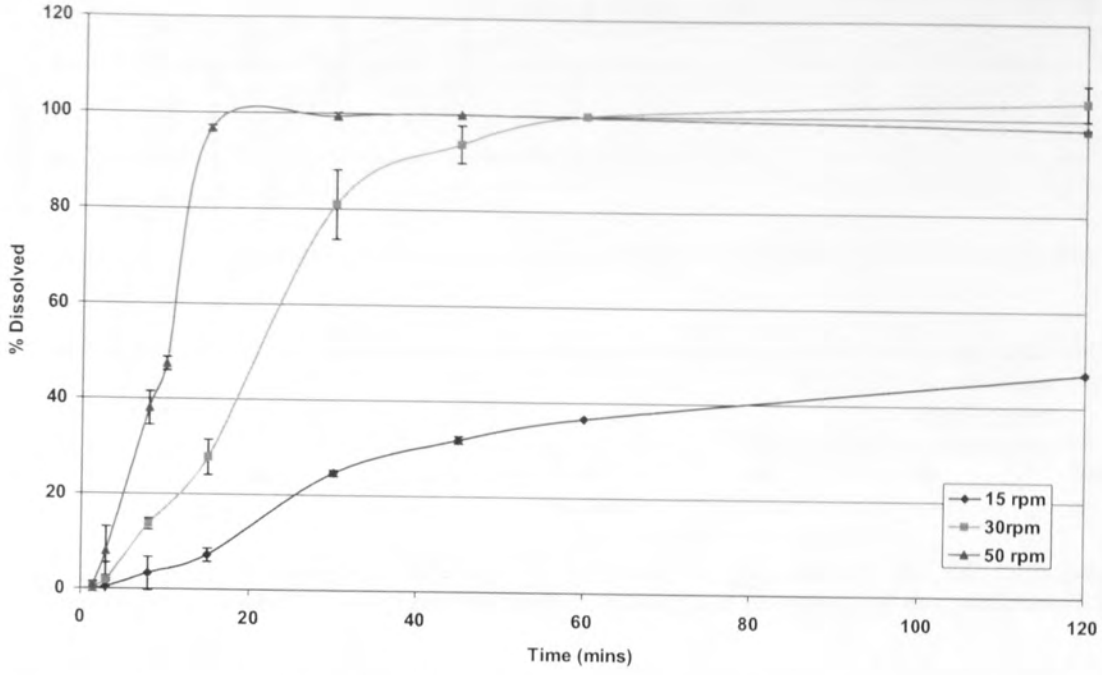


Figure 5.19- Paracetamol dissolution of wrap-coated G2 formulation on core formulation 1 (without sodium bicarbonate) with varying paddle speed *(0.05M HCl, n=3, mean±S.D.)*

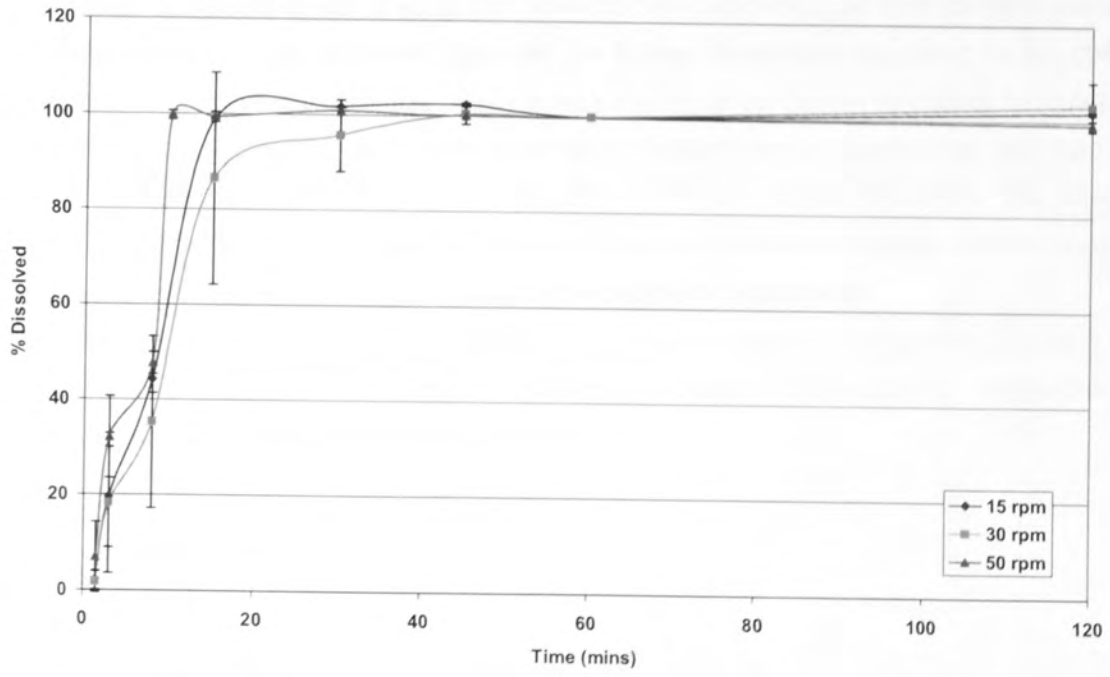


Figure 5.20- Paracetamol dissolution of wrap-coated G2 formulation on core formulation 2 (with sodium bicarbonate) with varying paddle speed *(0.05M HCl, 30 rpm, n=3, mean±S.D.)*

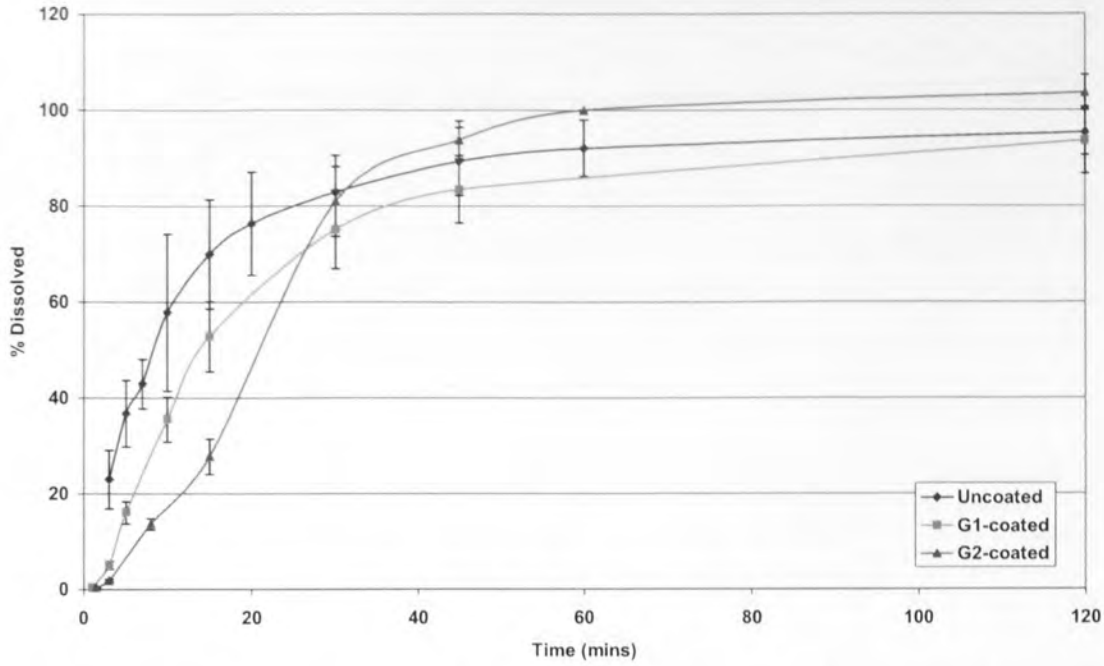


Figure 5.21- Paracetamol dissolution of uncoated, wrap-coated G1 and G2 formulations containing core formulation 1 (without sodium bicarbonate) *(0.05M HCl, 30 rpm, n=3, mean±S.D.)*

Pre-formed film formulations were selected according to the results described in Chapter 4 and section 5.2.4 in this chapter. Paracetamol dissolution from **G1** wrap-coated Panadol® was faster compared to **G2** wrap-coated Panadol® in 0.05M HCl, 30 rpm (Section 5.3.3.1). As expected, the uncoated tablet displayed the fastest dissolution compared to the coated formulations; at three minutes dissolution is significantly faster than wrap-coated formulations ($p<0.001$). At 15 minutes, **G2**-coated paracetamol dissolution is significantly less than the uncoated core and **G1**-coated core dissolution (Figure 5.21). Therefore the coating formulation has an effect on the drug release if the core does not contain excipients which facilitate a fast onset of the drug release, such as sodium bicarbonate.

The effect of the coating was also studied on the bicarbonate containing cores (Figure 5.22); at 3 minutes **G2**-coated formulations exhibited decreased dissolution in comparison to uncoated and **G1**-coated formulations ($p<0.01$).

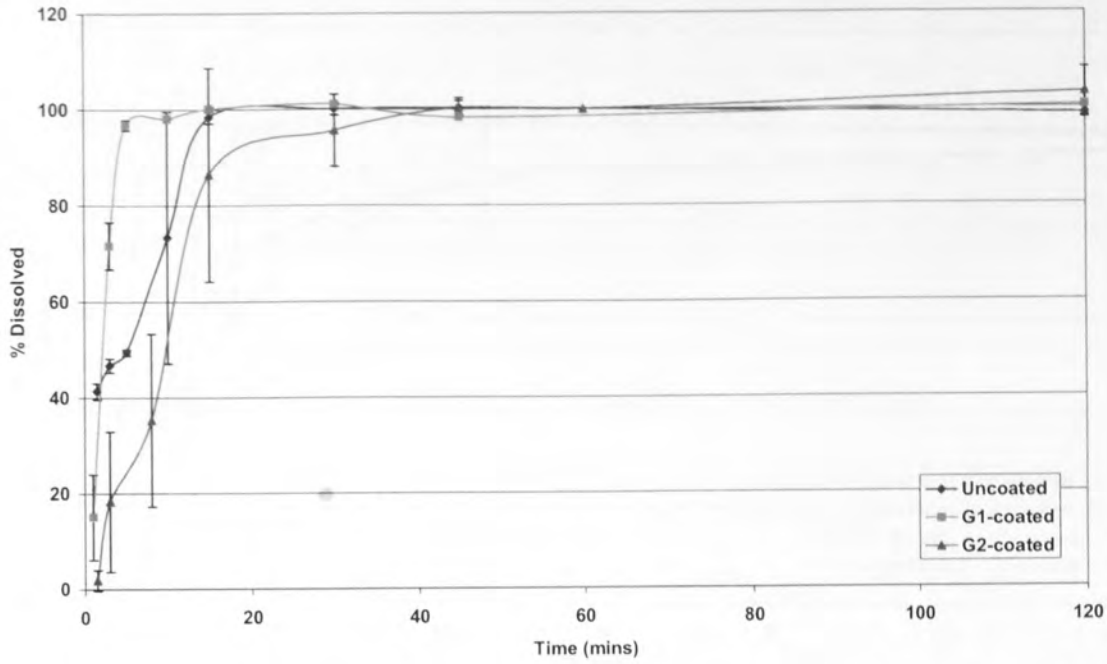


Figure 5.22- Paracetamol dissolution of uncoated, wrap-coated G1 and G2 formulations containing core formulation 2 (with sodium bicarbonate) *(0.05M HCl 30 rpm, n=3, mean±S.D.)*

5.3.4 Results and discussion for cellulose-based coatings

Several cellulose-based film-formulations were studied as pre-formed films and a limited number were identified as suitable for the wrap-coating technology. The most suitable film found was the **C1**-formulation (Table 5.3) and the pre-formed film had a high tensile strain with low elastic modulus. As discussed in previous sections, cellulose-based films were theoretically suitable for coating but did not adhere onto the tablet core with heating, therefore a spray of polymer solution was applied to the tablet cores prior to the wrap-coating process. An aqueous/organic polymer solution (5% w/v HPC in 50% v/v ethanol) was used as the glue for the coating process for tablet core formulations 1 and 2.

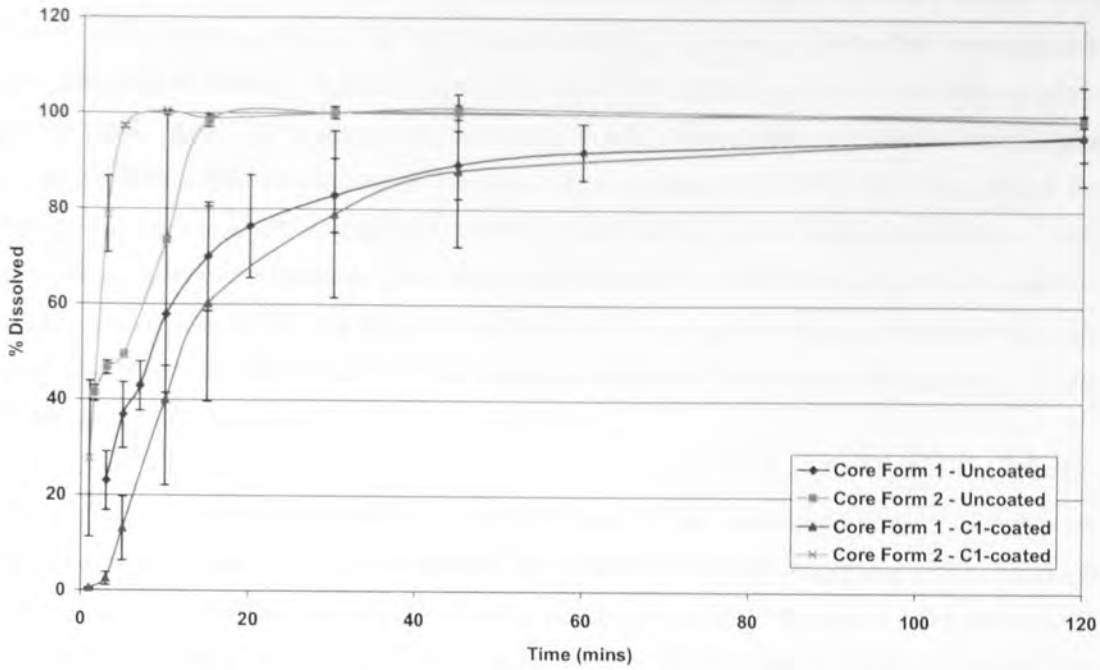


Figure 5.23- Paracetamol dissolution of uncoated, wrap-coated C1 formulations containing core formulation 1 (without sodium bicarbonate) and core formulation 2 (with sodium bicarbonate) *(0.05M HCl, 30 rpm, n≥3, mean±S.D.)*

Similarly to gelatin-coated formulations, the cores containing sodium bicarbonate are dissolved faster than core formulation 1. Uncoated and **C1**-coated versions of formulation 1 dissolve differently after 3 and 5 minutes whereby the coated core demonstrates an initial lag phase compared to the uncoated version. At later time points, however, the dissolution is similar (Figure 5.23). Wrap-coated (**C1**) sodium bicarbonate-containing formulation allows the dissolution process to be more consistent resulting in reduced variation compared to the uncoated formulation. Large standard deviations can be a result of core formulation as these tablets were manually compressed on tablet press. Also the dissolution is not decreased by the coating for the sodium bicarbonate containing formulations (Figure 5.23).

5.3.5 Conclusions for gelatin- and cellulose-based coatings

Gelatin is widely used in pharmaceutical applications due to its excellent film forming properties. It was also evident here that gelatin formulations can form robust films which can be utilised in the wrap-coating technology with ease. From initial wrap-coating studies (gelatin-glycerol formulations only), it was noted that the wrap-coating can affect the release rate of the active ingredient from the tablet core therefore there is a need for faster dissolving films for coating application. Dissolution of paracetamol wrap-coated solid dosage forms was not same between formulations coated with different coatings; initially in acid (30rpm) G2-

coated was slower compared to G1- and G3-coated cores, and at 15 minutes Panadol® was slower in dissolution compared to uncoated Panadol®, G1- and G3-coated formulations. From the results it seemed that G2-coated core was not as fast as other formulations; when the weight gain from the coating was measured, the G2-formulation had higher weight gain which could affect the dissolution of the core. The method of coating can also affect the dissolution of the core; dip-coated (G1-solution) formulations were slower dissolving in acid *versus* wrap-coated formulations. One reason for the slower dissolution could be the method of coating where solution forms stronger coating on the core once dipped whereas the wrap-coating may allow fast penetration of the dissolution medium underneath the coating leading to faster wetting of the core.

Usage of gelatin in the wrap-coating process proved to be successful and by varying the formulation, the required characteristics can be obtained *e.g.* fast dissolving films. Although the film-coating formulation can be designed to be fast dissolving, the tablet core formulation can override the effect of the coating as seen for the bicarbonate-containing coated core formulations (for both gelatin and cellulose-based coated cores). Although the pre-formed films had slight differences in mechanical or dissolution characteristics, it may be that these differences are not carried through to dissolution of the coated core and these small differences may not show at all in *in vivo*.

The wrap-coating process as described in this chapter was successfully applied for gelatin-based films whereas the cellulosic films were problematic due to non-adherence of the film itself onto the tablet core. A few coating studies were able to be carried out but the wrap-coating process, as described in this study, is not suitable for cellulose-based films.

5.4 Stability of paracetamol-based products

5.4.1 Introduction

A study to investigate the effect of humidity on dissolution was conducted on products which were wrap-coated with the gelatin-based film as high humidity can induce cross-linking in gelatin formulations (Digenis *et al.*, 1994) and therefore could affect the drug release. The wrap-coated formulations were stored for 1 month under ambient conditions and at high humidity, in order to investigate any differences. Also the effect of pepsin (O'Donnell *et al.*, 1997; Aikman *et al.*, 1998) on dissolution of gelatin-coated formulations was probed. The aim of the study was to determine the effect of humidity on the paracetamol release and whether the coating affects, for example, the initial release of the active ingredient.

5.4.2 Materials and methods

5.4.2.1 Materials

Materials are described in section 5.3.2.1.

5.4.2.2 Storage conditions

Panadol®, uncoated Panadol® and **G1** or **G2** wrap-coated formulations were stored at ambient temperature, in a closed container with a desiccator and in a closed container with saturated solution of sodium chloride which produces 75 % RH at room temperature. The formulations were kept under these two conditions for one month.

5.4.2.3 Dissolution

Dissolution was carried out in 0.05M HCl, 30 rpm with 900 mL of medium at 37 °C. In further studies, the effect of pepsin on the dissolution of gelatin-based wrap-coated formulations was explored, where three levels of pepsin were added to the dissolution media 0.8g/L, 1.6g/L and 3.2g/L.

5.4.2.4 Statistical analysis

Section 3.2.2.3 describes the statistical analysis used to assess the significance of the results.

5.4.3 Results and discussion

As a comparison for the coated formulations, the effect of humidity on the dissolution of Panadol® and uncoated Panadol® was also assessed. At early time points (5 and 10 minutes) dissolution of Panadol® initially is slower than Panadol® stored at 75 % RH for 1 month (Figure 5.24)– the initial lag period is eliminated after 1 month storage at high humidity. It may be that the has atmospheric water has plasticised the HPMC-coating further hence weakening it and resulting in a faster onset of dissolution (Villalobos *et al.*, 2006). Uncoated Panadol® dissolution did not change under the storage conditions applied ($p>0.05$). Also the dissolution of uncoated and **G1**-coated paracetamol cores (formulation 1) initially and after storage was similar, $p>0.2$ (Figures 5.25 and 5.26). Paracetamol dissolution after 1 month (Figure 5.27) is significantly faster at 10 and 15 minutes time points when compared to initial dissolution of paracetamol at t=0 ($p>0.05$). Wetting of the formulation may therefore be enhanced, leading to a faster initial dissolution rate.

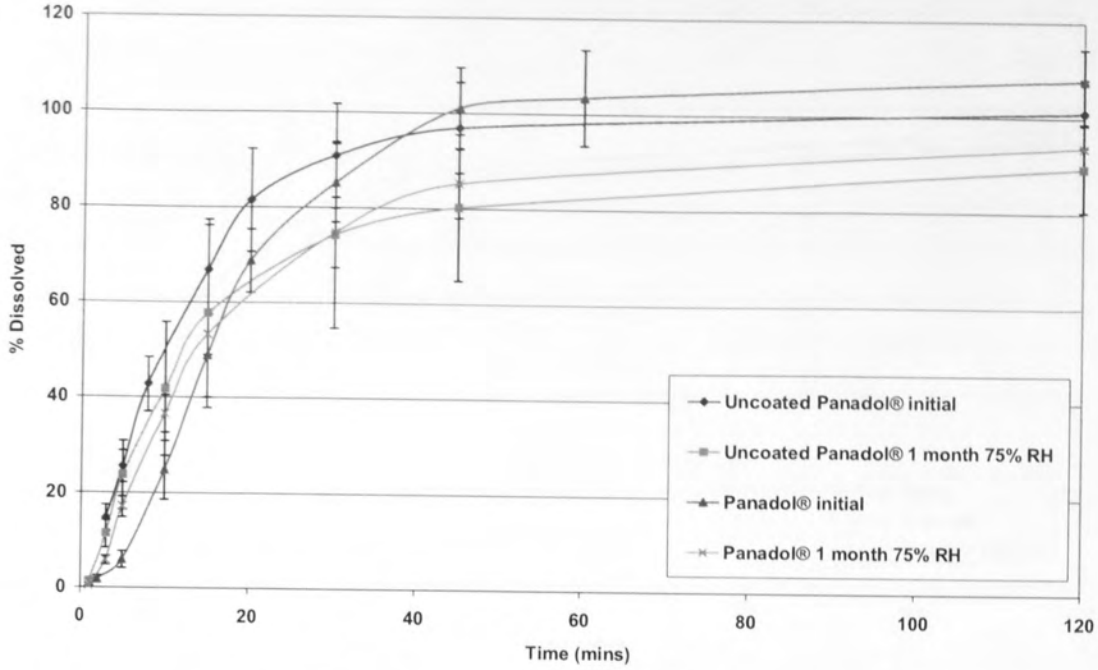


Figure 5.24- Paracetamol dissolution of uncoated Panadol® and Panadol® at start of stability and after 1 month in 75 % relative humidity *(0.05M HCl, 30 rpm, n=3, mean±S.D.)*

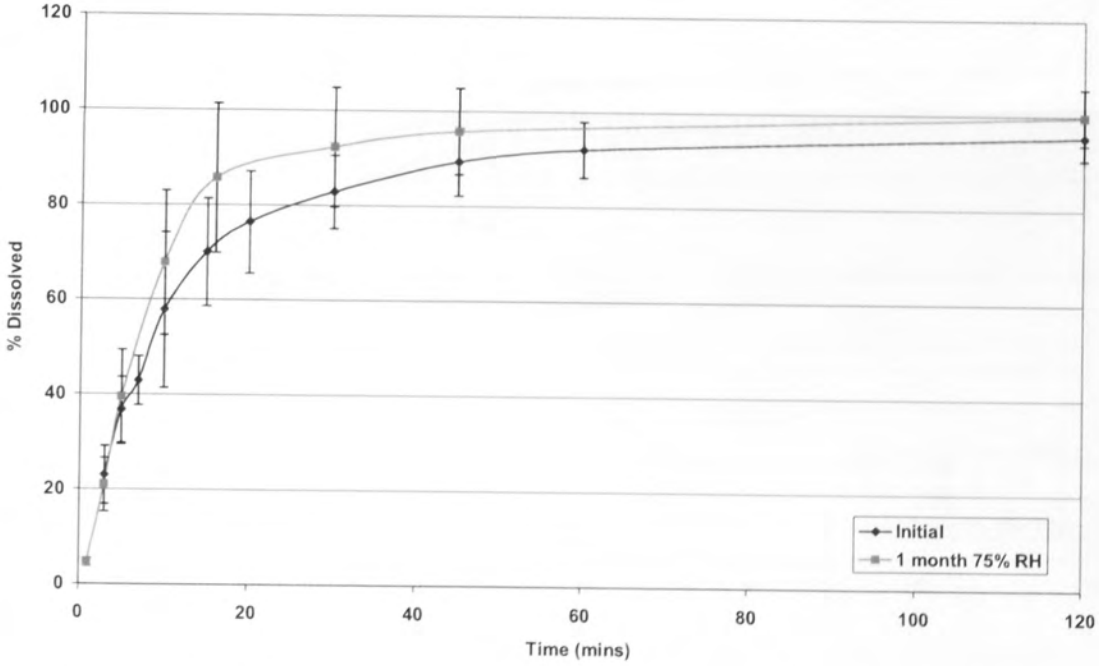


Figure 5.25- Paracetamol dissolution of uncoated core formulation 1 at start of stability and after 1 month in 75 % relative humidity *(0.05M HCl, 30 rpm, n=3, mean±S.D.)*

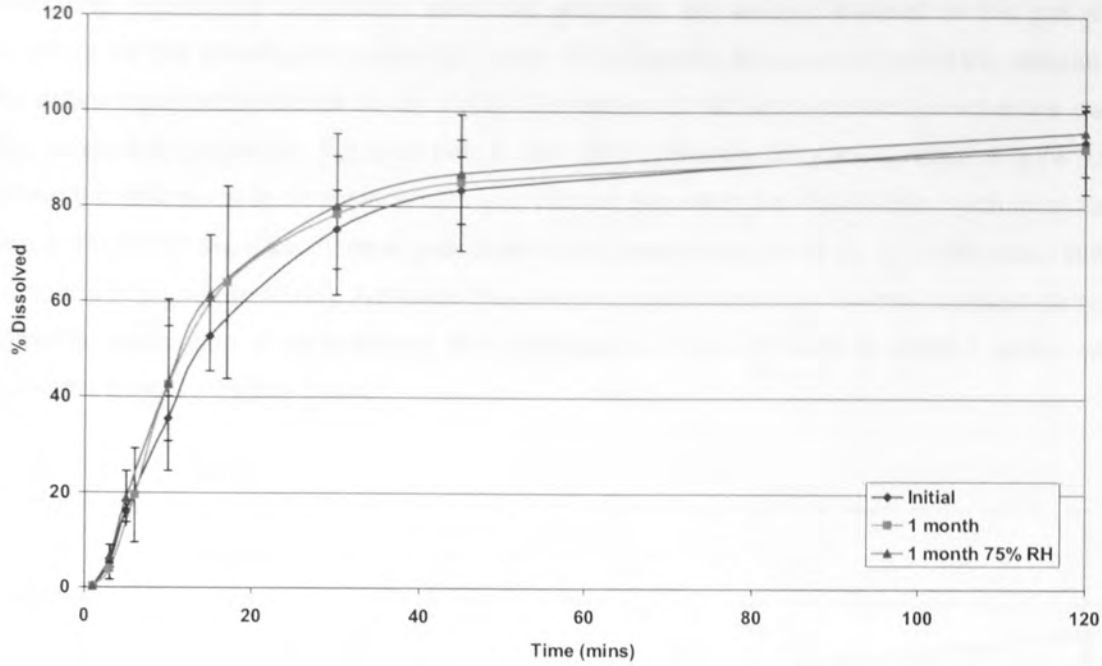


Figure 5.26- Paracetamol dissolution of G1-coated core formulation 1 at start of stability, after 1 month at ambient conditions and in 75 % relative humidity *(0.05M HCl,30 rpm, n=3, mean±S.D.)*

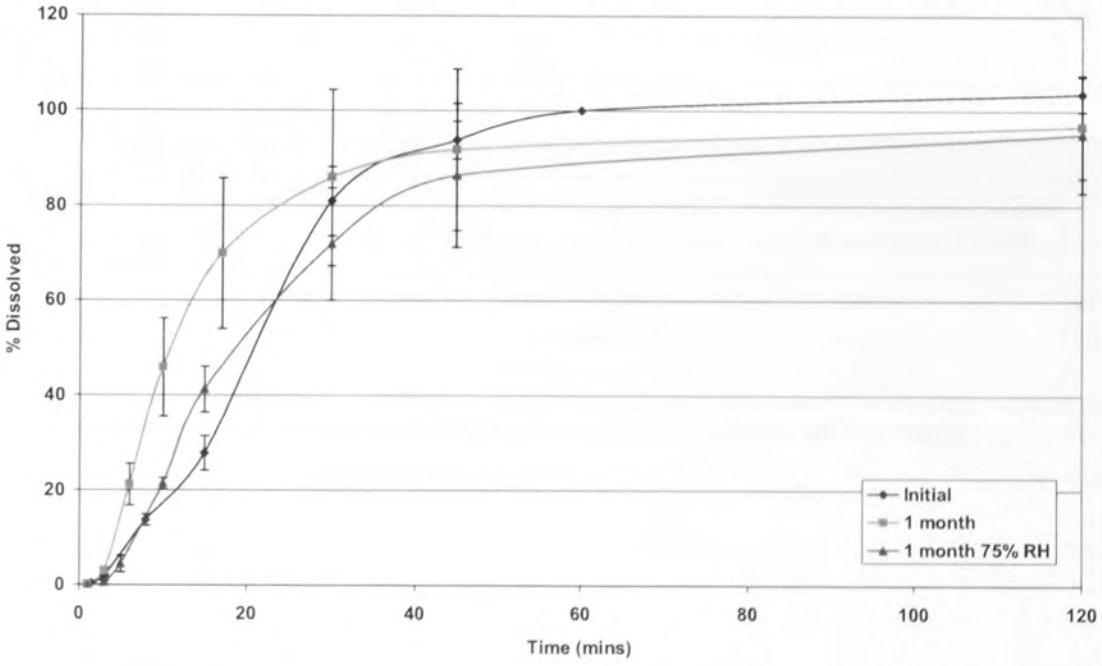


Figure 5.27- Paracetamol dissolution of G2-coated core formulation 1 at start of stability, after 1 month at ambient conditions and in 75 % relative humidity *(0.05M HCl,30 rpm, n=3, mean±S.D.)*

A Gelatin Capsule Working group has suggested that a second tier should be added to the standard USP and NDA/ANDA dissolution tests for gelatin capsules and gelatin-coated tablets where the inclusion of enzymes in the dissolution media would be allowed. The

reasoning behind the suggestion was that enzymes are always present in the gut and therefore aid the breakage of potentially cross-linked gelatin which could inhibit the release of the active ingredient (Aikman *et al.*, 1998). Dissolution of **G2** wrap-coated formulations were also studied in presence of pepsin before and after exposure to high humidity. Figure 5.28 shows the difference in dissolution with and without pepsin in the dissolution medium at zero time point where the dissolution is increased during early time points (3, 5, 10 minutes) in the presence of pepsin ($p<0.05$). Although the difference was significant before exposure to high humidity, dissolution of paracetamol after exposure to 75 % RH with or without pepsin was the same ($p>0.05$, Figure 5.29).

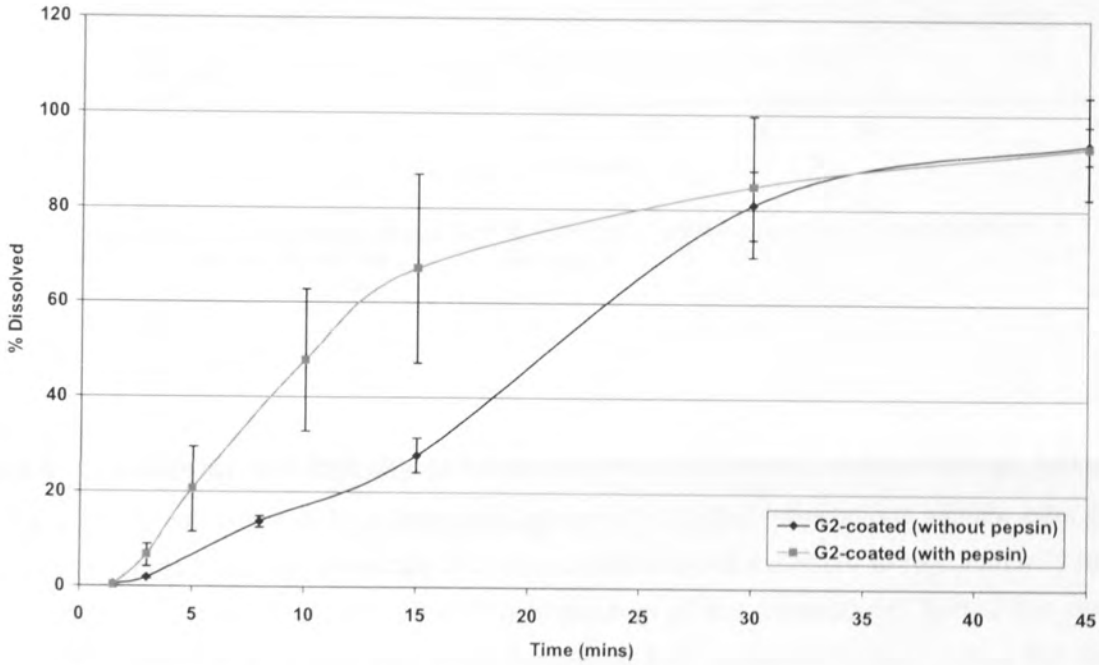


Figure 5.28- Paracetamol dissolution of G2-coated core formulation 1 in medium without and with pepsin 1.6g/L before exposure to humidity *(0.05M HCl, 30 rpm, n=3, mean±S.D.)*

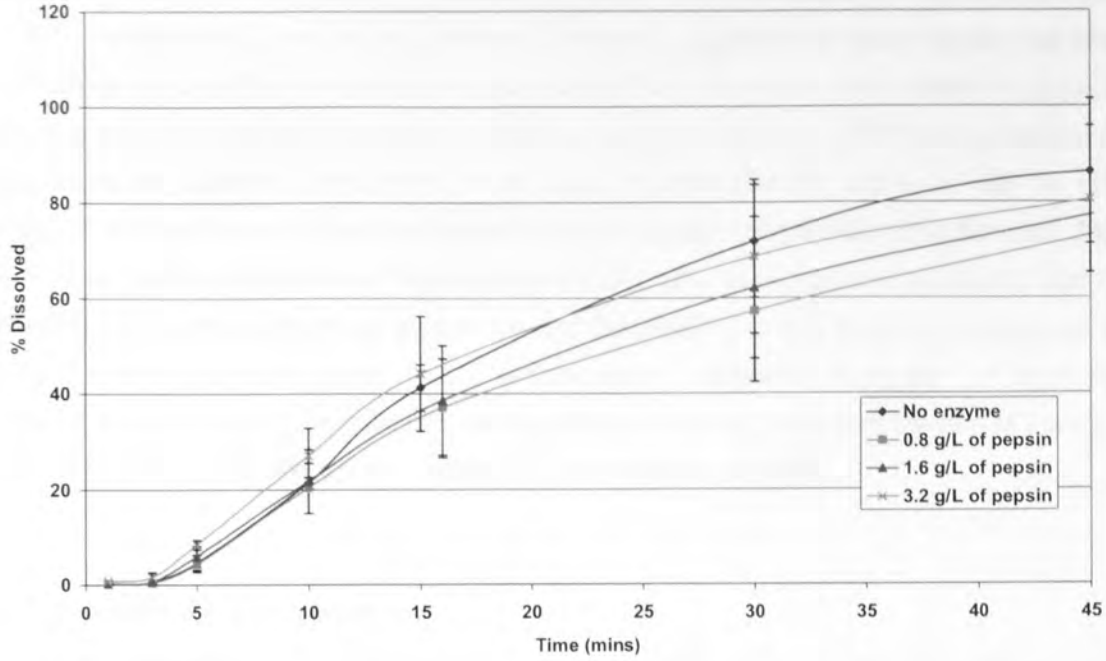


Figure 5.29- Paracetamol dissolution of G2-coated core formulation 1 after exposure to 75% RH for month *(0.05M HCl, 30 rpm, n=3, mean±S.D.)*

5.4.4 Conclusion for stability of paracetamol-containing coated dosage forms

This study did not show major differences between the coated formulations initially, after one month at RT and 75% RH therefore it can be concluded that exposure to high humidity for a short period of time should not affect the dissolution of the paracetamol from these novel coated dosage forms. It has also been suggested that enzymes (pepsin) affect the drug release *in vivo* where the pepsin aids the breakage of the coating polymer, typically gelatin. Addition of pepsin to the dissolution medium did not increase the dissolution of paracetamol. The increased dissolution effect in the presence of enzymes would only be evident if actual cross-linking of gelatin had occurred during the storage.

5.5 Dissolution of ibuprofen-based products

5.5.1 Introduction

Marketed ibuprofen products typically contain film- or sugar-coating which can inhibit the onset of drug release if the coating formulation is not optimised. Also formulation of the tablet core can affect the drug release especially as ibuprofen is a poorly soluble drug. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects which

makes it preferable medication in treatment of fever in combination with inflammation (BNF 2003), therefore fast onset of drug release is required. Ibuprofen is widely studied but effect of coating on ibuprofen release from solid dosage form has drawn little attention. Ibuprofen release from press-coated formulation was reported by Sirkiä *et al.* (1994) and some studies sugar-coated ibuprofen formulations have been reported (Saville, 2001) as well as other types of dosage forms such as fast dispersible formulations (Schiermeier and Schmidt, 2002; Fini *et al.*, 2008). Conventional film coatings on ibuprofen core may not be studied due low solubility of ibuprofen therefore it could be that fast dissolving thin polymer coatings do not play a role on ibuprofen dissolution. The film-coatings described in section 5.4 were also studied as wrap-coating formulations on ibuprofen-containing cores and the aim of the study was to determine the effect of the coating on dissolution of ibuprofen.

5.5.2 Materials and methods

5.5.2.1 Materials

Ibuprofen, lactose (filler/binder), maize starch (disintegrant), colloidal silicon dioxide (glidant), croscarmellose sodium (disintegrant), microcrystalline cellulose (binder/disintegrant) and magnesium stearate were supplied by GlaxoSmithKline, Dungarven, Ireland. Sodium chloride, potassium dihydrogen phosphate and di-sodium hydrogen orthophosphate dihydrate were purchased from Sigma-Aldrich, UK. Direct compression lactose was purchased from DMV International, Netherlands. The water was double distilled in the laboratory using Fisons Fi-Streem 4 litre bi distillation unit.

5.5.2.2 Solubility

Ibuprofen solubility was measured in Sørensen's phosphate buffer pH 6.8. Ibuprofen was added to the buffer until no more dissolved. The saturated solutions (n=3 for each condition) were left overnight into a shaking water bath (80 strokes per minute, RT and 37°C), the saturated solution was checked visually and pH adjusted to the starting pH with NaOH or HCl and if required, more ibuprofen was added. The solubility of ibuprofen in pH 6.8 was found to be 8.27 ± 0.19 mg ml^{-1} at 37 °C which agrees solubility results of Shaw (2001).

5.5.2.3 Direct compression mix

Excipients for direct compression (formulations Table 5.6) were accurately weighed on an Acculab balance (Sartorius Group ALC-80.4) or Mettler PC4000 (Mettler Instrumente AG). Excipients were sieved (710 µm sieve) and then mixed mechanically for 10 minutes. The direct compression mix was stored in a sealed container until further use.

Excipient	Function
Ibuprofen	API
Lactose DC	Binder/Filler
Microcrystalline cellulose	Binder/Disintegrant
Maize starch	Disintegrant
Colloidal silicon dioxide	Glidant
Croscarmellose sodium	Disintegrant
Magnesium stearate	Lubricant

Table 5.6- Ibuprofen core formulation

5.5.2.4 Compression

The tableting mass was compressed with a Manesty E2 Press using a capsule-shaped die with a break-line on one side of the tablet (I-Holland, UK). Tablets were compressed to result in a crushing strength of > 200 N, measured with a Schleuniger-4M Tablet Hardness tester. The same tablet shape and size was used for all core formulations and the fill-depth was set according to the appropriate strength of the tablet therefore the drug content between different core formulations was not constant. In order to compare different core formulations in the same figure, the dissolution profiles were adjusted so plateau of the profile was assumed to correspond to complete dissolution of the drug and the profiles were normalised to 100%.

5.5.2.5 Wrap-coating

Wrap-coating procedure described in detail in section 5.2.

5.5.2.6 Dissolution

Tablet dissolution was carried out as described in section 3.2.2.1. Additionally a number of studies were carried out in Sørensen's phosphate buffer pH 6.8 with temperature of the medium at 37.0 ± 0.5 °C with a paddle speed of 50.0 ± 0.5 rpm.

5.5.2.7 Statistical analysis

Section 3.2.2.3 describes the statistical analysis used to assess the significance of the results.

5.5.3 Results and discussion

Dissolution of the compressed ibuprofen (coated or uncoated) is faster than commercially available ibuprofen dosage forms (Chapter 3 and Figure 5.30) but there are no differences between the uncoated formulation *vs.* wrap-coated formulations in pH 6.8 buffer. The effect of paddle speed on dissolution of uncoated and G2-coated ibuprofen was studied in order to determine whether differences between the uncoated and G2-coated formulations would be evident if the paddle speed was slowed down (Figures 5.31 and 5.32). As expected, overall dissolution rates are slower at reduced paddle speeds, but if the uncoated core dissolution is compared to the **G2**-coated core, they are not different at selected 15, 30 nor 50 rpm paddle speeds. For these compressed ibuprofen formulations, it can be said that the coating does not play a role in the dissolution of ibuprofen but the core effect is more prominent. For the commercially available ibuprofen formulations it was discussed that the coating plays a role together with the core formulation (Chapter 3). These novel coating formulations are therefore successful formulations as they do not inhibit the onset of the drug release *in vitro*.

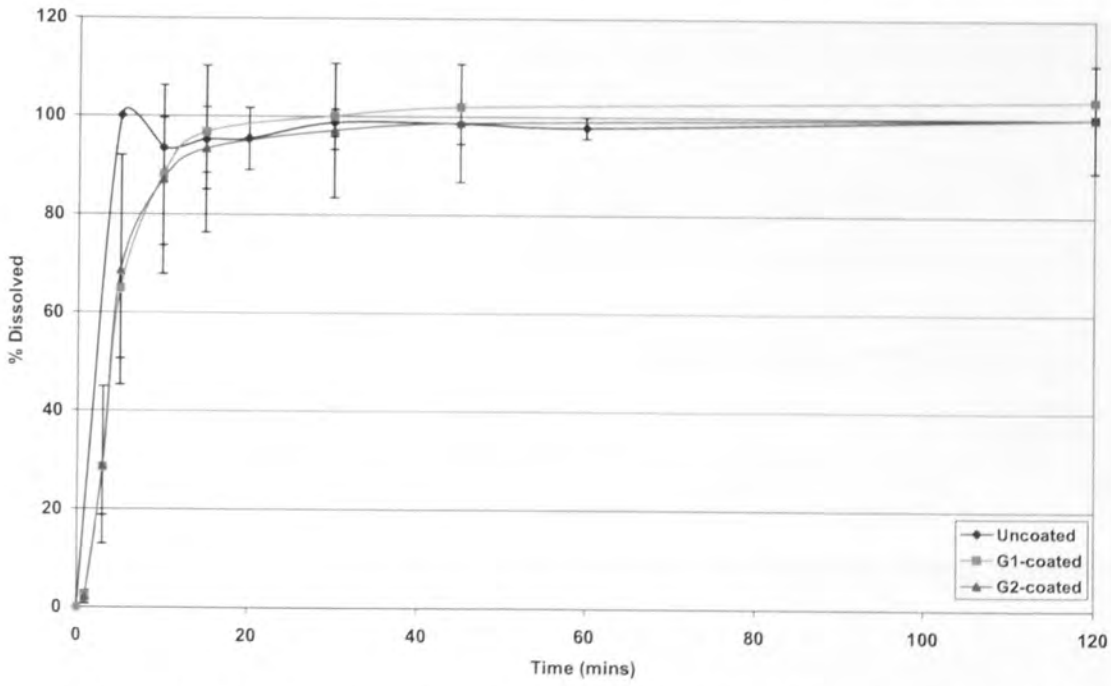


Figure 5.30- Ibuprofen dissolution of uncoated, G1-coated and G2-coated core formulation *(pH 6.8, 50 rpm, n≥3, mean±S.D.)*

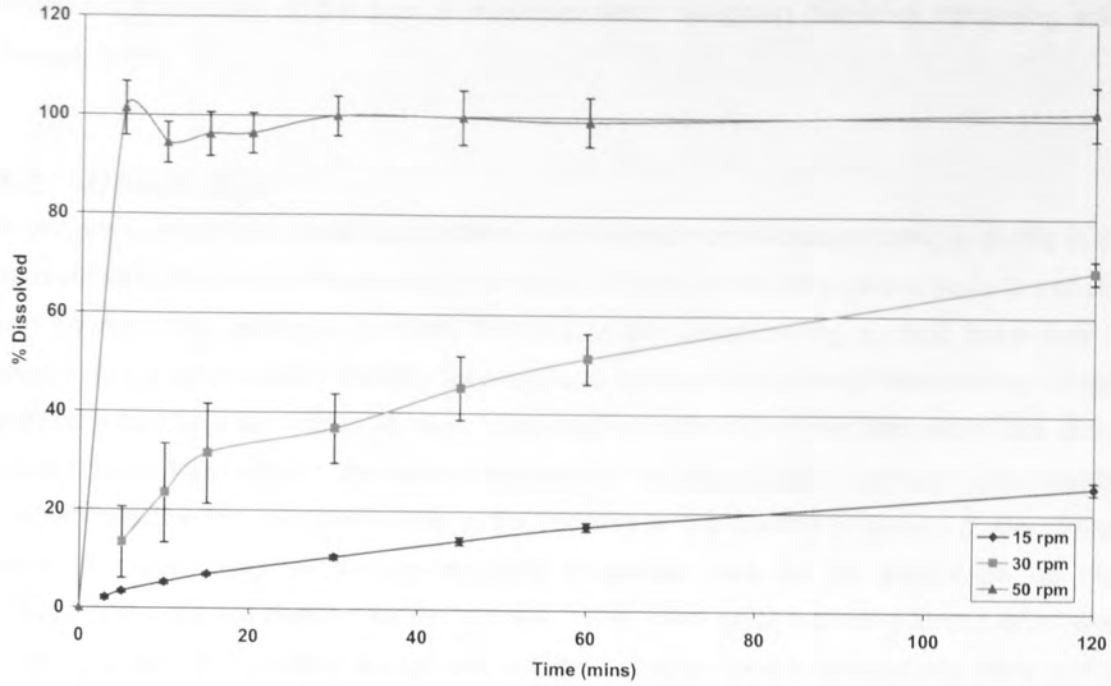


Figure 5.31- Ibuprofen dissolution of uncoated core formulation with varying paddle speed *(pH 6.8, 50 rpm, n=3, mean±S.D.)*

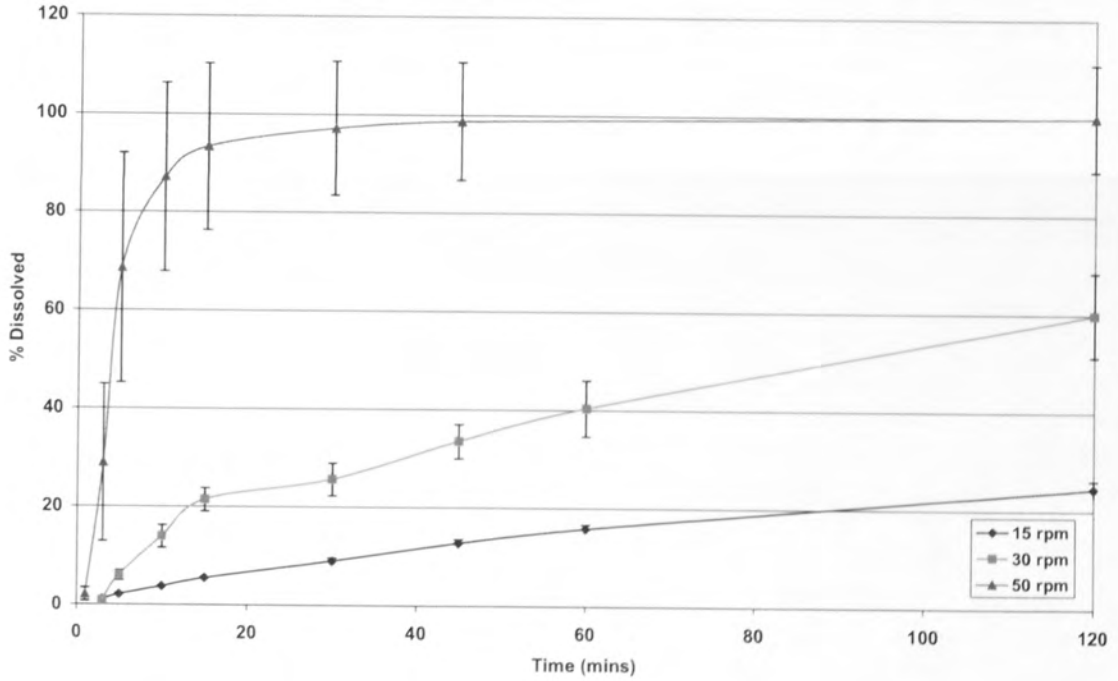


Figure 5.32- Ibuprofen dissolution of G2-coated core formulation with varying paddle speed *(pH 6.8, 50 rpm, n=3, mean±S.D.)*

5.5.4 Conclusion for stability of ibuprofen-containing coated dosage forms

The effect of the wrap-coating on the dissolution of ibuprofen was shown to not affect the dissolution of ibuprofen, even if the paddle speed for the dissolution test was varied.

Therefore formulation of the core is important when designing ibuprofen containing solid-dosage forms.

5.6 Conclusion

There are several commercial paracetamol and ibuprofen solid-dosage forms available in the market place. Majority of these dosage forms are tablets which are conventionally film coated and although film coating is probably the most widely used coating method, there may be room in the pharmaceutical industry for alternative methods for coating. Here another coating method was discussed and evaluated; wrap-coating method requires films which are strong enough to be handled and also elastic enough for the actual coating process. Also thermal properties of the film can play a role in the success of the coating process *e.g.* low melting point of gelatin and its thermo-reversible properties can be an advantage as high temperatures are not needed for the process. The novel gelatin coating formulations were successful with this coating equipment but the cellulose-based formulations were not as successful; this may be due to mechanical and thermal properties of the cellulose-based films.

Chapter 6-

Film formulations for intraoral delivery

6.1 Introduction

Conventional oral dosage forms consist of tablets and capsules which are swallowed before they start to dissolve and release the active ingredient. Solutions are also considered as oral dosage forms due to same method of administration. Active ingredients from these dosage forms are exposed to *e.g.* enzymes in the digestive tract which can cause first pass metabolism and therefore inefficiency in absorption (Pfisher and Ghosh, 2005). Orally disintegrating dosage forms could be an alternative way to deliver drugs without unwanted side effects. These are also considered as a suitable dosage form for patients, who are unable to swallow or require fast onset of the drug effect. Hoogstraate and Wertz (1998) describe additional advantages of buccal absorption as follows: not painful, buccal mucosa is well vascularised and very little irritation is expected.

As described in Chapter 1, there are already several orally disintegrating dosage forms in the market; typically these are freeze-dried products or tablets. Ciper and Bodmeier (2005) described Fastcaps, fast disintegrating gelatin-based capsules and HPMC-capsules which did not exhibit the same fast disintegration as gelatin-capsules. The same group introduced later on a modified conventional hard gelatin capsules by introducing small holes into the capsule shell which then allowed fast disintegration of the capsule shell (Ciper and Bodmeier, 2006). Eouani *et al.* (2001) studied PVP-based film formulations and found that carbopol 971P, polycarbophil and carrageenan with PVP formed mucoadhesive matrix whereas sodium carboxymethylcellulose (Na CMC) was extensively hydrated so that the detachement force from the mucosa was lowered. Some other bioadhesive intraoral dosage forms are reported for ibuprofen (Perioli *et al.*, 2004), nicotine (Ikinci *et al.*, 2004) and some film-based orally disintegrating dosage forms has been reported for lidocaine (Li Wan Po and Mhando, 1984; Okamoto *et al.*, 2002), salbutamol sulphate (Mashru *et al.*, 2005) and bupivacaine (Bernardo *et al.*, 2003). Although film-based orally disintegrating dosage forms are fairly widely reported in the scientific literature, not many are available in the market place. As an example there is Triaminic® which is a thin polymer film which is applied on the tongue. It dissolves fast and is used as cough suppressant and nasal decongestant containing dextromethorphan (3.67 mg) and phenylephrine HCl (2.5 mg) as active ingredients (Triaminic®, 2008).

Thin films were studied in Chapters 4 and 5 as tablet coatings but it may be possible to utilise these also as orally disintegrating dosage forms. Naratriptan hydrochloride is used as treatment for acute migraine attacks (BNF 2003) and so far it is only available as tablets (Naramig® 2.5 mg tablet by GSK) for which the onset of relief is determined to be after 1.5 h

(Christensen *et al.*, 2001). Due to nature of illness (acute) and relative potency, naratriptan was chosen as a model drug for the film formulations.

The aim of the study was to determine if these thin polymer films would be suitable as intraoral delivery systems. The films were formulated and studied for their dissolution, *in vitro* penetration through a membrane and also for their mechanical and thermal properties.

6.2 Materials and methods

6.2.1 Materials

Sodium hydroxide, sodium chloride, magnesium chloride, calcium chloride, citric acid, potassium carbonate, potassium dihydrogen phosphate, sodium phosphate and PBS (pH 7.4) buffer tablets were purchased from Sigma-Aldrich, UK. HPMC 5cp and HEC (MW ~95000) were a gift from Hercules, UK. Hydrochloric acid S.G 1.18 (37%) was purchased from Fisher Chemicals, UK. Naratriptan hydrochloride was received from GSK, Weybridge, UK. Tesco Spearmint and Wrigley's Extra Ice breath fresheners were purchased from a local retailer, Birmingham, UK. Tesco Spearmint films consisted of sodium alginate, carrageenan, carob gum, flavourings, modified tapioca starch, microcrystalline cellulose, water, xylitol, maltitol, mannitol, aspartame, sucralose, acesulfame K, glycerol, menthol, sucrose esters of fatty acids, malic acid, citric acid, brilliant blue FCF and tartrazine. Wrigley's Extra Ice film consisted of sodium alginate, maltodextrin, flavourings, water, microcrystalline cellulose, glycerine, carrageenan, starch, soybean lecithin, aspartame, sodium saccharin, acesulfame K, neohesperidine DC, citric acid and colour E133.

6.2.2 Preparation of films

Cast films were prepared as described in Chapter 4 and detailed formulations are described in Table 6.1.

6.2.3 Preparation of artificial saliva

Artificial saliva was prepared according to Parker *et al.*, (1999), where the following ingredients were added together: potassium dihydrogen phosphate (2.5mM L^{-1}), sodium phosphate (2.4mM L^{-1}), potassium carbonate (15mM L^{-1}), sodium chloride (10mM L^{-1}), magnesium chloride (1.5mM L^{-1}), calcium chloride (1.5mM L^{-1}) and citric acid (0.15mM L^{-1}). pH of the solution was adjusted to 6.7 with sodium hydroxide or hydrochloric acid. Artificial saliva was prepared fresh for each day of experiment.

6.2.4 Solubility of naratriptan hydrochloride

A saturated solution of naratriptan hydrochloride in 20 mL of buffer was prepared and pH of the solution was adjusted to required pH with 0.1M HCl or NaOH. The saturated solution of three replicates was incubated over night in a shaking bath (80 strokes/minute) at RT. pH 1.2 to 3 solutions were prepared using Sørensen's glycine buffer, pH 4 was prepared using Sørensen's citrate buffer and pH 5.8 to 8 were prepared using Sørensen's phosphate buffer. The saturated solutions were analysed by HPLC to determine naratriptan concentrations as described in Chapter 2.

6.2.5 Dissolution of films

Dissolution of the films was carried out as described in the Chapter 4 but the dissolution medium was artificial saliva, pH 6.7. All dissolution experiments were repeated three times and the samples were analysed by HPLC for the drug content and by microviscometry for the polymer release. The HPLC method is described in Chapter 2 and the microviscosity method is described in Chapter 4.

6.2.6 *In vitro* penetration tests

The penetration studies were carried out using Hanson Research Franz Cells with Variomag electronic stirrer, and Polyscience® temperature controller. The temperature of the medium was kept at 37.0 ± 0.5 °C with constant stirring at 500 rpm. The buffer in receiver consisted of 7 mL of PBS, pH 7.4 and the same buffer was used as the wetting/donor solution (100µL). Samples (2 mL) were taken at pre-determined time points and then immediately replaced with fresh buffer maintained at correct temperature. Film size used for the penetration studies was 1 cm^2 and the area of membrane exposed to medium was 1.77 cm^2. All studies were carried out as replicates of 4-6.

The porcine oesophageal and buccal tissues used as the membrane were obtained from slaughter house and they were immediately dissected and frozen at -70 °C. Once needed for studies, they were thawed, immersed in the 60 °C water for 1 minute and the epithelium was removed easily from the remaining tissue (Diaz-del Consuelo *et al.*, 2005).

6.2.7 Mechanical and thermal analysis

Thermal properties, tensile strength and puncture strength tests were also carried out as described in Chapter 4.2.

6.2.8 Statistical analysis

Section 3.2.2.3 describes the statistical analysis used to assess the significance of the results.

6.3 Results and discussion

6.3.1 Solubility of naratriptan hydrochloride

The solubility of naratriptan hydrochloride (from now on called naratriptan) was measured over a pH range in order to determine the solubility profile of the naratriptan (Figure 6.1). The pKa of naratriptan 9.7 therefore naratriptan is in its ionised form in pH under its pKa *i.e.* at all physiological pHs. The lower solubility in acidic conditions may be due to interaction of ionised naratriptan with buffer solution, possibly forming a less soluble salt complex.

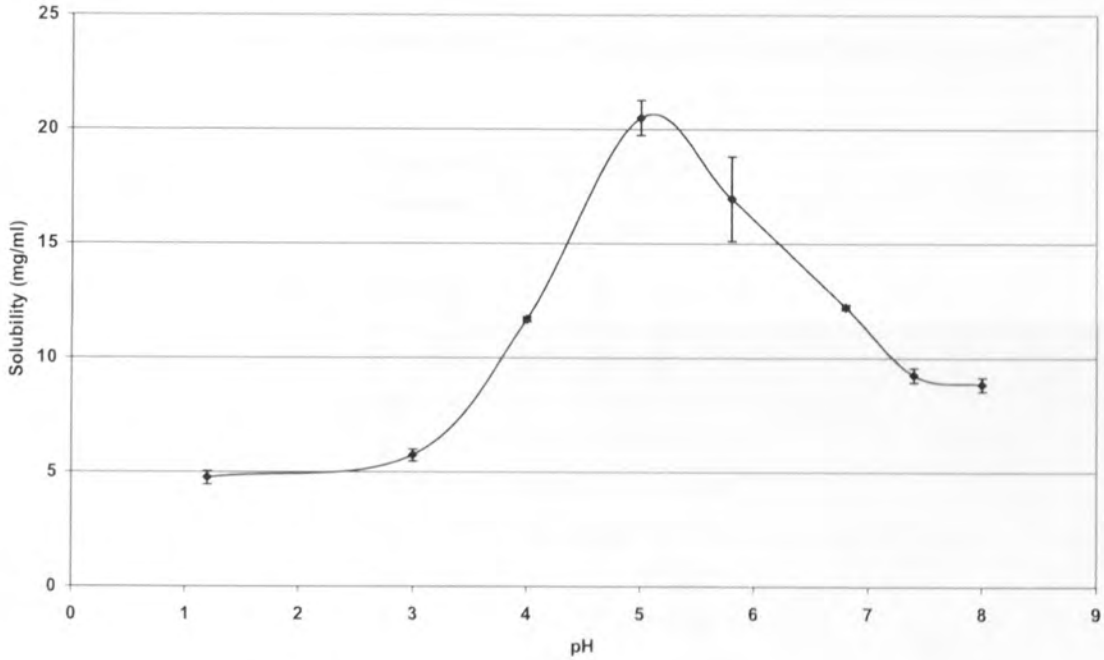
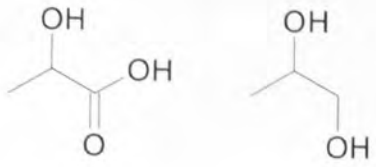


Figure 6.1- Solubility of naratriptan in various pH conditions *(n=3, mean±S.D.)*

6.3.2 Formulations

The described naratriptan work was carried out following the pre-formed film and coating studies (Chapter 4 and 5). According to previously described pre-formed film results two polymers, hydroxypropylmethylcellulose (HPMC) and hydroxyethylcellulose (HEC) were chosen as the basis of the film formulations due to their different nature and mechanical properties believed to affect the dissolution of the pre-formed films (Chapter 4); HPMC-based

films are typically stiffer compared to HEC-containing films and can affect the dissolution of the polymer matrix. Both of these basic formulations were then formulated with plasticisers, DL-lactic acid (DL-LA) and propylene glycol (PG), (Figure 6.2). Six film formulations were chosen for the study of novel dosage form for naratriptan. The actual compositions of the formulations are described in Table 6.1.



DL-LA PG

Figure 6.2- Molecular structures of DL-LA (MW 90.08 g mol^{-1}) and PG (MW 76.09 g mol^{-1})

	% with 1% (w/w) naratriptan in the formulation solution			
Formulation	HEC (w/w)	HPMC (w/w)	DL-LA (w/w)	PG (w/w)
A	**5**	-	-	-
B	-	**5**	-	-
C	**5**	-	**3.75**	-
D	-	**5**	**3.75**	-
E	**5**	-	-	**3.75**
F	-	**5**	-	**3.75**

Table 6.1- Formulations for naratriptan-containing films

6.3.3 Dissolution of polymer matrix

Dissolution of the films was carried out as described in section 6.2.4 and the changes in the viscosity of the dissolution medium were used to determine release of the formulation and the naratriptan concentration in the dissolution medium was analysed by HPLC. Only plasticiser- containing HEC-films showed similar dissolution profiles for analysis by microviscometry and HPLC (Figure 6.3). Figure 6.4 shows dissolution profiles of formulation

A which does not contain plasticiser and the lag on polymer release is significantly increased ($p=0.01$) compared to the HPLC-data. Due to these differences in the drug and polymer matrix release, these two methods are treated separately here.

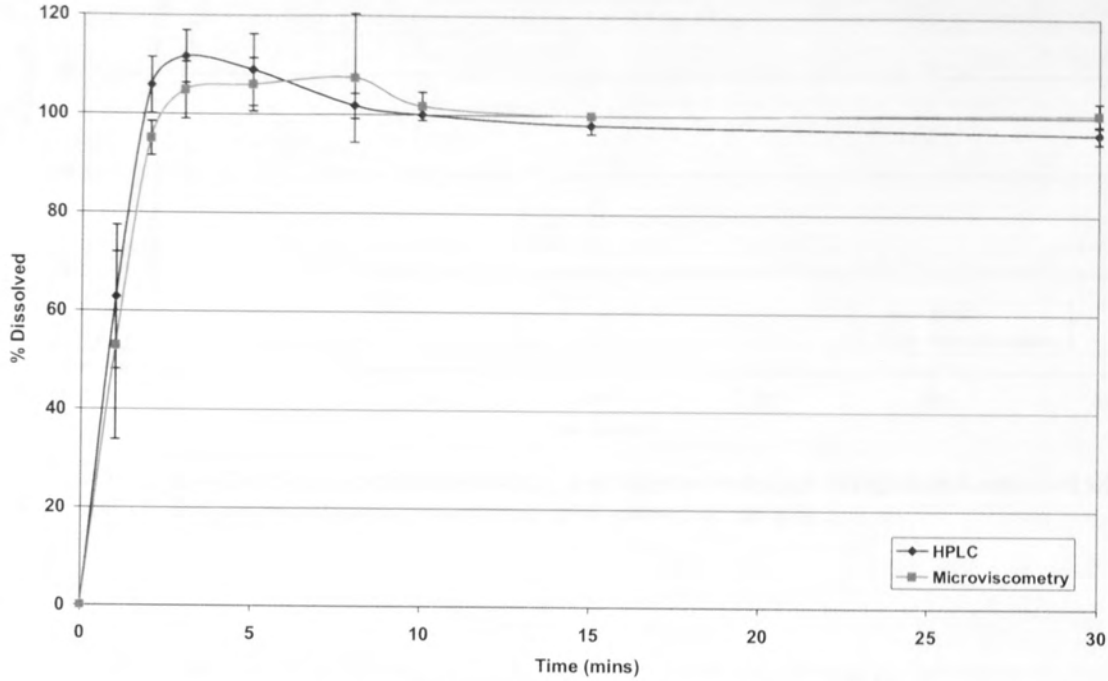


Figure 6.3- Dissolution profiles naratriptan and polymer matrix for formulation C analysed with HPLC and microviscometer, respectively *(n=3, mean±S.D., pH 6.7)*

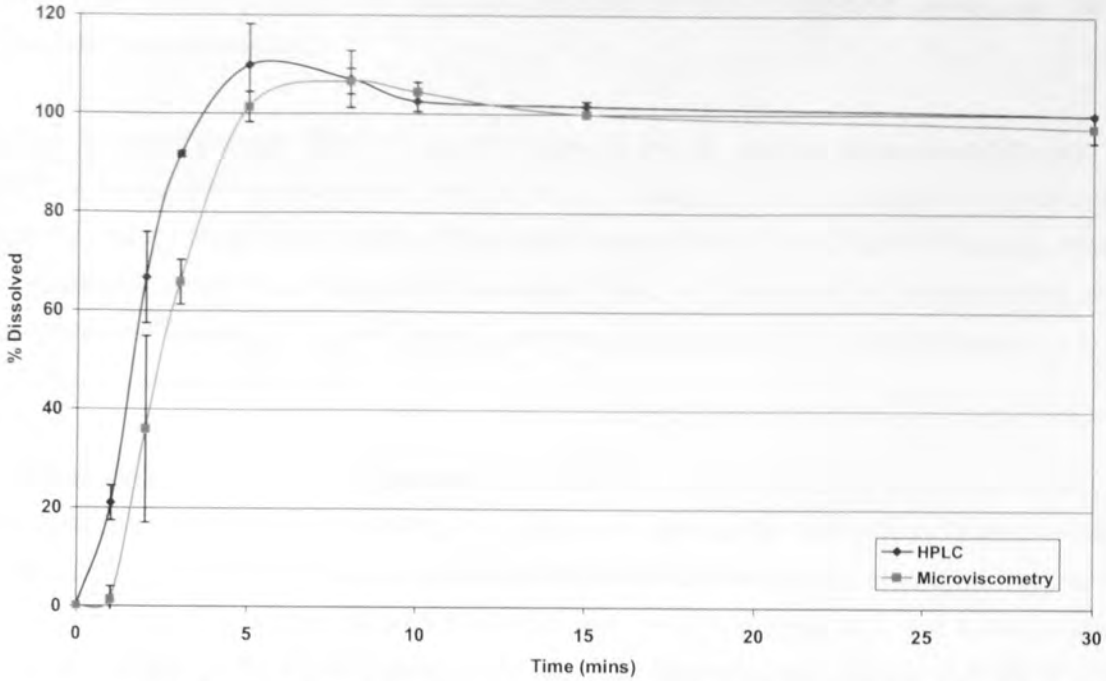


Figure 6.4- Dissolution profiles naratriptan and polymer matrix for formulation A analysed with HPLC and microviscometer, respectively *(n=3, mean±S.D., pH 6.7)*

	Microviscosity		HPLC	
Formulation	K_d (% min^{-1})	t_{lag} (min)	K_d (% min^{-1})	t_{lag} (min)
A	32.27 ± 1.74	1.01 ± 0.05	32.11 ± 1.18	0.10 ± 0.05
B	23.33 ± 27.11	-1.94 ± 2.80	44.60 ± 9.20	-0.01 ± 0.01
C	47.54 ± 1.74	-0.04 ± 0.13	52.92 ± 2.85	-0.06 ± 0.07
D	44.01 ± 16.30	0.48 ± 0.22	44.62 ± 9.17	-0.01 ± 0.01
E	54.58 ± 6.17	0.13 ± 0.03	55.51 ± 5.60	0.02 ± 0.05
F	12.68 ± 8.60	-2.46 ± 4.99	33.35 ± 4.42	-0.01 ± 0.01

Table 6.2- Dissolution rate and lag times of polymer matrix and naratriptan hydrochloride using microviscosity and HPLC analysis *(mean ± S.D., n=3, pH 6.7)*

The lag time for all formulations analysed by microviscometry was similar for the formulations ($p>0.05$). For polymer dissolution there is a high level of variability in dissolution rates suggesting that dissolution still happens so fast that the variation at start can be high but 100 % dissolution is reached in less than 5 minutes. Only formulation F deviates from this statement where the 100 % dissolution takes over 5 minutes (Figure 6.5). The design of the fast dissolving film formulations for intraoral delivery were successful as there is typically only 2-3 time points where dissolution happens. The limitation of the dissolution method for the

films is the sampling; it is done manually therefore addition of sampling points prior 100% dissolution is not possible.

Cellulose-based polymer films without plasticiser (A and B), are the same once dissolved in artificial saliva and no differences can be seen. Addition of PG as plasticiser significantly ($p<0.01$) slows down dissolution of the HPMC-based film (F) at 2 and 3 minutes when compared to same film formulation containing HEC (E) (Figure 6.5). In figure 6.6, the formulations containing DL-LA (C and D) are the same except at 1 minute where film D is significantly slower ($p=0.042$).

Addition of plasticiser typically increases the dissolution of the film as the plasticiser enters in between the polymer chains resulting in a softer and weaker film which may facilitate faster dissolution. This phenomenon is evident with HEC-formulations where, prior reaching 100 % dissolution, the film without plasticisers is slowest, $p<0.01$ (Figure 6.7). For HPMC-based films, formulation D (DL-LA film) was at 2 minutes significantly ($p=0.02$) faster than film F (PG film), otherwise it cannot be said that dissolution of the three formulations were different from each other (Figure 6.8).

There are some commercially orally disintegrating dosage forms, but no film formulations were available at the time of this study. A similar dosage form are the Tesco's and Wrigley's breath fresheners films which do not contain any active pharmaceutical ingredient. The dissolution of these films is fast as expected due to nature of the product (Figure 6.9). Also as comparison in the same Figure 6.9, it can be seen that the dissolution process can be controlled by designing the formulation according to needs *i.e.* by changing the formulations the dissolution can be slower or inclusion of higher viscosity polymer may result in much slower dissolution and possibly slower drug release.

Swelling of the films was also carried out according to the method described in Chapter 4, but the film dissolution was too rapid for any data to be measured.

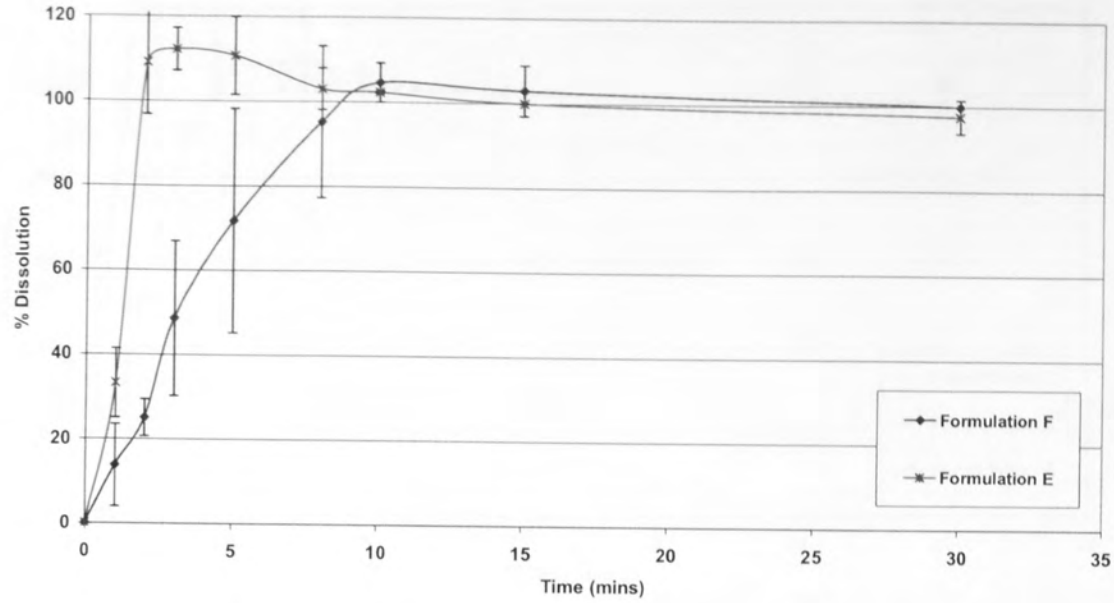


Figure 6.5- Polymer dissolution of naratriptan-containing polymer films F and E (analysed by microviscometry) in artificial saliva *(n=3, mean±S.D., pH 6.7.)*

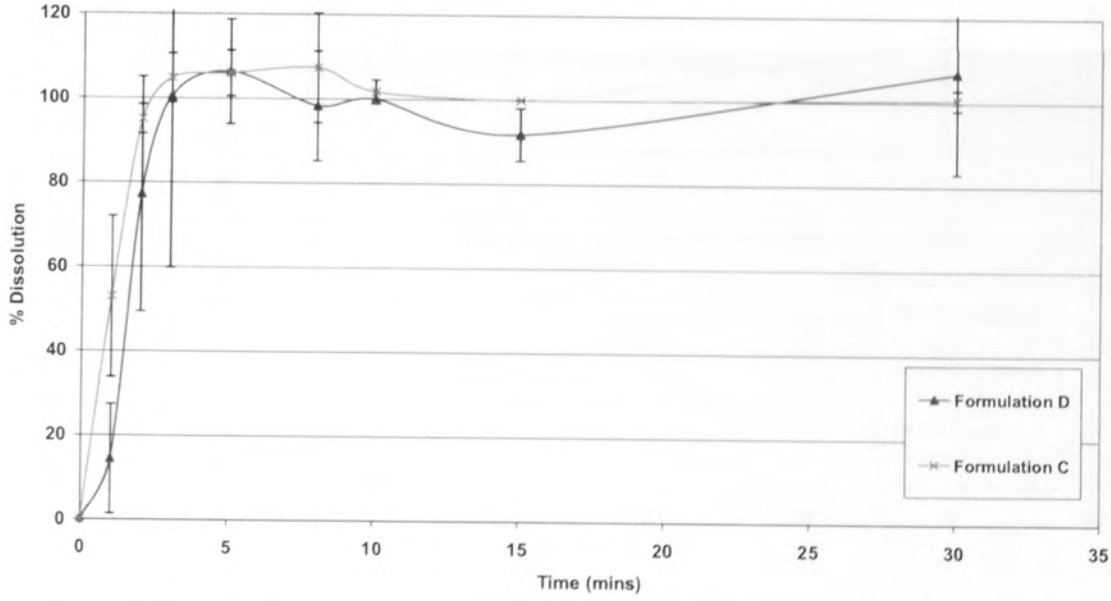


Figure 6.6- Polymer dissolution of naratriptan-containing polymer films D and C (analysed by microviscometry) in artificial saliva *(n=3, mean±S.D., pH 6.7.)*

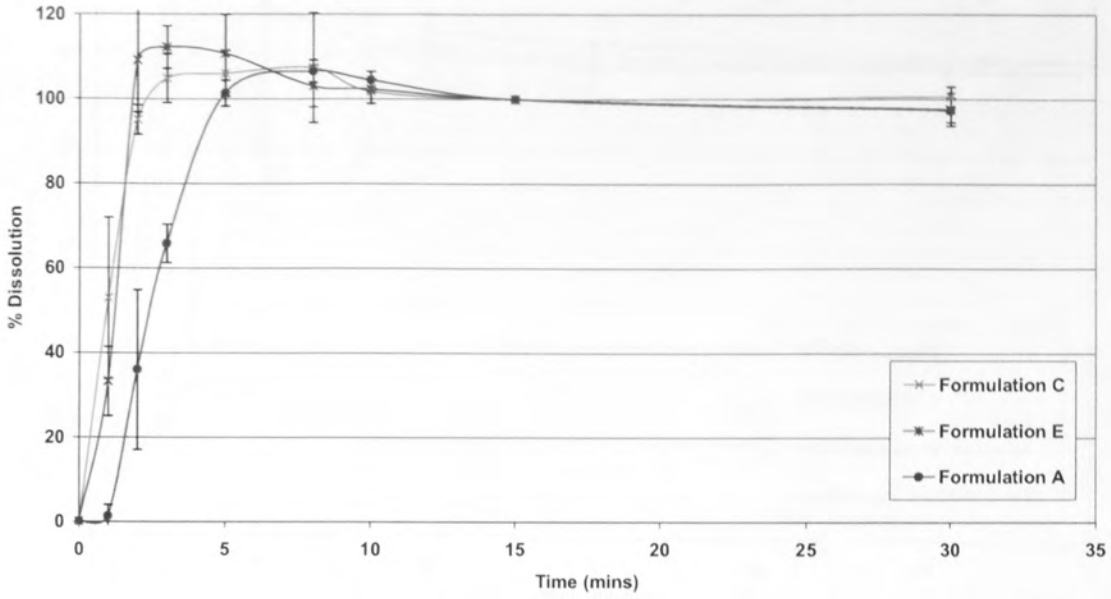


Figure 6.7- Polymer dissolution of naratriptan-containing polymer films C, E and A (analysed by microviscometry) in artificial saliva *(n=3, mean±S.D., pH 6.7.)*

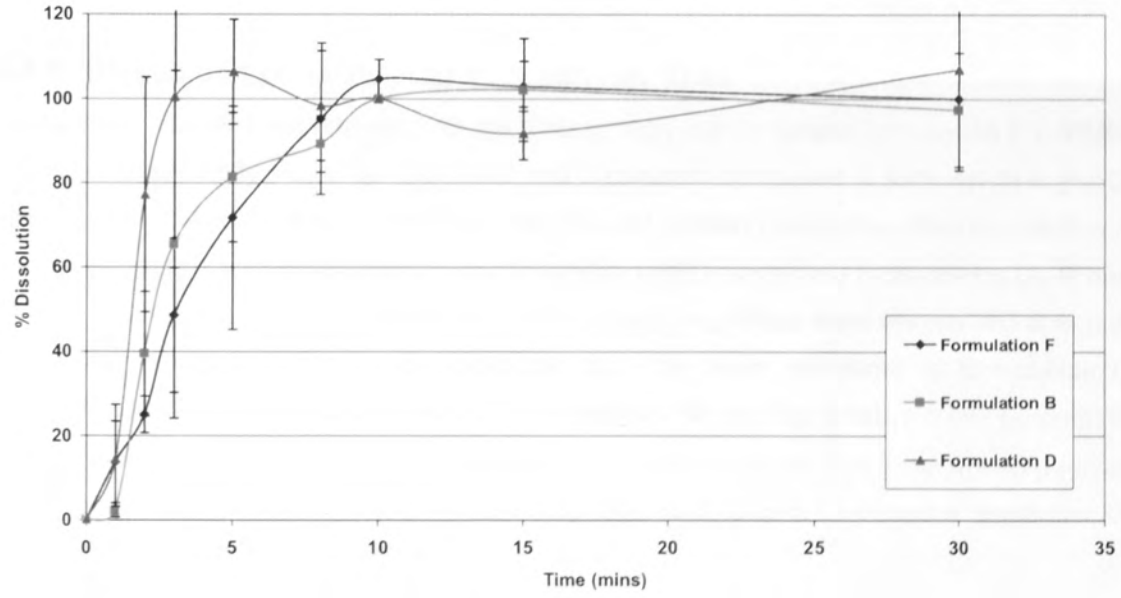


Figure 6.8- Polymer dissolution of naratriptan-containing polymer films F, B and D (analysed by microviscometry) in artificial saliva *(n=3, mean±S.D., pH 6.7)*

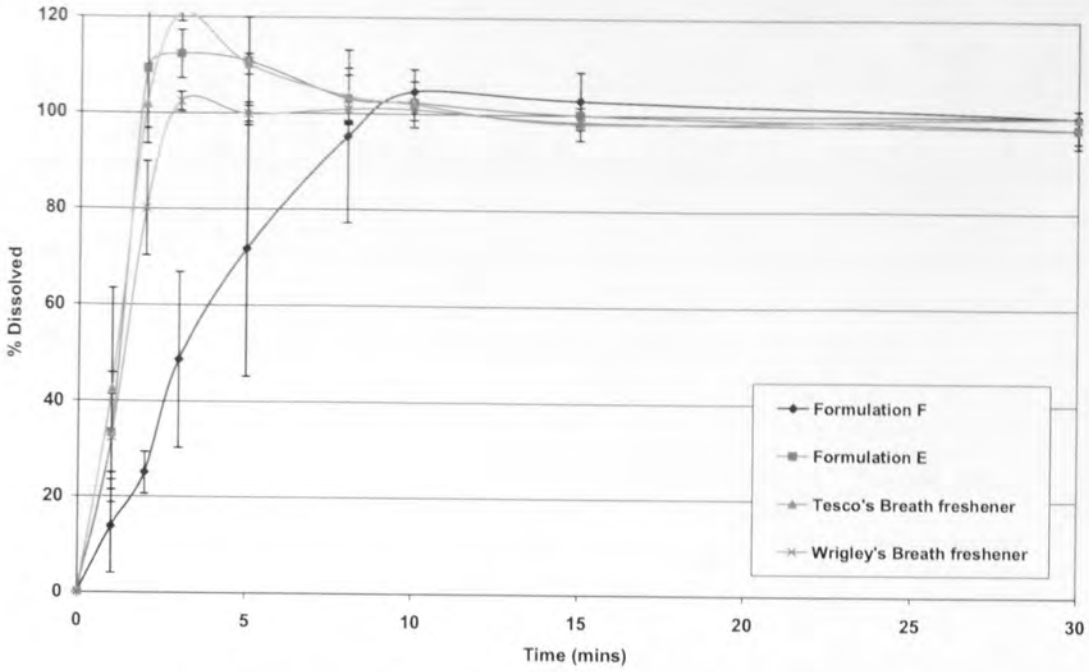


Figure 6.9- Polymer dissolution of naratriptan-containing polymer films F, E and drug-free commercially available Tesco's and Wrigley's breath freshener (analysed by microviscometry) in artificial saliva *(n=3, mean±S.D., pH 6.7.)*

6.3.4 Dissolution of naratriptan from polymer films

Same trend can be seen here as with microviscometry results where formulation F (HPMC-based) is significantly slower ($p<0.02$, at 2 and 3 minutes) compared to formulation E (HEC-based); both formulations are plasticised with PG and contain naratriptan. Also formulation A without plasticiser had the slowest drug release from HEC-containing formulations (A, C and E) with significance of $p<0.04$. Rate of dissolution and lag times were shown in Table 6.2; formulation A showed significantly increased lag time when compared to formulation C (contains DL-LA as plasticiser), $p<0.02$. The majority of the lag times for the naratriptan dissolution are close to zero or have negative values which indicate that there are no delay in the drug release from the film matrix (Table 6.2). Figures 6.10 to 6.13 show the dissolution of naratriptan from the film formulations.

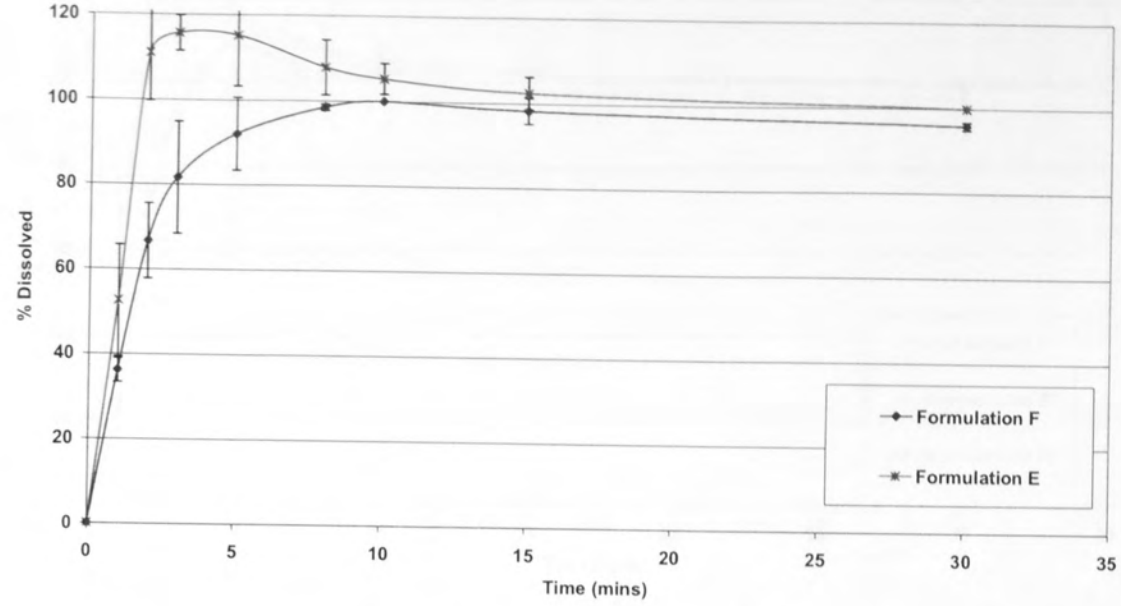


Figure 6.10- Dissolution of naratriptan from films F and E (analysed by HPLC) in artificial saliva *(n=3, mean±S.D., pH 6.7.)*

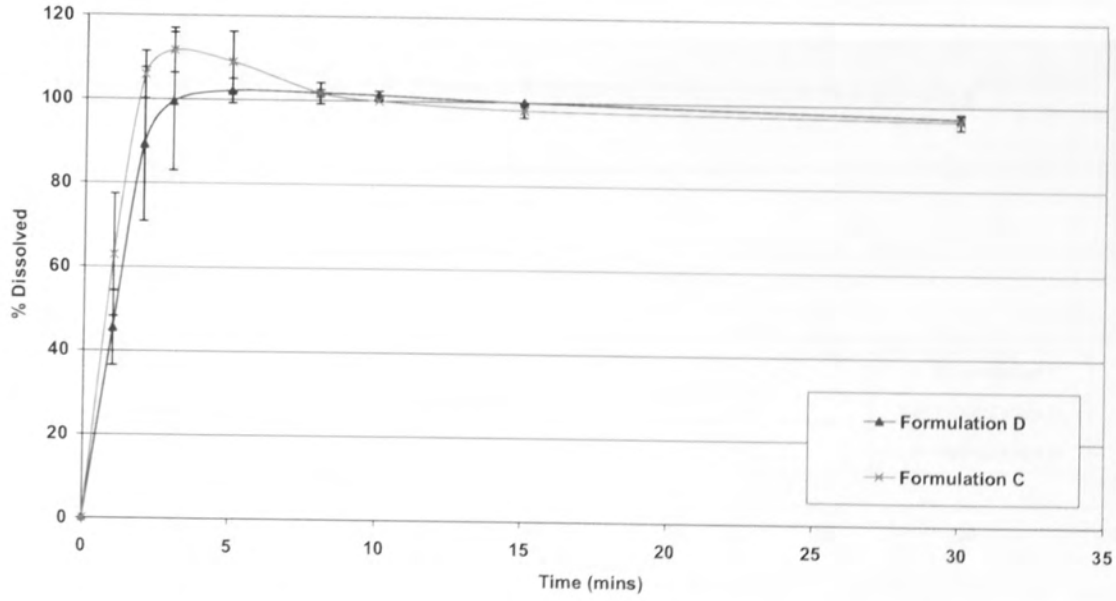


Figure 6.11- Dissolution of naratriptan from films D and C (analysed by HPLC) in artificial saliva *(n=3, mean±S.D., pH 6.7.)*

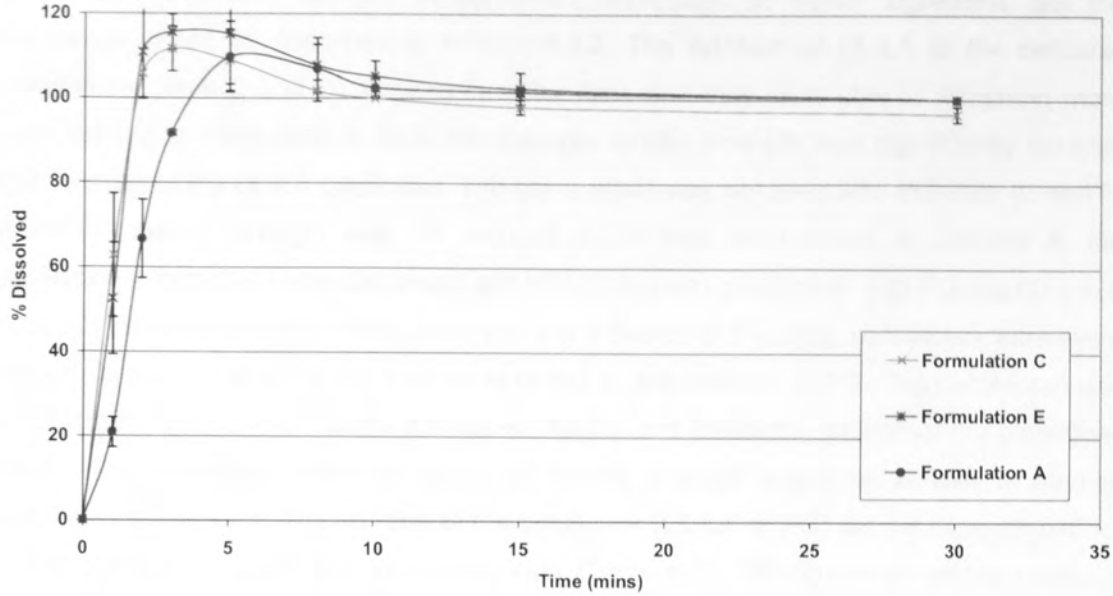


Figure 6.12- Dissolution of naratriptan from films C, E and A (analysed by HPLC) in artificial saliva *(n=3, mean±S.D., pH 6.7.)*

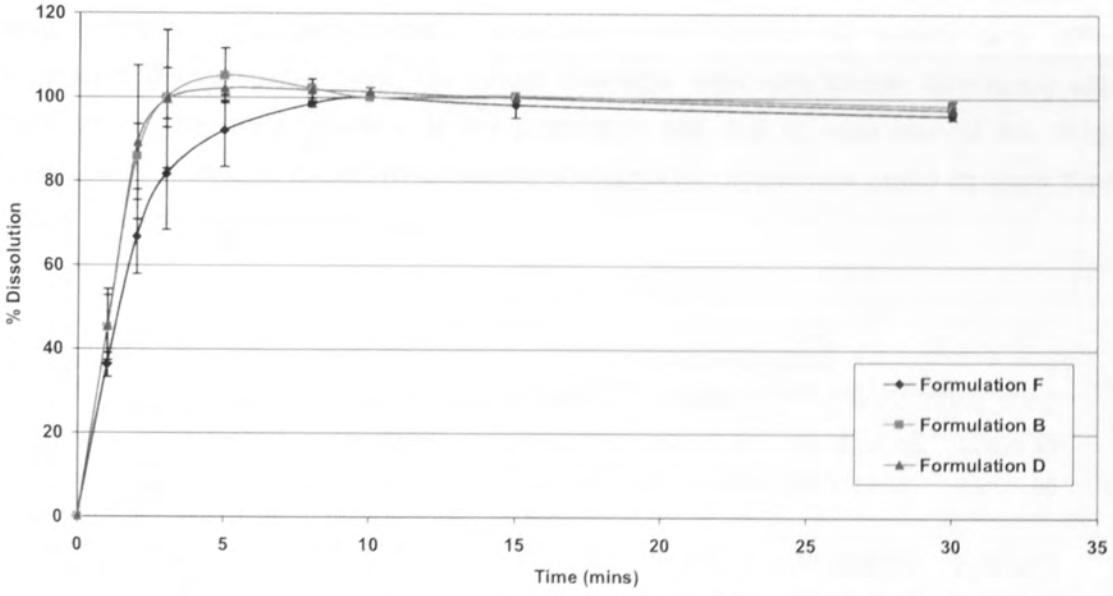


Figure 6.13- Dissolution of naratriptan from films F, B and D (analysed by HPLC) in artificial saliva *(n=3, mean±S.D., pH 6.7.)*

6.3.5 Mechanical and thermal studies

Films were formulated so that all contained naratriptan as active ingredient, but the formulation varied as described in section 6.3.2. The addition of DL-LA to the cellulose formulations (films C and D) resulted in softer films and they were able to withstand more strain leading to more flexible films; for example tensile strength was significantly lowered after addition of the DL-LA plasticiser. The same effect was not seen with PG-films (E and F) where the tensile strength was not reduced which was unexpected. In Chapter 4, the plasticising effect of PG was discussed and HPMC film was plasticised with PG resulting in a reduction in tensile strength. Here, however, the inclusion of the drug, naratriptan, conveys a strength to the film which is not then superceded by the addition of PG. The naratriptan can move in between polymer chains and cause rigidity and therefore counteract the plasticiser effect. The plasticizing effect of DL-LA on tensile strength was seen already in studies described in Chapter 4. The addition of the plasticiser (DL-LA or PG) did not have any effect on the puncture strength and puncture strain (Table 6.3). Differences in trends between tensile and puncture properties could be due to the different physical work applied on the film *i.e.* in tensile test the film is pulled apart whereas in the puncture test the probe is driven through the film describing more the rupture of the film.

As comparison for the puncture properties, the commercially available Tesco's and Wrigley's breath freshener films were tested; these films were significantly weaker and stiffer compared to the formulated films. The breath freshener films were broken very easily with fingers which may be a problem at the production site due to weakness of the films. Mechanical properties of these film formulations support this hypothesis where stronger films dissolve more slowly (section 6.3.3).

Formulation	Tensile properties			Puncture properties		
	σ_t (MPa)	ε_t (%)	EM_t (MPa)	σ_p (MPa)	ε_p (%)	EM_p (MPa)
A	8.56±1.32	69.53±5.35	0.12±0.02	12.48±0.94	126.05±27.68	0.30±0.13
B	48.20±2.40	4.52±0.82	13.29±2.00	20.17±3.08	22.21±2.95	3.21±0.96
C	4.91±1.25	116.67±19.48	0.03±0.01	-	-	-
D	19.56±3.92	6.60±2.26	6.37±1.70	15.60±4.29	18.96±2.72	2.38±0.70
E	8.01±1.60	72.65±6.82	0.08±0.02	12.22±2.44	100.45±18.06	0.25±0.08
F	50.32±1.40	5.03±0.98	14.03±2.36	17.23±2.63	20.84±2.98	3.28±0.35
Tesco	-	-	-	0.66±0.03	4.51±0.96	3.94±0.31
Wrigley	-	-	-	0.66±0.07	4.15±1.95	3.04±0.30

Table 6.3- Mechanical properties of naratriptan containing films and drug free breath fresheners*(key: Table 6.1; σ_t tensile strength; ε_t tensile strain; EM_t tensile elastic modulus; σ_p puncture strength; ε_p puncture strain; EM_p puncture elastic modulus; - too sticky to handle or sample size too small for the test; n≥3; mean ± S.D.)*

Formulation	DSC- Melting temperature	TGA- moisture content
	T (°C)	(%)
A	235.58±27.27	9.19±0.48
B	203.51±11.01	4.67±0.39
C	216.55±13.61	8.35±0.56
D	210.27±6.56	6.66±0.58
E	195.52±1.02	8.45±0.19
F	208.94 ±9.69	4.37±0.05

Table 6.4- Melting temperature and % moisture content of naratriptan containing films *(key:T_g transition temperature; n=3 mean ± S.D.)*

The literature value for melting point of naratriptan is 246 °C (GSK) which agrees with the result obtained here for melting of naratriptan at 246.9 °C. All formulated films demonstrated a lower transition temperature/melting which may be due to drug-excipient interaction. Figure 6.14 shows a typical DSC trace where can be seen T_g for naratriptan closely followed by the melting.

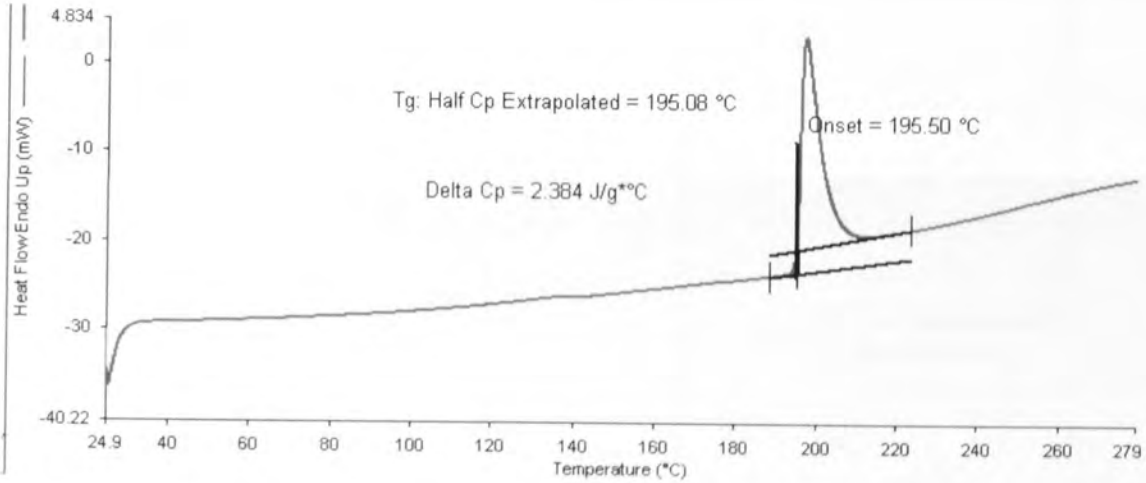


Figure 6.14- A typical DSC trace of film formulation E

6.3.6 *In vitro* permeation study

Initially the study set-up was done utilising 2 types of viskin tubing in order to optimise the technique. Two pore sizes of visking tubing were used (2-18/32" and 7000/2) to see if there are any differences in the diffusion of saturated naratriptan solution (0.5 mL aqueous naratriptan solution) through the membrane and the larger pore size allowed faster diffusion and the standard deviations were small (results not shown here). It was thought that the formulation may have an effect on the transfer of the drug and therefore the effect of

formulation design on drug diffusion through buccal mucosa was studied. In the literature it has been proposed that the most inner layer of oesophageal mucosa can be used in permeation studies instead of buccal mucosa as it is very similar in structure and its permeation properties (Diaz-del Consuelo, 2005) hence these two different kinds of tissue was compared. Ease of preparation of the oesophageal tissue makes it more desirable for the use in the penetration studies. Figure 6.15 shows the penetration of saturated naratriptan solution through the two mucosae and although the profiles seem very different, they are not significantly different from each other ($p>0.05$). This is due to large standard deviations on buccal tissue penetration; the removal of tissue from porcine and preparation prior to penetration studies is difficult due to unevenness of the buccal area (thickness and breakages in the tissue). According to these results the oesophageal tissue was used in the penetration studies for the formulated films.

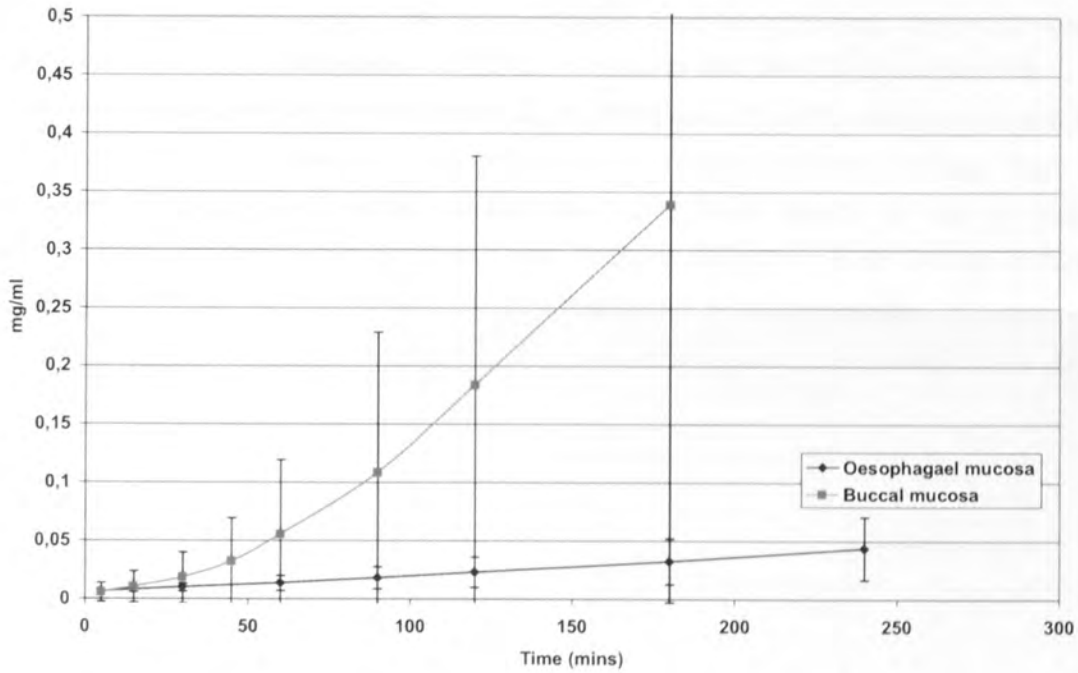


Figure 6.15- Comparison of penetration of saturated solution of naratriptan through oesophageal and buccal mucosa *(n=3, mean±S.D.)*

Formulation	Cumulative amount absorbed ($Q_{60\ min}$) ($\mu g\ cm^{-2}$)
A	2.80 ± 4.11
B	40.09 ± 56.73
C	109.47 ± 118.83
D	83.22 ± 10.21
E	0.11 ± 0.43
F	4.47 ± 5.91

Table 6.5- Cumulative amount absorbed of naratriptan containing films *(key: n=4-6; mean ± S.D.)*

The cumulative amount absorbed at 60 minutes was calculated, taking into account samples removed and dilution of the receiver medium, and typically DL-LA-containing films facilitated faster naratriptan penetration through the mucosa compared to other formulations (film D significantly faster compared to the other non-DL-LA-containing films, Table 6.5) Also in Figure 6.16, the faster penetration of DL-LA containing film (film D) is evident with a fast onset of diffusion ($p<0.05$ for formulation D *vs.* formulation B and D until 15 minutes time point). General trends can be seen in the results: penetration was slowest from PG-containing films but due to large standard deviations, these results are not significantly different from film formulation B These large standard deviations could be due to use of animal tissue as well as errors arising from the robustness of the formulation.

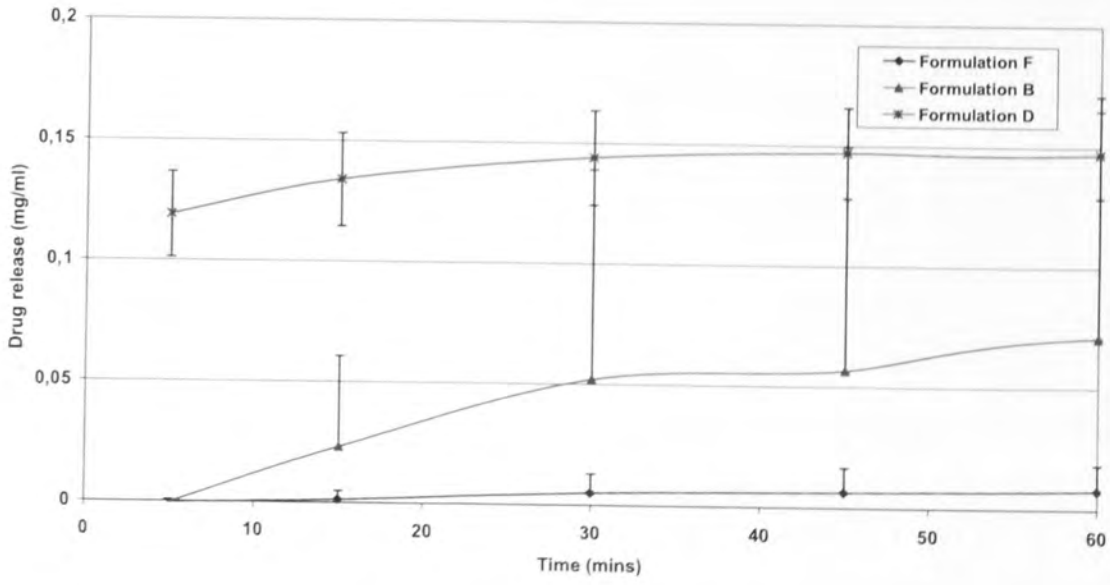


Figure 6.16- Comparison of naratriptan penetration of HPMC-film formulations (F, D, B respectively) through oesophageal mucosa *(n=4-6, mean±S.D.)*

6.4 Conclusion

Naratriptan-containing films were probed for their properties and it was found that dissolution properties can vary with the formulation; HEC-containing films were faster dissolving when a plasticiser was included in the formulation. HPMC-films are typically stronger and stiffer than HEC-containing films which is also evident in this study. The strength of the film can also contribute to the dissolution characteristics of the films leading to slower dissolution. Although decrease in dissolution here is referred as slow, it is still fast as majority of the films dissolve completely within 5 minutes. *In vitro* penetration studies showed that cumulative amount absorbed through mucosa was lower for PG-containing films where as mean values for DL-LA-films were much bigger despite the fact that standard deviations were large and only formulation D was significantly different from other formulations. Overall it can be said that by varying the formulation, the properties of the film can be varied and designed according to the requirements for the intraorally dissolving dosage form.

Chapter 7-

General discussion

As mentioned in the Introduction of this thesis, the need for new molecular entities and product formulations is a major driver for growth in pharmaceutical industry. Discovery of new molecular entities is very challenging and majority of the new found drug molecules do not get as far as clinical phase I in the pharmaceutical development process due to many different reasons *e.g.* it does not have pharmacological effect, the molecule is too toxic, its production is difficult that it would cost a lot to produce therefore bringing the final cost of the product too high and also unfortunately if the product is thought not to have a profitable business case. As the flow of sufficient new molecular entities seem to be diminished in recent years, it forces pharmaceutical industry to look for additional ways of bringing in the business. A supergenerics business is one way of bringing in more market value for the products or active pharmaceutical ingredients (API). The term supergeneric describes, for example, generic API which has been found to be effective for another indication other than it was originally used for. Or if the route of administration of the API is novel and is more effective compared to the original product, the new product can be said to be supergeneric. This branch of pharmaceutical business may be increasing as it can provide patent protection therefore exclusivity in the market area (Charles, 2005). Overall, increasing the growth in pharmaceutical industry is getting harder therefore also the pharmaceutical processes need to evolve to be more efficient.

Typically pharmaceutical processes are fairly old *i.e.* they were discovered long time ago and they might still be used as nothing more efficient has been invented. Also the processes which are used in pharmaceutical manufacturing have been unknown or closed processes where it has not been monitored what is actually happening inside the process and only by sampling together with experience of the operator, the end point of the process could be identified. Fortunately, in recent years, the popularity of applying Process Analytical Technology (PAT)- and Quality by Design (QbD)-thinking is leading to more efficient processes which are also better known processes. Also it may be that processes in the future are continuous where the analysis of intermediates is not needed. As discussed in Chapter 1, in pharmaceutical oral dosage forms are usually conventionally coated utilising spray techniques *i.e.* they are coated using a pan or fluid-bed equipment. Typically conventional coatings are immediate release and exist to protect the core, mask the bitter taste of the core and make the product identifiable. Conventional coating method is also an old process but it has been kept for decades as it works for cores which are not sensitive for moisture (or if only organic solvents are used) or for mechanical stress. Conventional coating formulation has typically a basic formulation which is then altered according to the needs of the coated product in question but the shelf-life of the liquid coating formulation is not long therefore it has to be prepared often. Conventional coating techniques used to employ

organic solvents in the coating formulation but mainly due to safety reasons most preferred solvent for the coating process is water. However some of the excipients and active ingredients used for the tablet core formulations are moisture sensitive therefore application of aqueous-based coatings could lead problems in the quality of the finished products. Also, it would be useful to streamline production in order to be more efficient hence saving money and time (PAT and QbD). As discussed earlier, there may be a room for new processes in pharmaceutical production which could make it more efficient: an alternative method to coat solid-dosage forms, tablets, was proposed by Kessel *et al.* (2002). This technique utilises a dry pre-formed film which is pulled around tablets with vacuum hence there is no need for aqueous or organic solvents during the actual coating process and the tablet cores are not exposed to moisture or to such mechanical stress as for example in pan coating method. The film formulation can be designed so that one thin film formulation can be utilised in coatings of many tablet cores despite of which API or product is in question. Also the shape of the tablet is not an issue as the film is pulled around the tablet therefore all sides of the core will be coated evenly. Possibly only cores with sharp edges should be avoided; sharp edges can also be problematic in the conventional coating method leading to friability and edge wear issues. If the stability of the film formulation is good, it could be manufactured *e.g.* on a roll where it can be taken for the coating process when necessary. This way the timing for the coating manufacture can be optimised and done only every so often. Also there is always some waste coating formulation which is not used and the waste cannot be utilised in the next batch in conventional coating method because it would not be sufficient amount for coating of full batch. But in the wrap-coating method, the excess film could be collected and possibly re-used in the manufacture of next batch of the film coating. Also the wrap-coating apparatus could be attached to a tableting machine where the cores would end up straight in the coating process; the cores could be organised on supports by vacuum and the wrap-coating process could start. Potentially, in the wrap-coating method, there could be many advantages over conventional coating methods where the process could be more efficient, it could be used for many more products and it would be continuous process with less stress on the tablet cores.

In order to validate the need for fast dissolving film as tablet coating, the drug release from commercially available solid-dosage form products as well as from some prototype formulations provided by GSK was studied. It was identified from the results in Chapter 3 that although the additional polymer coatings did not have a large effect on the rate of dissolution, they did have an effect on the lag times. The dissolution of solid-dosage forms can therefore be affected by several issues such as coating formulation, thickness, coating method as well as the core formulation which plays a role in the dissolution process. As many things can

affect the release of the drug, there are many options for formulator to design the dosage form to ensure the desired release is achieved. In this thesis work, due to findings in Chapter 3, the properties of the film formulations as pre-formed films were studied and the effect of these films as tablet coatings utilised on the wrap-coating technology was probed. As it was recognised, the tablet coating can play a role in the release rate of the active ingredient therefore formulation and characterisation of the films were carried out initially. Gelatin was chosen as polymer for the primary studies due to its excellent film-forming properties and thermo-reversible characteristics.

Gelatin was proven to be excellent choice for the novel film-formulations as several formulations were prepared successfully with varying characteristics. A rapid dissolution of the film was required for the paracetamol- and ibuprofen-containing cores due to their indication and necessity for the tablet to dissolve as quickly as possible so that the drug is in solution and available for absorption as fast as possible without dissolution of the tablet coating being the rate limiting step for absorption. Gelatin-containing formulations were formulated with various plasticisers, surfactants, disintegrants, carbonates and unusual excipient as plasticiser, citric acid in order to see the effect of formulation on the dissolution and mechanical properties. It was found that formulations with PEG200 and Brij35 as well as DL-lactic acid and Tween40 gave stable, fast dissolving films which were therefore selected to be taken forward for the actual film-coating studies. Also as a comparison, a slower dissolving film was progressed through to the coating studies to determine whether slight differences in the dissolution of pre-formed films affected the release of the drug from the coated solid-dosage form ($MgCO_3$-containing film). Due to the animal origin of gelatin, alternative cellulose-based films were studied in order to determine their suitability for the wrap-coating technology as they are typically used in pan-coating techniques. HPMC-based films were successfully made and the inclusion of plasticisers was influencing the mechanical characteristics, but the overall stiffness of the films was so high that they were not suitable for the wrap-coating technology. Depolymerisation of HPMC in order to shorten the length of the polymer chain and then to able the plasticiser molecules to move in between the polymer chains to result in more soft and flexible films was carried out but the effect was so small that these depolymerised HPMC-films were not seen as suitable for the wrap-coating process. Alternative cellulose-based polymers were formulated with plasticiser and it was found that HPC- and HEC-containing films were much more flexible than HPMC-films and there was a possibility that HEC-containing films would be suitable for the new wrap-coating technology. Formulation consisting of HEC and DL-LA was therefore used in the actual coating studies which are described in Chapter 5.

The film formulations described in Chapter 4 were not immediately suitable for the wrap-coating process as they required an additional degree of flexibility for the coating process. All re-formulated films were found to be successful formulations for the wrap-coating process and the mechanical properties were changed as a result of the re-formulation: especially the tensile strain was increased to over 120 % and the elastic modulus was lowered to 0.2 MPa or even lower. The dissolution properties of the pre-formed films were not affected as a results of re-formulation, only dissolution rate of $MgCO_3$-containing film (pH 5.8) was increased to similar level with all other formulations therefore the decreased rate of dissolution at pH 5.8 was lost. It was evident from the results that the formulation of the film coat can play a role on the onset of the drug release but usually if the tablet core contains dissolution-enhancing excipients, the effect from the tablet coating is lost. For example, tablet cores with sodium bicarbonate were manufactured and coated and the release rate of the active ingredient was as high from uncoated formulations as from wrap-coated formulations. Also in Chapter 5, wrap-coating technology was compared to dip-coated formulations using the same base formulation for both methods. The G2 –formulation (containing gelatin, glycerol, $MgCO_3$ and Brij35) showed that the coating method affects the release of the active ingredient, where the dip-coated core possessed a slower dissolution compared to wrap-coated core. Cellulose-based coatings were not found to be suitable for the wrap-coating technology due to non-adherence of the coating to the tablet core.

Overall the wrap-coating technology could be utilised in the future as a novel coating technology as this study proved that a suitable coating formulation can be obtained. Advantages of this technology are that it can be used for moisture sensitive cores and for cores which are friable. If this technology was developed further it could also be used as part of continuous process in production where the tablets could be coated immediately after tableting without need for manufacture and store the whole bulk batch prior the coating process. This technology could also be used, for example, for controlled release formulations which were not studied here. The requirements for CR-formulations are so different that issues with non-fast-dissolving formulations would be hidden under the CR-formulation effect.

As the designed thin polymer films for coating method were easy to manufacture, it was evaluated if these could be used as intra-oral formulations too. There are several intra-oral formulations designed for orally disintegrating dosage forms which dissolve in the oral cavity and therefore release the active ingredient and absorb through intra-oral mucosa directly to the systematic circulation. There are tablets, sprays, films, powders and wafers which can be applied intra-orally but sometimes the limitation of these dosage forms is the amount of a

drug which can be formulated into the dosage form. Thin films are utilised in breath fresheners (Tesco's, Wrigley's, Pfizer's) but so far they have not contained any active ingredients in the UK. The cellulosic-films designed here, initially for the coating purposes, were studied also for their suitability as orally disintegrating dosage forms. These formulations were successful as very fast dissolution (100 % under 3 minutes) of the polymer matrix and drug was obtained; formulation containing naratriptan hydrochloride, hydroxyethylcellulose and propyleneglycol was as fast dissolving as commercially available breath fresheners. Unfortunately only a very small amount of naratriptan (approximately 200µg/1cm^2 film) was incorporated into the film therefore the selection of the drug for these kind of dosage forms would have to be done with careful consideration. It may be that only very potent drugs could be used in these kinds of thin film dosage forms. Also it has to be taken into consideration that some of the dissolved formulation can be accidentally swallowed when the onset of the drug would not be as fast as desired or part of the available drug can be lost *e.g.* due to first pass metabolism. Great advantage of this kind of intra-oral dosage forms is that they can be taken without water and it is also suitable for people with swallowing difficulties. This kind of formulations could be also attractive for children and animals as they are much easier to take than conventional tablets. If these thin films were aimed at children or animals, then the formulator should take into consideration that taste masking would play an important role in the formulation.

As part of the further work, which could be carried out on the basis of this thesis, is to critically look at the wrap-coating machine which was here purpose build for the work. It is a very manual piece of equipment and it cannot be modified if needed *i.e.* the film is always positioned right above the tablet bed which means that if the film is heated at high temperature, then also the tablet cores are exposed to the heat. This does not pose a problem at lower temperatures and short exposure times (as used in this work) but if the film polymer requires higher and longer heat, then it may become a problem. Therefore further work should be started with re-design of the coating machine. This would require a close collaboration with an engineers and specialists where the development work of the equipment could be carried out simultaneously with formulation work. This would allow the trials with so called difficult formulations and the coating equipment could be designed in such way that it could be altered according to requirements of the film formulation. This way it could also be designed to be more user friendly, less manual and also more flexible. Stability of the pre-formed films and evaluation of the scale-up should be also done as part of future work.

In conclusion, the designed novel gelatin-film formulations were successful for the current wrap-coating method and formulations were obtained where the effect from the coating was not affecting the release of the APIs from the solid dosage form. This is essential, especially when drugs in question are used mainly for acute pain. Also the utilisation of the cellulose-based films as intra-oral dosage form was success in this thesis work.

References

Abdelbary G., Prinderre P., Eouani C., Joachim J., Reynier J.P. and Piccerelle P. (2004) "The preparation of orally disintegrating tablets using a hydrophilic waxy binder" International Journal of Pharmaceutics **278**(2): 423-433.

Aikman, M., Augsburger L., Berry I., Bodenmiller J., Brandon S., Bottom C., Buhay N., Dunn M., Fang F., Cirotta D, Cole E, Ganey M., Guyer G., Goff H., Gray V.A., Grelle D., Hepp P.L., Hoiberg C., Kumkumian C.S., Lesko L., Light T., Malinowski H.J., Mhatre R.M., Molzon J., Nguyen H., Noory C., Ofner C., Rippere R.A., Scarpetti D., Schwede R., Schmuff N., Schwier J., Shah V.P., Stroud N., Shiu G.K., Tilman L.L., Wang J.T., White T., Williams B., Williams R.L. and Wood R. (1998) "Collaborative development of two-tier dissolution testing for gelatin capsules and gelatin-coated tablets using enzyme-containing media" Pharmacopeial Forum, The United States Pharmacopeial Convention **24**(5): 7045-7050.

Ashford M. (2002a) "Introduction to biopharmaceutics" In Pharmaceutics The science of dosage form design Edited: Aulton M. E., London, Churchill Livingstone, pp.213-216.

Ashford M., (2002b) "Bioavailability- physicochemical and dosage form factors" In Pharmaceutics The science of dosage form design Edited: Aulton M. E., London, Churchill Livingstone, pp 234-252.

Al-Dujaili H., Florence A.T. and Salole E.G. (1986a) "The Adhesiveness of Proprietary Tablets and Capsules to Porcine Esophageal Tissue" International Journal of Pharmaceutics **34**(1-2): 75-79.

Al-Dujaili H., Florence A.T. and Salole E.G. (1986b) "In vitro assessment of the adhesiveness of film-coated tablets" International Journal of Pharmaceutics **34**: 67-74.

Artusi M., Santi P., Colombo P. and Junginger H.E. (2003) "Buccal delivery of thiocolchicoside: in vitro and in vivo permeation studies" International Journal of Pharmaceutics **250**(1): 203-213.

Arvanitoyannis I., Psomiadou E., Nakayama A., Aiba S. and Yamamoto N. (1997) "Edible films made from gelatin, soluble starch and polyols, Part 3" Food Chemistry **60**(4): 593-604.

Arvanitoyannis I. S., Nakayama A. and Aiba S.I. (1998a) "Chitosan and gelatin based edible films: state diagrams, mechanical and permeation properties" Carbohydrate Polymers **37**(4): 371-382.

Arvanitoyannis I., Nakayama A. and Aiba S.I. (1998b) "Edible films made from hydroxypropyl starch and gelatin and plasticised by polyols and water" Carbohydrate Polymers **36**(2-3): 105-119.

ASTM International (2002) Standard test method for tensile properties of thin plastic sheeting, ASTM International **D 882-02**: 1-10.

Aulton M.E. (1995) "Mechanical properties of film coats" In Pharmaceutical coating technology Edited: Cole G., Hogan J. and Aulton M., Taylor & Francis Ltd, pp. 288-362.

Aulton M.E. and Twitchell A.M. (1995) "Solution properties and atomization in film coating" In Pharmaceutical coating technology Edited: Cole G., Hogan J. and Aulton M., Taylor & Francis Ltd, pp. 64-117.

Aulton M.E. and Twitchell A.M. (1995) "Film coat quality" In Pharmaceutical coating technology Edited: Cole G., Hogan J. and Aulton M., Taylor & Francis Ltd, pp. 363-408.

Ayranci E., Buyuktas B.S. and Cetin E.E. (1997) "The effect of molecular weight of constituents on properties of cellulose-based edible films" Food Science and Technology-Lebensm.-Wiss. Technol. **30**(1): 101-104.

Balasubramaniam J., Kumar M.T., Pandit J.K. and Kant S. (2004) "Gellan-based scleral implants of indomethacin: In vitro and in vivo evaluation" Drug Delivery **11**(6): 371-379.

Banker G. S., Peck G.E. and Baley G. (1980) "Tablet formulation design" In Pharmaceutical dosage forms: tablets Edited: H. A. Lieberman and L. Lachman. New York, Marcel Dekker, Inc. **1:** 61-107.

Banner Pharmacaps (2004) "Three Out Of Four Consumers Prefer Soflet® Gelcaps" Retrieved 26th October 2006 from http://www.banpharm.com/technologiesSofletGelcap.cfm.

Bannwarth B. and Pehourcq F. (2003) "Pharmacological rationale for the clinical use of paracetamol: Pharmacokinetic and pharmacodynamic issues" Drugs **63**: 5-13.

Batchelor H.K. and Conway B.R, (2007) "Chapter 7. Drug delivery for infections of the GI tract" In Advanced Drug Formulation Design to Optimize Therapeutic Outcomes Edited: J.T. McConville, D.R. Taft and R.O Williams, Taylor & Francis, Drugs and the pharmaceutical sciences v.172, pp.217-244.

Bateman D. N. (2000) "Triptans and migraine" The Lancet **355**(9207): 860-861.

Béchard S.R., Quraishi O. and Kwong E. (1992) "Film coating: effect of titanium dioxide concentration and film thickness on the photostability of nifedipine" International Journal of Pharmaceutics **87**: 133-139.

Bernardo M.V., Blanco M.D., Sastre R.L., Teijon C. and Teijon J.M. (2003) "Sustained release of bupivacaine from devices based on chitosan" Il Farmaco **58** (11) 1187-1191.

Berta N.I. (1987) "Gelatin coated caplets and process for making same", Pat.app.no.016914. U.S., McNeil Lab, Inc.

Bigi A., Cojazzi G., Panzavolta S., Roveri N. and Rubini K. (2002) "Stabilization of gelatin films by crosslinking with genipin" Biomaterials **23**(24): 4827-4832.

Bigi A., Panzavolta S. and Rubini K. (2004) "Relationship between triple-helix content and mechanical properties of gelatin films" Biomaterials **25**(25): 5675-5680.

Bioprogress (2003) "Tabwrap™" Retrieved 31st October 2006 from http://www.bioprogress.com/films/applications.php?Application_ID=4.

Bodmeier R. and Paeratakul O. (1993) "Dry and Wet Strengths of Polymeric Films Prepared from an Aqueous Colloidal Polymer Dispersion, Eudragit RS30D" International Journal of Pharmaceutics **96**(1-3): 129-138.

Bontempo I., Piretta L., Corazziari E., Michetti F., Anzini F. and Torsoli A. (1994) "Effects of Intraluminal Acidification on Esophageal Motor-Activity" Gut **35**(7): 884-890.

Botting R. and Ayoub S.S. (2005) "COX-3 and the mechanism of action of paracetamol/acetaminophen" Prostaglandins, Leukotrienes and Essential Fatty Acids **72**(2): 85-87.

BNF (2003) "BNF 46" British National Formulary 46 Royal Pharmaceutical Society of Great Britain, British Medical Association, London.

Buckton G., Adeniyi A.A., Saunders M. and Ambarkhane A. (2006) "HyperDSC studies of amorphous polyvinylpyrrolidone in a model wet granulation system" International Journal of Pharmaceutics **312**(1-2): 61-65.

Bussemer T., Peppas N.A. and Bodmeier R. (2003) "Time-Dependent Mechanical Properties of Polymeric Coatings Used in Rupturable Pulsatile Release Dosage Forms" Drug Development and Industrial Pharmacy **29**(6): 623-630.

Cable C.G. (2001) "Sodium bicarbonate" In The Handbook of Pharmaceutical Excipients on CD-ROM Edited: Rowe R. C., Sheskey P.J. and Owen S.C., London, Pharmaceutical Press.

Charles S.A. (2005) "Supergenerics: a better alternative for biogenerics" Drug Discovery Today **10** (8): 533-535.

Chandrasekharan N. V., Dai H., Roos K.L.T., Evanson N.K., Tomsik J., Elton T.S. and Simmons D.L. (2002) "COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure, and expression" Proceedings of the National Academy of Sciences of the United States of America **99**(21): 13926-13931.

Ciper M. and Bodmeier R. (2005) "Preparation and characterization of novel fast disintegrating capsules (Fastcaps) for administration in the oral cavity" International Journal of Pharmaceutics **303**(1-2): 62-71.

Ciper M. and Bodmeier R. (2006) "Modified conventional hard gelatin capsules as fast disintegrating dosage form in the oral cavity" European Journal of Pharmaceutics and Biopharmaceutics **62**(2) 178-184.

Collins J. (2006) "Orion Pharma Finishes RFID Trial" RFID Journal Retrieved 24th October, 2006, from http://www.rfidjournal.com/article/articleview/2365/.

Colorcon Inc. (2003a) "Brand protection- Brand identification" Retrieved 26th October 2006, from http://www.colorcon.com/best/c09_brand_auth.html.

Colorcon Inc. (2003b) "Brand protection- High definition printing" Retrieved 26th October 2006, from http://www.colorcon.com/best/c04_high_def.html.

Coma V., Sebti I., Pardon P., Pichavant F.H. and Deschamps A. (2003) "Film properties from crosslinking of cellulosic derivatives with a polyfunctional carboxylic acid" Carbohydrate Polymers **51**(3): 265-271.

Danjo K., Higuchi F. and Otsuka A. (1995) "Release of Lidocaine from Polymer Film Dosage Forms" Chemical & Pharmaceutical Bulletin **43**(10): 1759-1763.

Das N. G. and Das S.K. (2004) "Development of mucoadhesive dosage forms of buprenorphine for sublingual drug delivery" Drug Delivery **11**(2): 89-95.

Debley J. S., Carter E.R., Gibson R.L., Rosenfeld M. and Redding G.J. (2005) "The Prevalence of Ibuprofen-sensitive Asthma in Children: A Randomized Controlled Bronchoprovocation Challenge Study" The Journal of Pediatrics **147**(2): 233-238.

Digenis, G. A., Gold T.B. and Shah V.P. (1994) "Cross-Linking of Gelatin Capsules and Its Relevance to Their in-Vitro in-Vivo Performance" Journal of Pharmaceutical Sciences **83**(7): 915-921.

Dionne R. A. and McCullagh L. (1998) "Enhanced analgesia and suppression of plasma [beta]-endorphin by the S(+)-isomer of ibuprofen" Clinical Pharmacology & Therapeutics **63**(6): 694-701.

Donescu D., Gosa K., Diaconescu I., Carp N. and Mazare M. (1980) "A Study of Degradation Reaction of Hydroxyethylcellulose in Presence of Potassium Persulfate" Colloid and Polymer Science **258**(12): 1363-1366.

Drugbank (2008) "metoclopramide" Retrieved 30th August 2008, from http://www.drugbank.ca/drugs/DB01233.

Dulery B.D., Petty M.A., Schoun J., David M. and Huebert N.D. (1997) "A method using a liquid chromatographic-electrospray-mass spectrometric assay for the determination of antimigraine compounds: preliminary pharmacokinetics of MDL 74,721, sumatriptan and naratriptan, in rabbit" Journal of Pharmaceutical and Biomedical Analysis **15**(7): 1009-1020.

Eouani C., Piccerelle P.H., Prinderre P., Bourret E. and Joachim J. (2001) "In-vitro comparative study of buccal mucoadhesive performance of different polymeric films" European Journal of Pharmaceutics and Biopharmaceutics **52**(1) 45-55.

Etman M. A. and Naggar V.F. (1990) "Thermodynamics of paracetamol solubility in sugar-water cosolvent systems" International Journal of Pharmaceutics **58**(3): 177-184.

Felton L.A., Shah N.H., Zhang G., Infeld M.H., Malick A.W. and Mcginity J.W. (1996) "Physical-mechanical properties of film-coated soft gelatin capsules" International Journal of Pharmaceutics **127**(2): 203-211.

Fini A., Fazio G. and Ferozi G. (1995) "Solubility and solubilization properties of non-steroidal anti-inflammatory drugs" International Journal of Pharmaceutics **126**(1-2): 95-102.

Fini A., Bergamante V., Ceschel G.C., Ronchi C. and Fonseca de Moraes C.A. (2008) "Fast dispersible/slow releasing ibuprofen tablets" European Journal of Pharmaceutics and Biopharmaceutics **69** (1) 335-341.

Florence A. T. and Attwood D. (1998a) "Properties of the solid state" Physicochemical Principles of Pharmacy London, Pharmaceutical Press, pp.5-35.

Florence A. T. and Attwood D. (1998b) "Drug absorption and routes of administration" Physicochemical Principles of Pharmacy London, Pharmaceutical Press, pp.376-448.

FMC Biopolymer (2005) "Ac-Di-Sol(R)" Retrieved 1st December 2006, from http://www.fmcbiopolymer.com/Pharmaceuticals/Products/AcDiSol/tabid/569/Default.aspx.

Ford J.L. (1999) "Thermal analysis of hydroxypropylmethylcellulose and methylcellulose: powders, gels and matrix tablets" International Journal of Pharmaceutics **179**(2): 209-228.

Fung R. M. and Parrott E.L. (1980) "Measurement of film-coating adhesiveness" Journal of Pharmaceutical Sciences **69**(4): 439-441.

Gaziano J. M. and Gibson C.M. (2006) "Potential for Drug-Drug Interactions in Patients Taking Analgesics for Mild-to-Moderate Pain and Low-Dose Aspirin for Cardioprotection" The American Journal of Cardiology **97**(9, Supplement 1): 23-29.

Ghebre-Sellassie I., Nesbitt R.U. and Wang J. (1997) "Eudragit aqueous dispersions as pharmaceutical controlled release coatings" In Aqueous polymeric coatings for

pharmaceutical dosage forms Edited: J. W. McGinity. New York, Marcel Dekker, Inc. Drugs and the pharmaceutical sciences v.79: 267-286.

Giunchedi P., Juliano C., Gavini E., Cossu M. and Sorrenti M. (2002) "Formulation and in vivo evaluation of chlorhexidine buccal tablets prepared using drug-loaded chitosan microspheres" European Journal of Pharmaceutics and Biopharmaceutics **53**(2): 233-239.

Goth S., Lin L., Mann T. and Gabbott P. (2003) "HyperDSC A breakthrough method for materials characterization" Application Note Thermal Analysis: http://las.perkinelmer.com/content/ApplicationNotes/APP_HyperDSCMatlsCharactztn.pdf.

Gramaglia D., Conway B.R., Kett V.L., Malcolm R.K. and Batchelor H.K. (2005) "High speed DSC (hyper-DSC) as a tool to measure the solubility of a drug within a solid or semi-solid matrix" International Journal of Pharmaceutics **301**(1-2): 1-5.

Grattan T., Hickman R., Darby-Doeman A., Hayward M., Boyce M. and Warrington S. (2000) "A five way crossover human volunteer study to compare the pharmacokinetics of paracetamol following oral administration of two commercially available paracetamol tablets and three development tablets containing paracetamol in combination with sodium bicarbonate or calcium carbonate" European Journal of Pharmaceutics and Biopharmaceutics **49**(3): 225-229.

GSB Flavor Creators (2008) Retrieved 1st December 2008, from www.gsbflavorcreators.com/pharmaceuticalcatalog.pdf.

Guest R.T. (2005) "Croscarmellose sodium" In Pharmaceutical Excipients Retrieved on 26th February 2009, from http://www.medicinescomplete.com/mc/excipients/current/ Edited: Rowe R. C., Sheskey P.J. and Owen S.C.

Harris Interactive Survey (2003) "40 % of American Adults Report Experiencing Difficulty Swallowing Pills; National Survey Shows Many Failed to Take Medication as Directed Because of Difficulty Swallowing Pills", on PR Newswire Retrieved on 26th February 2009 from http://www.highbeam.com/doc/1G1-112187875.html.

Harwood J. (2001) "Hydroxyethylcellulose" In The Handbook of Pharmaceutical Excipients on CD-ROM Edited: Rowe R. C., Sheskey P.J. and Owen S.C., London, Pharmaceutical Press.

Harwood J. (2001) "Hydroxypropylcellulose" In The Handbook of Pharmaceutical Excipients on CD-ROM Edited: Rowe R. C., Sheskey P.J. and Owen S.C., London, Pharmaceutical Press.

Harwood J. (2001) "Hydroxypropylmethylcellulose" In The Handbook of Pharmaceutical Excipients on CD-ROM Edited: Rowe R. C., Sheskey P.J. and Owen S.C., London, Pharmaceutical Press.

Hercules Inc. (2005) Aqualon pharmaceutical excipients brochure.

Heinamaki J.T., Lehtola V.M., Nikupaavo P. and Yliruusi J.K. (1994) "The mechanical and moisture permeability properties of aqueous-based hydroxypropyl methylcellulose coating systems plasticised with polyethylene glycol" International Journal of Pharmaceutics **112**(2): 191-196.

Hind G. (2001) "The end of gelatin" Drug Delivery and Formulation: Innovations in Pharmaceutical Technology **April**: 117-121.

Hogan J.E. (1995) "Film-coating materials and their properties" In Pharmaceutical coating technology Edited: Cole G., Hogan J. and Aulton M., Taylor & Francis Ltd, pp. 6-52

Hogan J. (2001) "Colouring agenst" In The Handbook of Pharmaceutical Excipients on CD-ROM Edited: Rowe R. C., Sheskey P.J. and Owen S.C., London, Pharmaceutical Press.

Hogan J. (2002) "Coating of tablets and multiparticulates" In Pharmaceutics The science of dosage form design Edited: Aulton M. E., London, Churchill Livingstone, pp.441-448.

Huang X. and Brazel C.S. (2001) "On the importance and mechanisms of burst release in matrix-controlled drug delivery systems" Journal of Controlled Release **73**(2-3): 121-136.

ICH Topic Q 2 B (1996) Validation of analytical procedures: Methodology, The European Agency for the Evaluation of medicinal products.

Ikinci G., Senel S., Wilson C.G. and Sumnu M. (2004) "Development of a buccal bioadhesive nicotine tablet formulation for smoking cessation" International Journal of Pharmaceutics **277**(1-2): 173-178.

ISO 527-1 (1993) Plastics- Determination of tensile properties- Part 1: General principles, International Organisation for Standardization.

Jackson S. J. and Perkins A.C. (2001) "In vitro assessment of the mucoadhesion of cholestyramine to porcine and human gastric mucosa" European Journal of Pharmaceutics and Biopharmaceutics **52**(2): 121-127.

Jackson S.J., Bush D. and Perkins A.C. (2001) "Comparative scintigraphic assessment of the intragastric distribution and residence of cholestyramine, Carbopol 934P and sucralfate" International Journal of Pharmaceutics **212**(1): 55-62.

Johnson J.L. and Skinner G.W. (1989) "High gloss cellulose tablet coating" Patent 4,931,286 U.S., Aqualon Company.

Johnson K., Hathaway R., Leung P. and Franz R. (1991) "Effect of triacetin and polyethylene glycol 400 on some physical properties of hydroxypropyl methylcellulose free films" International Journal of Pharmaceutics **73**(3): 197-208.

Jones B. (2002) "Hard gelatin capsules" In Pharmaceutics The science of dosage form design Edited: Aulton M. E., London, Churchill Livingstone, pp.449-460.

Jones W. J. and Francis J.J. (2000) "Softgels: Consumer perceptions and market impact relative to other oral dosage forms" Advances in Therapy **17**(5): 213-221.

Kalantzi, L., Reppas C., Dressman J.B., Amidon G.L., Junginger H.E., Midha K.K., Shah V.P., Stavchansky S.A. and Barends D.M. (2006) "Biowaiver monographs for immediate release solid oral dosage forms: Acetaminophen (Paracetamol) - Commentary" Journal of Pharmaceutical Sciences **95**(1): 4-14.

Kelly K., O'mahony B., Lindsay B., Jones T., Grattan T.J., Rostami-Hodjegan A., Stevens H.N.E. and Wilson C.G. (2003) "Comparison of the rates of disintegration, gastric emptying, and drug absorption following administration of a new and a conventional paracetamol formulation, using gamma scintigraphy" Pharmaceutical Research **20**(10): 1668-1673.

Kessel S. R., Povey I.D. and Nowak E.Z. (2002) Patent WO02098394 Method of tablet enrobing. GB, Bioprogress Tech. Int. Inc. (US).

Krogars K., Antikainen O., Heinämäki J., Laitinen N. and Yliruusi J. (2002) "Tablet film-coating with amylose-rich maize starch" European Journal of Pharmaceutical Sciences **17**(1-2): 23-30.

Krieger O.J. (1987) "Liquid chromatographic determination of acetaminophen in tablets - collaborative study" Association of Official Analytical Chemists **70**: 212.

Krugliak P., Hollander D., Ma T.Y., Tran D., Dadufalza V.D., Katz K.D. and Le K. (1989) "Mechanisms of Polyethylene Glycol-400 Permeability of Perfused Rat Intestine" Gastroenterology **97**(5): 1164-1170.

Lawrence M.J. (2005) "Polyoxyethylene sorbitan fatty acid esters" In The Handbook of Pharmaceutical Excipients on CD-ROM Edited: Rowe R.C., Sheskey P.J. and Owen S.C., London, Pharmaceutical Press.

Lazaridou A., Biliaderis C.G., and Kontogiorgos V. (2003) "Molecular weight effects on solution rheology of pullulan and mechanical properties of its films" Carbohydrate Polymers **52**(2): 151-166.

Lee M.G. (2001) "Lactic acid" In The Handbook of Pharmaceutical Excipients. on CD-ROM Edited: Rowe R. C., Sheskey P.J. and Owen S.C., London, Pharmaceutical Press.

Levy M.C. and Andry M.C. (1987) "Microencapsulation par reticulation interfaciale de gelaitine" S.T.P. Pharmaceutical Science **3**: 644-651.

Li Wan Po A. and Mhando J.R. (1984) "Formulation of sustained-release products: dissolution and diffusion-controlled release from gelatin films" International Journal of Pharmaceutics **20**(1-2): 87-98.

Lukasik K.V. and Ludescher R.D. (2006a) "Effect of plasticiser on dynamic site heterogeneity in cold-cast gelatin films" Food Hydrocolloids **20**(1): 88-95.

Lukasik K.V. and Ludescher R.D. (2006b) "Molecular mobility in water and glycerol plasticised cold- and hot-cast gelatin films" Food Hydrocolloids **20**(1): 96-105.

Macheras P., Reppas C. and Dressman J.B. (1995) Biopharmaceutics of orally administered drugs Hemel Hempstead, Ellis Horwood Limited.

Malich A.W. (2001) "Docusate sodium" In The Handbook of Pharmaceutical Excipients on CD-ROM Edited: Rowe R. C., Sheskey P.J. and Owen S.C., London, Pharmaceutical Press.

Manca D. and Rovaglio M. (2003) "Modeling the controlled release of microencapsulated drugs: theory and experimental validation" Chemical Engineering Science **58**(7): 1337-1351.

Marvola M., Vahervuo K., Sothmann A., Marttila E. and Rajaniemi M. (1982) "Development of a Method for Study of the Tendency of Drug Products to Adhere to the Esophagus" Journal of Pharmaceutical Sciences **71**(9): 975-977.

Maul K. A. and Schmidt P.C. (1995) "Influence of different-shaped pigments on bisacodyl release from Eudragit L 30 D" International Journal of Pharmaceutics **118**(1): 103-112.

Maurer P. H. (1954) "Antigenicity of oxypolygelatin and gelatin in man" Journal of Experimental Medicine **100**: 497-513.

McCargar L., Crail D., Dansereau R., Myers W. and Lane M. (2001) "The in-vitro porcine adhesion model is not predictive of the esophageal transit of risedronate tablets in humans" International Journal of Pharmaceutics **222**(2): 191-197.

McGregor C. and Bines E. (2008) "The use of high-speed differential scanning calorimetry (Hyper-DSC(TM)) in the study of pharmaceutical polymorphs" International Journal of Pharmaceutics **350**(1-2): 48-52.

McGregor C., Saunders M.H., Buckton G. and Saklatvala R.D. (2004) "The use of high-speed differential scanning calorimetry (Hyper-DSC(TM)) to study the thermal properties of carbamazepine polymorphs" Thermochimica Acta **417**(2): 231-237.

McNeil Consumer Healthcare (1998 - 2006) "Tylenol Extra Strength Rapid Release Gels, Laser-drilled Design, Rapid Release" Retrieved 1st November 2006, from http://www.tylenol.com/page.jhtml?id=tylenol/news/subprrg.inc.

Mehta A. M. (1997) "Procesing and equipment considerations for aqueous coatings" In Aqueous polymeric coatings for pharmaceutical dosage forms Edited: J. W. McGinity. New York, Marcel Dekker, Inc. Drugs and pharmaceutical sciences v.79: 287-326.

Miller-Chou B.A. and Koenig J.L. (2003) "A review of polymer dissolution, Progress in polymer science" Progressive Polymer Science **28**: 1223-1270.

Miralles M.J., Mcginity J.W. and Martin A. (1982) "Combined water-soluble carriers for coprecipitates of tolbutamide" Journal of Pharmaceutical Sciences **71**: 302-304.

Murrell W. (1879) "Nitroglycerin as a remedy for angina pectoris" Lancet **151**: 225-227.

Möller H., Grelier S., Pardon P. and Coma V. (2004) "Antimicrobial and Physicochemical Properties of Chitosan–HPMC-Based Films" Journal of Agricultural and Food Chemistry (**52**)21, 6585-6591.

Nagai T., Obara S., Kokubo H. and Hoshi N. (1997) "Application of HPMC and HPMCAS of aqueous film coating of pharmaceutical dosage form" In Aqueous polymeric coatings for pharmaceutical dosage forms Edited: J. W. McGinity. New York, Marcel Dekker, Inc. Drugs and the pharmaceutical sciences v.79: 177-225.

Nerurkar J., Jun H.W., Price J.C. and Park M.O. (2005) "Controlled-release matrix tablets of ibuprofen using cellulose ethers and carrageenans: effect of formulation factors on dissolution rates" European Journal of Pharmaceutics and Biopharmaceutics **61**(1-2): 56-68.

NewsBlaze (2006) "New Study Shows Oval Film-Coated Tablets are Easier to Swallow Than Uncoated Tablets or Caplets, or Gelatin Capsules" Retrieved 12th November, 2006, from http://newsblaze.com/story/20061011072215000O1.pz/topstory.html.

Nicolazzo J. A., Reed B.L. and Finnin B.C. (2003) "The effect of various in vitro conditions on the permeability characteristics of the buccal mucosa" Journal of Pharmaceutical Sciences **92**(12): 2399-2410.

Nimmo J., Heading R.C., Tothill P. and Prescott L.F. (1973) "Pharmacological modification of gastric emptying: effects of propantheline and metoclopramide on paracetamol absorption" British Medical Journal (1) 587-589.

O'Donnell P. B. and McGinity J.W. (1997) "Mechanical properties of polymeric films prepared from aqueous polymeric dispersions" In Aqueous polymeric coatings for pharmaceutical

dosage forms Edited: J. W. McGinity. New York, Marcel Dekker, Inc. Drugs and the pharmaceutical sciences, v.79: 517-548.

O'Donnell P. B., Wu C., Wang J., Wang L., Oshlack B., Chasin M., Bodmeier R. and McGinity J.W. (1997) "Aqueous pseudolatex of zein for film coating of solid dosage forms" European Journal of Pharmaceutics and Biopharmaceutics **43**(1): 83-89.

Obara, S. and McGinity J.W. (1994) "Properties of Free Films Prepared from Aqueous Polymers by a Spraying Technique" Pharmaceutical Research **11**(11): 1562-1567.

Owen S.C. (2005) "Potassium sorbate" In Pharmaceutical Excipients Retrieved on 26th February 2009, from http://www.medicinescomplete.com/mc/excipients/current/ Edited: Rowe R. C., Sheskey P.J. and Owen S.C.

Parsons D. (2001) "Carboxymethylcellulose sodium" In The Handbook of Pharmaceutical Excipients on CD-ROM Edited: Rowe R. C., Sheskey P.J. and Owen S.C., London, Pharmaceutical Press.

Perkins A.C., Wilson C.G., Frier M., Blackshaw P.E., Dansereau R.J., Vincent R.M., Wenderoth D., Hathaway S., Li Z.Q. and Spiller R.C. (2001) "The use of scintigraphy to demonstrate the rapid esophageal transit of the oval film-coated placebo risedronate tablet compared to a round uncoated placebo tablet when administered with minimal volumes of water" International Journal of Pharmaceutics **222**(2): 295-303.

Pfizer Inc. (2006) "Capsule products- Press-fit(R) Gelcaps" Retrieved 26th October 2006, from http://www.capsugel.com/products/pressfit.php.

Pfister W. R. and Ghosh T.K. (2005) "Intraoral Delivery Systems: An Overview, Current Status, and Future Trends" Drug delivery to the oral cvity: Molecules to market Edited: T. K. Ghosh and W. R. Pfister. Boca Raton, Taylor & Francis. Drugs and the pharmaceutical sciences, Vol. 145: 1-40.

Pfizer Inc. (2006) "Consumer FAQ's About Capsules: What are capsules made of?" Retrieved 15th December 2006, from http://www.capsugel.com/faq.php.

Phaechamud T., Koizumi T. and Ritthidej G.C. (2000). "Chitosan citrate as film former: compatibility with water-soluble anionic dyes and drug dissolution from coated tablet" International Journal of Pharmaceutics **198**(1): 97-111.

Pharmaca Fennica (2008) Lääketietokekus Oy, Painoyhtymä Oy, Porvoo, Finland.

PharmWeb (2006) "Paracetamol Information Centre" Retrieved 15th December 2006, from http://www.pharmweb.net/pwmirror/pwy/paracetamol/pharmwebpic.html.

Phoqus Ltd (2006) "Phoqus- UniQ™ Brand enhancement and protection" Retrieved 26th October, 2006, from http://www.phoqus.com/fsysuniq.html.

Porter S. C. and Bruno C.H. (1990) "Coating of pharmaceutical solid-dosage forms" In Pharmaceutical dosage forms: Tablets Edited: H. A. Lieberman, L. Lachman and J. B. Schwartz. New York, Marcel Dekker, Inc. **3:** 77-160.

Potthast H., Dressman J.B., Junginger H.E., Midha K.K., Oeser H., Shah V.P., Vogelpoel H. and Barends D.M. (2005) "Biowaiver monographs for immediate release solid oral dosage forms: Ibuprofen" Journal of Pharmaceutical Sciences **94**(10): 2121-2131.

Price J.C. (2001) "Gelatin" In The Handbook of Pharmaceutical Excipients on CD-ROM Edited: Rowe R. C., Sheskey P.J. and Owen S.C., London, Pharmaceutical Press.

Price J.C. (2001) "Glycerin" In The Handbook of Pharmaceutical Excipients on CD-ROM Edited: Rowe R. C., Sheskey P.J. and Owen S.C., London, Pharmaceutical Press.

Price J.C. (2001) "Polyethylene glycol" In The Handbook of Pharmaceutical Excipients on CD-ROM Edited: Rowe R. C., Sheskey P.J. and Owen S.C., London, Pharmaceutical Press.

Radebaugh G. W., Murtha J.L., Julian T.N. and Bondi J.N. (1988) "Methods for evaluating the puncture and shear properties of pharmaceutical polymeric films" International Journal of Pharmaceutics **45**(1-2): 39-46.

Rama Rao K.V. and Singh S. (2002) "Sensitivity of gelatin raw materials to cross-linking" Pharmaceutical Technology **December**: 42-46.

Rama Rao K.V., Pakhale S.P. adn Singh S. (2003) "A film approach for the stabilization of gelatin preparations against cross-linking" Pharmaceutical Technology **April** 54-63.

Reddy T.T. and Tammishetti S. (2004) "Free radical degradation of guar gum" Polymer Degradation and Stability **86**(3): 455-459.

Repka M. A., Gutta K., Prodduturi S., Munjal M. and Stodghill S.P. (2005) "Characterization of cellulosic hot-melt extruded films containing lidocaine" European Journal of Pharmaceutics and Biopharmaceutics **59**(1): 189-196.

Rostami-Hodjegan A., Shiran M.R., Ayesh R., Grattan T.J., Burnett I., Darby-Dowman A. and Tucker G.T. (2002a) "A new rapidly absorbed paracetamol tablet containing sodium bicarbonate. I. A four-way crossover study to compare the concentration-time profile of paracetamol from the new paracetamol/sodium bicarbonate tablet and a conventional paracetamol tablet in fed and fasted volunteers" Drug Development and Industrial Pharmacy **28**(5): 523-531.

Rostami-Hodjegan A., Shiran M.R., Tucker G.T., Conway B.R., Irwin W.J., Shaw L.R. and Grattan T.J. (2002b) "A new rapidly absorbed paracetamol tablet containing sodium bicarbonate. II. Dissolution studies and in vitro/in vivo correlation" Drug Development and Industrial Pharmacy **28**(5): 533-543.

Rowe R. C. (1981) "The Cracking of Film Coatings on Film-Coated Tablets - a Theoretical Approach with Practical Implications" Journal of Pharmacy and Pharmacology **33**(7): 423-426.

Rowe R. C. (1997) "Defects in aqueous film-coated tablets" In Aqueous polymeric coatings for pharmaceutical dosage forms Edited: J. W. McGinity. New York, Marcel Dekker, Inc. Drugs and pharmaceutical sciences v.79: 419-440.

Sakellariou P., Rowe R.C. and White E.F.T. (1985) "The thermomechanical properties and glass transition temperatures of some cellulose derivatives used in film coating" International Journal of Pharmaceutics **27**(2-3): 267-277.

Sakellariou P., Hassan A. and Rowe R.C. (1993) "Plasticisation of aqueous poly(vinyl alcohol) and hydroxypropyl methylcellulose with polyethylene glycols and glycerol" European Polymer Journal **29**(7): 937-943.

Saville D. (2001) "Influence of storage on in-vitro release of ibuprofen from sugar coated tablets" International Journal of Pharmaceutics **224**(1-2): 39-49.

Shaw L. R. (2001) "The development of a novel *in vitro* model suitable for prediction of bioavailability" Ph.D. thesis: 1-386, Aston University, Birmingham, UK.

Schiermeier S. and Schmidt P.T. (2002) "Fast dispersible ibuprofen tablets" European Journal of Pharmaceutical Sciences **15** (3) 295-305.

Shaw L.R., Irwin W.J., Grattan T.J. and Conway B.R. (2005) "The effect of selected water-soluble excipients on the dissolution of paracetamol and ibuprofen" Drug Development and Industrial Pharmacy **31**(6): 515-525.

Singh B. N. and Kim K.H. (2000) "Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention" Journal of Controlled Release **63**(3): 235-259.

Singh S., Rama Rao K.V., Venugopal K. and Manikandan R. (2002) "Alteration in dissolution characteristics of gelatin-containing formulations - A review of the problem, test methods, and solutions" Pharmaceutical Technology **April**: 36-58.

Sirkiä T., Salonen H., Veski P., Jurjenson H. and Marvola M. (1994) "Biopharmaceutical evaluation of new prolonged-release press-coated ibuprofen tablets containing sodium alginate to adjust drug release" International Journal of Pharmaceutics **107** (3): 179-187.

Smith P.K., Krohn R.I., Hermanson G.T., Mallia A.K., Gartner F.H., Provenzano M.D., Fujimoto E.K., Goeke N.M., Olson B.J. and Klenk D.C. (1985) "Measurement of Protein Using Bicinchoninic Acid" Analytical Biochemistry **150**(1): 76-85.

Sobral P. J. A., Menegalli F.C., Hubinger M.D. and Roques M.A. (2001) "Mechanical, water vapor barrier and thermal properties of gelatin based edible films" Food Hydrocolloids **15**(4-6): 423-432.

Squier C. A. and Wertz P.W. (1996) "Structure and function of the oral mucosa and implications for drug delivery" In Oral mucosal drug delivery Edited: M. J. Rathbone. New York, Marcel Deccer Inc. Drugs and the pharmaceutical sciences, Vol.74: 1-26.

Streisand J. B., Busch M.A., Egan T.D., Smith B.G., Gay M. and Pace N.L. (1998) "Dose proportionality and pharmacokinetics of oral transmucosal fentanyl citrate" Anesthesiology **88**(2): 305-309.

Sungthongjeen S., Puttipipatkhachorn S., Paeratakul O., Dashevsky A. and Bodmeier R. (2004) "Development of pulsatile release tablets with swelling and rupturable layers" Journal of Controlled Release **95**: 147-159.

Swisher D. A., Lee Sendelbeck S. and Fara J.W. (1984) "Adherence of various oral dosage forms to the esophagus" International Journal of Pharmaceutics **22**(2-3): 219-228.

Tallury P., Alimohammadi N. and Kalachandra S. (2007) "Poly(ethylene-*co*-vinyl acetate) copolymer matrix for delivery of chlorhexidine and acyclovir drugs for use in the oral environment: Effect of drug combination, copolymer composition and coating on the drug release rate" Dental Materials **23**(4): 404-409.

New Scientist (2006) "A sick business" New Scientist **191**(2568): 5-5.

Triaminic® (2008) Retrieved 15th July 2008, from http://www.triaminic.com/us_en/products/31616CR_ingredients.shtml.

Vanin F.M., Sobral P.J.A., Menegalli F.C., Carvalho R.A. and Habitante A. (2005) "Effects of plasticisers and their concentrations on thermal and functional properties of gelatin-based films" Food Hydrocolloids **19**(5): 899-907.

Villalobos, R., Hernández-Muñoz P. and Chiralt A. (2006) "Effect of surfactants on water sorption and barrier properties of hydroxypropyl methylcellulose films" Food Hydrocolloids **20**(4): 502-509.

Vishwanathan K., Bartlatt M.G. and Stewart J.T. (2000) "Determination of antimigraine compounds rizatriptan, zolmitriptam, naratriptan and sumatriptan in human serum by liquid chromatography/electrospray tandem mass spectrometry" Rapid Communication of Mass Spectrometry **14**(3): 168-172.

Vueba M. L., Batista de Carvalho L.A.E., Veiga F., Sousa J.J. and Pina M.E. (2004) "Influence of cellulose ether polymers on ketoprofen release from hydrophilic matrix tablets" European Journal of Pharmaceutics and Biopharmaceutics **58**(1): 51-59.

Washington N., Washington C. and Wilson C.G. (2001) Physiological Pharmaceutics Barriers to drug absorption, Taylor and Francis, London and New York .

Waterman K. C. and Fergione M.B. (2003) "Press-coating of immediate release powders onto coated controlled release tablets with adhesives" Journal of Controlled Release **89**(3): 387-395.

Wilson C.G., Washington N., Norman S., Greaves J.L., Peach J.M. and Pugh K. (1988) "A gamma scintigraphic study to compare oesophageal clearance of "Expidet" formulations, tablets and capsules in supine volunteers" International Journal of Pharmaceutics **46**(3): 241-246.

Wurster D. E. (1953) "Method of applying coating onto edible tablets or the like" Patent 2, 648, 609 U.S.

Yang L. and Paulson A.T. (2000) "Mechanical and water vapour barrier properties of edible gellan films" Food Research International **33**(7): 563-570.

Yoo J.-W., Dharmala K. and Lee C.H. (2006) "The physicodynamic properties of mucoadhesive polymeric films developed as female controlled drug delivery system" International Journal of Pharmaceutics **309**(1-2): 139-145.

Zaccaron C.M., Oliveira R.V.B., Guiotoku M., Pires A.T.N. and Soldi V. (2005) "Blends of hydroxypropyl methylcellulose and poly(1-vinylpyrrolidone-co-vinyl acetate): Miscibility and thermal stability" Polymer Degradation and Stability **90**(1): 21-27.