DRUG RELEASE FROM PELLETS AND MATRICES BASED ON CELLULOSE ETHERS

BY
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ABSTRACT

This thesis examines the use of hydroxypropylmethylcellulose (HPMC) of different viscosities and ethylcellulose aqueous dispersion (Surelease), alone or in combination with each other, to control the release of metoclopramide hydrochloride or diclofenac sodium from coated pellets or matrices.

The glass transitions of the polymeric films were determined by thermomechanical analysis and used as a guideline to select the inlet air temperature in coating operation. The coating procedure was performed using Accela-Cota. Matrices were prepared either by direct compression or wet granulation. Compendial dissolution methodology was used to determine drug release from coated pellets as well as matrices. Release exponents indicating release mechanisms were calculated from the dissolution data.

The release of both drugs from coated pellets decreased as the coating load of HPMC increased. However HPMC did not control drug release rate and the majority of both drugs released in less than 1 h. The release exponents for metoclopramide hydrochloride release from HPMC E5 and HPMC E15 coated pellets were ~0.45 and ~0.46 respectively. The corresponding value for diclofenac sodium was ~0.50. These values of n indicate that diffusion is the predominant mechanism for drug release from HPMC coated pellets.

The release of both drugs controlled with application of Surelease on drug-layered pellets. Increasing coating load of Surelease extensively decreased the release rates of both drugs and increased the lag times before controlled release was achieved. The release exponent for metoclopramide hydrochloride was independent of coating load and the mean value was ~0.60 indicating predominantly diffusion controlled release. However the value of n for diclofenac sodium was higher at low coating loads suggesting erosion controlled mechanism and decreased as the coating load increased, indicating more diffusion controlled mechanism. The mean value was ~0.70. Inclusion of HPMC increased the release rates of both drugs. The Surelease:HPMC ratio had a major role in the release rates of drugs. Addition of HPMC into Surelease did not change the release exponent for metoclopramide hydrochloride (~0.57) from that of Surelease alone and diffusion remained the main mechanism controlling drug release. However the release exponent (~1.28) increased for diclofenac sodium release upon addition of HPMC indicating erosion controlled mechanism. Application of 2% seal-coat of HPMC E5 prior to Surelease resulted in decrease in the release rates of both drugs. However the exponent n and consequently release mechanism remained unchanged for either metoclopramide hydrochloride (~0.60) or diclofenac sodium (~0.69). Generally release of diclofenac sodium from Surelease or Surelease/HPMC coated pellets was faster than metoclopramide hydrochloride. This was attributed mainly to the interaction of the latter drug with the anionic surfactant ammonium oleate present in the Surelease coat. The interaction of metoclopramide hydrochloride with ammonium oleate was confirmed by dialysis studies.

Drug release from HPMC matrices was controlled by the polymer content and viscosity. The drug release was also dependent on the solubility of the drugs. Metoclopramide hydrochloride released faster than diclofenac sodium. The release exponent for metoclopramide hydrochloride was in the range of 0.53-0.64. The corresponding value for diclofenac sodium was 0.59-0.80. Therefore a combination of diffusion and erosion controlled the release of either drug. The higher value of n for diclofenac sodium may indicate the greater role for erosion than was the case for metoclopramide hydrochloride.

The incorporation of Surelease into HPMC K4M matrices considerably decreased the release rate of metoclopramide hydrochloride while that of diclofenac sodium was less affected. The conversion of metoclopramide hydrochloride to its base form was proposed as an explanation. The release exponents for Surelease granulated matrices was ~0.56 for both drugs indicating diffusion mainly controlled the mechanism of release.

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CHAPTER 1. INTRODUCTION

1.1 THE CONCEPT OF CONTROLLED DRUG RELEASE

For many years, the major focus of drug research activities has been the synthesis or discovery of potent drugs with new kinds of biological activity. While this remains an interesting area of research, much attention has also been paid to the delivery of the active substance (Langer and Peppas, 1981).

In solid dosage forms, the drug must dissolve before it can be absorbed by the body, as depicted in Figure 1.1. Here K_r and K_a are constants indicating the rate of release of drug from the dosage form and the rate of absorption of the drug from the gastrointestinal tract, respectively.

The rate of appearance of the drug in the blood depends on which step is the rate limiting step. The rate of drug release from a conventional dosage form is rapid and absorption through the gastrointestinal wall is usually the rate-limiting step (Schwartz and Ando, 1983). The drug is rapidly liberated from a conventional dosage form, depending on the rate of its disintegration and the dissolution of the drug. A high concentration is quickly reached in the blood, and then drug concentration falls until the next dose. As a result, fluctuating concentration profiles of the drug are observed either in the blood or in tissue, where high concentrations alternate with low concentrations producing an alternation of overdosing and underdosing of the drug. The fluctuating drug levels in the blood and tissues obtained with conventional dosage

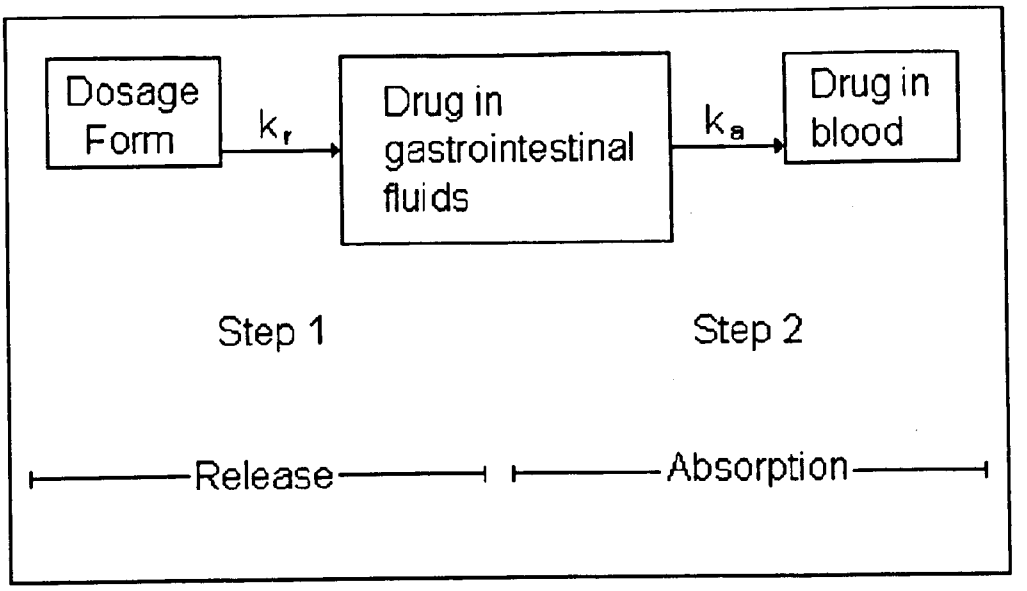


Figure 1.1 Schematic diagram representing the steps before a drug appears in the blood (after Schwartz and Ando, 1983).

forms may lead to an excessive use of the drug and to an insufficient influence on the disease (Langer and Peppas, 1981). Moreover, initial overdosing is responsible for a high frequency of side effects which may lead to other illness or damage (Langer and Peppas, 1981).

However in controlled and sustained release products, the release of drug from the dosage form rather than the absorption of the drug into the blood is the rate-limiting step. The curves of plasma drug level as a function of time for conventional, sustained release and controlled release dosage forms are shown in Figure 1.2.

The development of an ideal, orally-administered drug delivery system which aims

at providing a sustained, relatively constant release of drug during passage through the gastrointestinal tract (GIT) irrespective of variation in pH, surface tension and viscosity within GIT, has been the focus of recent research (Kallstrand and Ekman, 1983; Suryakusuma and Jun, 1984; Baveja et al, 1987).

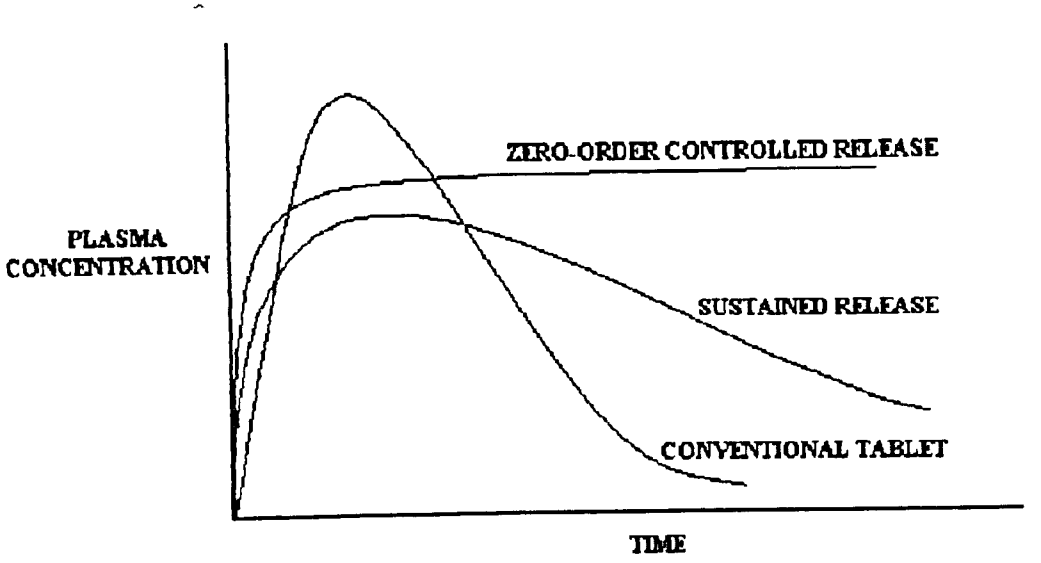


Figure 1.2. Plasma drug concentration-profiles for a conventional tablet or capsule formulation, a sustained release formulation and a zero-order controlled release formulation (after Grass and Robinson, 1990).

The reasons for increasing attention in the field of controlled release delivery systems arise as a result of the general problems associated with the administration of conventional dosage forms, as explained above, and also:

a) As a result of undesirable drug properties, such as short biological half-life or local irritation.

b) Through the nature of the disease state.

c) For reasons of patient compliance since the decrease in frequency of daily doses is more convenient.

d) Most importantly, to improve the efficacy and safety of a drug through proper temporal and/or spatial control of drug release (Li et al, 1987).

1.2 TERMINOLOGY OF CONTROLLED RELEASE DOSAGE FORM

The concept of controlled release dosage forms is quite old, consequently a confusing range of names and terms have been used to describe these systems synonymously. Some terms refer to the duration of release or drug action such as continuous action or long lasting; other terms indicate the rate of drug action such as slow release or slow acting while others refer to the frequency of drug release, such as repeat action. As controlled release dosage forms are one of subgroups of modified release dosage forms therefore, to explain controlled release drug delivery systems it is necessary to define the modified release dosage forms.

1.2.1 MODIFIED RELEASE DOSAGE FORMS

Modified release dosage forms are defined as preparations that modify the rate and/ or time and/ or site of release of active ingredient, in order to accomplish therapeutic objectives which can not be achieved by conventional dosage forms (Caramella et al, 1995).

1.2.1.1 Classification of modified release systems

Modified release dosage forms may be classified according to (Caramella et al, 1995):

- The route of administration (e.g. oral, parenteral),
- The type of release (e.g. delayed, slow, prolonged),
- The release mechanism (e.g. diffusion, dissolution), and
- The type of technical system (e.g. matrix, reservoir).

Generally the terms which can be used for classification of modified release dosage forms based on "the type of release" are:

1.2.1.1.1 Delayed release: This term defines systems which do not release their active component immediately after administration, but do so at a later time. Examples include enteric-coated products (Madan, 1985a).

1.2.1.1.2 Sustained release: These systems are designed to release rapidly a predetermined fraction of total dose as a loading dose and to maintain the therapeutic level of the drug for an extended period of time by slowing the rate of drug release (Maden, 1985a).

1.2.1.1.3 Repeat action: A repeat action dosage form initially releases the equivalent of a conventional single dose of the drug and then another single dose of the drug at some later time. Thus, repeat action dosage forms are not sustained release since they neither reduce the size of the dose nor extended the duration of action (Grass

and Robinson, 1990).

1.2.1.1.4 Controlled release: Controlled release indicates that the release of drug from the dosage form occurs in some planned, predictable and slower than normal, manner. In other words, controlled release dosage forms deliver the drug at a specific planned and controlled rate (Schwartz and Ando, 1983).

1.3 THE THERAPEUTIC OBJECTIVES OF CONTROLLED RELEASE DOSAGE FORMS

Controlled drug delivery systems generally aim to (Li et al, 1987):

1- Sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body. The undesirable side effects resulting from fluctuations in the concentrations of drug in the blood are concomitantly minimized.

2- Localize drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue or organ. Implant devices are obvious examples.

3- Target drug action by using carriers (such as microspheres or nanoparticles for pulmonary delivery) or by preparation of chemical derivatives of the drug which are activated at the target site and deliver the drug to a particular "target" cell type.

1.4 ADVANTAGES OF CONTROLLED RELEASE DOSAGE FORMS

There are many advantages to formulating drugs into controlled release products. The main ones include:

a) An increase in the time interval between doses which in turn leads to a reduction

in dosing frequency (Welling, 1983).

b) Reduced fluctuation in circulating drug concentrations by maintaining drug concentrations in a therapeutically desirable range for a longer period (Langer, 1980; Chow, 1987).

c) Increased patient compliance by decreasing the frequency of dosing (Welling, 1983; Madan, 1985a).

d) Avoidance of night-time dosing (Baker, 1987; Chow, 1987).

e) Reduction in gastrointestinal irritation and other dose-related side effects (Langer and Peppas, 1981).

However these advantages must be weighed against the potential disadvantages.

1.5 DISADVANTAGES OF CONTROLLED RELEASE DOSAGE FORMS

Controlled release dosage forms have several potential disadvantages which include:

a) A high cost per unit dose (Langer, 1980).

b) Unpredictable and often poor in vitro to in vivo correlations (Welling and Dobrinska, 1987).

c) Dose dumping. As these systems usually contain larger quantities of drug than conventional dosage forms, any failure in the performance of these systems could therefore lead to a sudden release of a high quantity of the drug (Li et al, 1987).

d) A reduced potential for dosage adjustment. The loss of controlled release properties due to fracture of the dosage form limits the dosing adjustment with some controlled release formulations when a fraction of a tablet is needed to be administered (Welling and Dobrinska, 1987).

e) An increased potential for first-pass clearance and, as a result, poor systemic availability. As first-pass metabolism is a saturable process, a significant reduction in bioavailability would be anticipated if the drug was released slowly. This is because as the release rate of a drug is slowed, the possibility of saturating the hepatic metabolizing enzymes becomes smaller (Welling, 1983).

g) Toxicity or lack of biocompatibility of the polymeric materials (vehicles) used. These may cause acute or chronic local inflammatory responses (Langer and Peppas, 1981)

h) Production of harmful by-products from the polymer if it is biodegradable (Langer and Peppas, 1981).

1.6 FACTORS INFLUENCING THE DESIGN AND PERFORMANCE OF CONTROLLED RELEASE DOSAGE FORMS

A number of factors affect the design of controlled release products. These include:

1- Drug properties: The physicochemical properties of a drug such as stability, solubility, partitioning characteristics, charge and its extent of protein binding affect the design and performance of controlled release doasge forms (Li et al, 1987).

2- Route of drug delivery: The performance of a controlled release system may be affected by the route of administration. For example, first-pass effects or gastrointestinal motility affect the bioavailability of a drug administrated by the oral route (Li et al, 1987).

3- Target site: To reduce side effects, it is preferable to localize the optimum drug concentration in the target organ or tissue. This may be achieved by local

administration of the drug or by the use of carriers. However, most macromolecules or carriers are not able to pass through the absorptive surfaces of most routes. In this case intravascular or intra-arterial administration is inevitable (Li et al, 1987).

4- Acute or chronic therapy: The design of a controlled delivery system is different depending on whether cure or control of a condition is expected. For example, the design of a contraceptive implant, active over a one year, would be completely different from that of an antibiotic for acute therapy (Li et al, 1987).

5- The patient: Whether the patient is ambulatory or bedridden, young or old etc, can influence the design of a controlled release product. For example, an intramuscular injection may cause different effects in a bedridden patient with little muscle movement compared with the movement of a ambulatory patient (Li et al, 1987).

1.7 APPLICATIONS OF CONTROLLED RELEASE TECHNOLOGIES

Numerous studies into controlled drug delivery are indicative of recent developments in the design of novel systems. They are not limited to oral dosage forms. These systems have been used in parenteral dosage forms (Tice and Cowsar, 1984) buccal/sublingual (Abrams, 1984), rectal (Nishihata et al, 1983), nasal (Hussain et al, 1984), vaginal (Yotsuyanagi et al, 1975), transdermal (Good, 1983) and ocular (Stratford et al, 1983) systems.

1.8 GENERAL DESIGN OF ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

Most controlled release dosage forms consist of two parts: the first part immediately

releases its content in order to provide the therapeutic drug concentration as rapidly as possible. The second part is the sustained release portion which has been designed to provide prolonged blood levels. Obviously, the heart of the system is the sustained release component (Madan, 1985b). A variety of techniques have been used to prepare controlled release drug delivery systems. In some cases, the combination of more than one technique has been used in order to maximize their advantages and minimize their drawbacks (Hui et al, 1987). Most oral controlled release systems use dissolution, diffusion, or a combination of both mechanisms, to retard drug release. These systems are discussed below.

1.8.1 CLASSIFICATION OF ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEMS

1.8.1.1 Dissolution controlled release

In sustained release formulations employing dissolution as the rate limiting step, drug release is controlled by dissolution of a polymer. Most of the products based on dissolution controlled release provide either an encapsulated or a matrix dissolution control.

a) Encapsulated dissolution control: In these types of controlled delivery systems individual drug particles or granules are coated with a slowly dissolving material such as beeswax or glycerol palmitostearate. The coated particles can be either compressed directly into tablets or placed into capsules.

b) Matrix dissolution control: This involves compressing the drug with a slowly

dissolving carrier into a tablet.

1.8.1.2 Diffusion controlled release

Diffusion is the movement or transport of drug molecules due to random thermal energy from a more concentrated reservoir to a less concentrated site (Schwartz and Ando, 1983). There are basically two types of diffusion controlled systems:

a) Reservoir devices: In these systems, a core of drug is surrounded by a water-insoluble polymeric material. The drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet (figure 1.3A).

b) Matrix devices: In these systems, a solid drug is dispersed in an insoluble matrix. The rate of drug release is dependent on the rate of drug diffusion through the polymer (figure 1.3B).

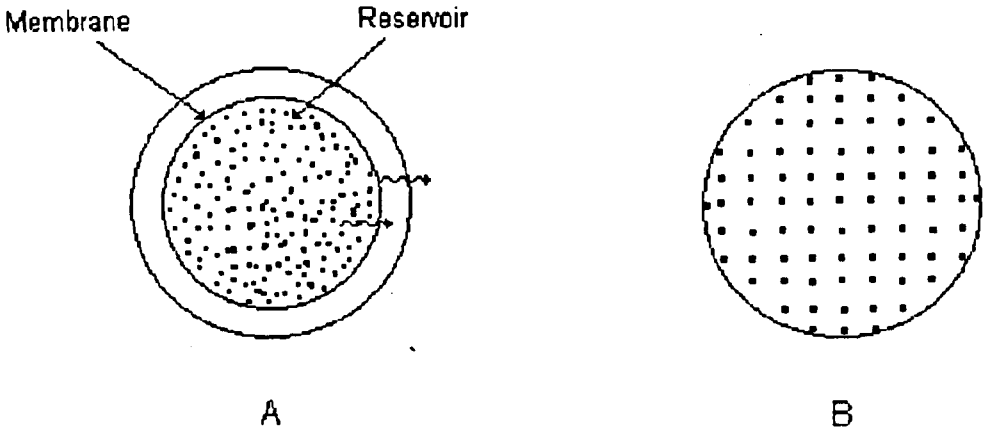


Figure 1.3. Schematic representation of diffusion-controlled drug release. A. Diffusion control of drug release via a reservoir device. B. Diffusion control of drug release via a matrix (after Hui et al, 1987).

1.8.1.3 Diffusion and dissolution controlled systems

This system is based on a combination of diffusion and dissolution types of control. Their main feature is that the drug core is enclosed with a partially soluble membrane. Dissolution of part of the membrane allows for diffusion of the contained drug through pores in the polymer coat (figure 1.4).

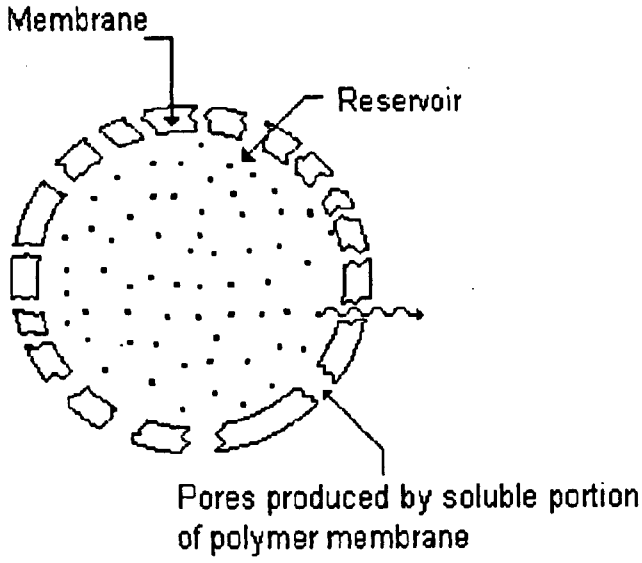


Figure 1.4. Schematic representation of a diffusion and dissolution controlled system (after Park et al, 1984).

1.8.1.4 Ion-exchange resins

Resins are water-insoluble materials containing salt-forming groups in repeating positions on the resin chain. Ion-exchange resins have been used as drug carriers for preparing sustained delivery by releasing the drug from the complex over approximately 8 to 12 h into the gastrointestinal tract (Park et al, 1984). The drug

is released from this system as a result of an ion exchange and depends mainly on the pH and ionic concentration of the dissolution medium (Caramella et al, 1995).

1.8.1.5 pH-independent formulations

When a drug formulation is administered orally, it encounters several pH environments ranging from 7 in the mouth, 1 to 4 in the stomach and 5 to 7 in the small intestine (Hui et al, 1987). Since most drugs are either weak acids or weak bases, their release from sustained release formulations is pH dependent.

To achieve a pH-independent drug release, buffers can be added to the formulation to help maintain a constant pH. Salts of phosphoric acid, phthalic acid, citric acid, tartaric acid or amino acids are preferred, because of their physiological acceptability (Park et al, 1984).

1.8.1.6 Osmotically controlled release

In this type of drug delivery system, osmotic pressure is the driving force that generates constant drug release. This system is fabricated by applying a semipermeable membrane around a core of an osmotically active drug or a core of an osmotically inactive drug in combination with an osmotically active salt. A delivery orifice is drilled in each system by laser or by a high-speed mechanical drill. The semipermeable membrane lets water, but not the drug, diffuse through the membrane freely. Drug is released through the orifice. The unique feature of this system is that the drug release is independent of pH (Caramella et al, 1995). A

schematic diagram for this system is shown in Figure 1.5.

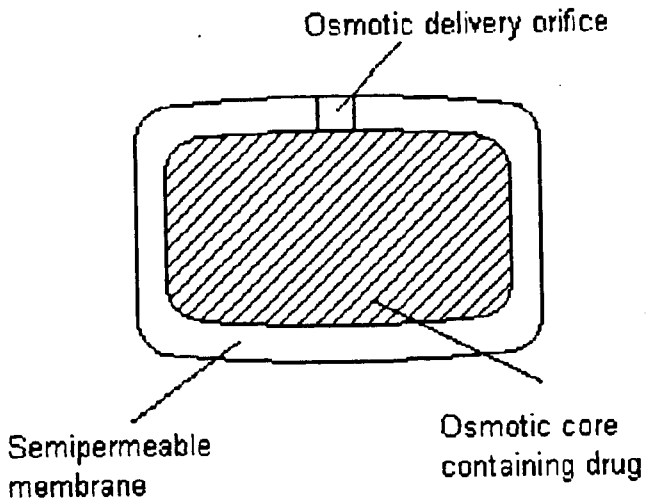


Figure 1.5. Schematic representation of an osmotically controlled system (after Hui et al, 1987).

1.8.1.7 Altered density formulations

The gastrointestinal transit time varies from one individual to another (Hui et al, 1987). Among the factors that influence the gastrointestinal transit time are the physical properties of the delivery system and the presence of food (Welling and Dobrinska, 1987). Several methods have been developed to prolong the residence time of a drug delivery system in the gastrointestinal tract. One method is the use of bioadhesion, which is based on the adherence of bioadhesive polymers to the mucin/epithelial surface of the gastrointestinal tract (Li et al, 1993). Another method is by changing the density of a formulation by using either high or low density pellets (Park et al, 1984).

a) High density pellets: In these systems, the density of the pellets must exceed that of normal stomach content. In preparing such formulations, the drug can be coated onto a heavy core or mixed with heavy inert materials such as barium sulphate, titanium dioxide, iron powder or zinc oxide (Hui et al, 1987). The rate at which pellets are distributed through the small intestine depends on their density. Devereux et al (1990) claimed that increasing the density of pellets from 1.5 $g.cm^{-3}$ to 2.8 $g.cm^{-3}$ prolonged their gastrointestinal residence time.

b) Low density pellets: In these systems, the density of the pellets is lower than that of the gastric juice. Empty globular shells are used as the carrier. Conventional capsules, polystyrol, or even popcorn are all candidates as carriers (Park et al, 1984). The surfaces of empty shells are coated with a polymeric material and then further coated by a drug-polymer matrix using a polymeric material which shows dissolution controlled of the drug release. The final product floats on the gastric juice for an extended period while the drug is slowly released (Hui et al, 1987).

As this thesis examines drug release from coated multiparticulate systems and hydrophilic matrices therefore the description of these systems along with factors influencing the release of drug from them will be presented below.

1.9 MODIFIED RELEASE COATINGS

The film-coating process involves spray-depositing a formulation onto the surface of a tablet, granule or pellet. The coating formulation consists mainly of polymer,

plasticiser, colorant and other possible additives, dissolved or dispersed in either an aqueous or organic solvent.

Tablets and other solid dosage forms may be coated for a variety of reasons such as to mask unpleasant tastes and odours, to hide mottled or discoloured tablet surfaces and to protect from gastric fluids those drugs which are acid-labile. Another application of film coating is to provide a semipermeable membrane which limits the release of a drug from its respective dosage form (Rowe, 1985a). The process of coating should be capable of producing a dosage form which is evenly coated with the film layer (Mehta and Jones, 1985). In an ideal coating process each layer of coating is applied uniformly and is dried completely before tablets or beadlets are recycled for further coating. The surface of coated tablets or beadlets should appear smooth and continuous. If the coating process or coating formulation is not optimized, the deposition of the film onto the substrate would fail to spread uniformly leaving an imperfect film (Li et al, 1991).

The United States Pharmacopeia / National Formulary (1995) described three types of coating:

1- Plain coatings which are applied to improve the taste and appearance of the dosage form or to protect it from light or moisture.

2- Delayed release coatings which are better known as enteric coatings and are applied to protect acid sensitive drugs from the low pH of the stomach contents.

3- Sustained release coatings which are used to modify the release rate of the active

substance from the dosage form.

1.9.1 CONTROLLED RELEASE COATED DOSAGE FORMS

Controlled release products based on sustained release coatings may be formulated as single-unit dosage forms such as tablets or multiple-unit dosage forms (multiparticulate systems) such as pellets. Single-unit preparations consist of one non-disintegrating unit while multiple-unit formulations consist of a unit which disintegrates in the stomach into a large number of sub-units.

1.9.2 MULTIPARTICULATE SYSTEMS

There are various types of substrates which can be used in the production of multiparticulate systems. These substrates include (Porter and Bruno, 1990):

a) Drug crystals and powders,

b) Extruded and spheronised drug granules,

c) Sugar seeds or non-pariels which are layered with the drug,

d) Ion-exchange resin particles containing the drug, and

f) Small compressed tablets containing the drug.

Generally multiparticulate systems can be categorized as *minigranules* or *microgranules* (Follonier and Doelker, 1992). The first class correspond to the pellets, while the second class include microcapsules and microspheres. Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into free-flowing, spherical or semi-spherical units, referred to as pellets

(Ghebre-Sellassie, 1989). Based on their structure, pellets can be classified into the following groups (Knoch, 1994):

a) Pellets with homogeneous distribution of drug in a carrier. These pellets may already show sustained release or may need to be coated with a suitable polymer to achieve sustained release.

b) Pellets in which the drug is applied to an inert core such as sugar spheres.

A schematic diagram of the different types of controlled release multiparticulate systems is shown in Figure 1.6.

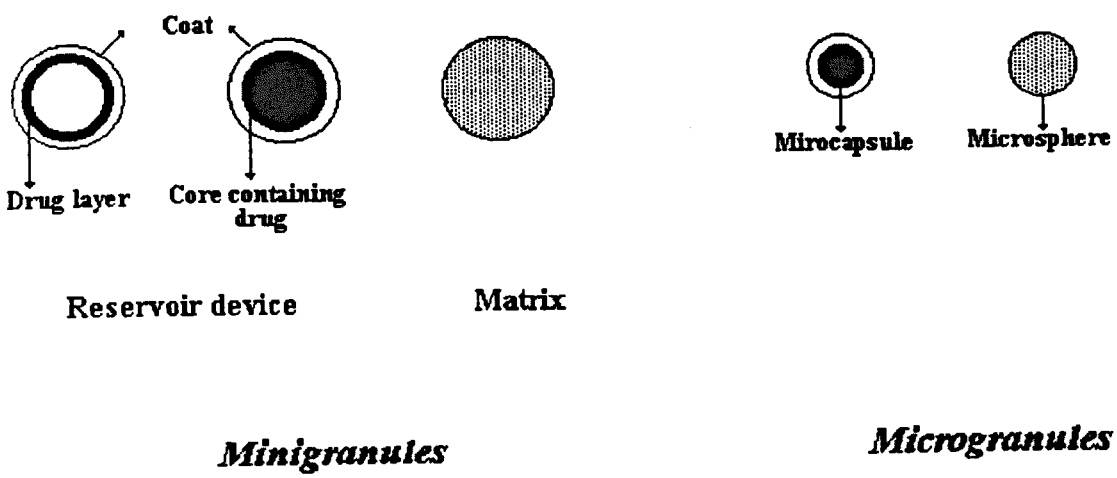


Figure 1.6. Schematic representation of controlled release multiparticulate systems (after Follonier and Doelker, 1992).

1.9.2.1 Advantages of multiparticulate systems

It has been asserted that products based on a multiunit system comprising many small pellets, offer potential advantages over single unit preparations. Pellet mixtures are attractive in appearance, easily mixed when combinations of different active

agents are required. They also flow freely and pack uniformly thereby alleviating problems in handling and packaging (Connie and Hadley, 1970; Ghebre-Sellassie et al, 1985; Story, 1989). Pelletization enables the incorporation of incompatible active substances into the same product, or even into the same pellet, by situating the active substances in different layers and/or by separating the layers from each other with coatings (Lehmann and Dreher, 1979). Furthermore cores, because of their spherical shape, have the lowest surface area to volume ratio and are easy to coat (Rowe, 1985b). They also offer a practicable method to control the site and rate of drug distribution in the gastrointestinal tract (Niskanen et al, 1990).

However, the main advantage of pellets is their in vivo behaviour. This benefit is obtained by administering the controlled release in the form of tablets or capsules that disintegrate in the gastrointestinal tract. When the pellets have a diameter of <1.0-1.5 mm, they pass the pylorus even when the sphincter is closed and spread out over a large surface area in the stomach and small intestine (Bechgaard and Nielsen, 1978). This yields a more predictable drug release profile by reducing local differences in the gastrointestinal environment. In addition, this is reported to minimise the risk of local mucosal damage (Bechgaard and Nielsen, 1978; Bechgaard, 1982; Flament et al, 1994). Moreover, since each dose consists of many subunits, there is a better statistical assurance of drug release (Lordi, 1986) and the risk of dose dumping is reduced (Davis et al, 1984; Ganderton, 1985)

1.9.2.2 Manufacture of multiparticulate systems

The techniques which are used in the production of either un-coated or coated multiparticulate systems include the use of rotating pans, extruder/spheronisers, fluidized bed and microencapsulation.

1- Rotating pans

The use of a conventional coating pan in the production of pellets is a slow process, lasting several days or weeks to process a single batch of material. Products with a high drug content >50% can be produced by the addition of the drug in powder form, although the addition of drug as a solution or suspension is common (Ghebre-Sellassie, 1989). Coating pans are used for one or more of the following (Chambliss, 1989):

a) The formation of pellets from dry powder, granules or crystals.

b) The addition of drug as a dry powder onto an inert substrate.

c) The addition of drug in the form of a solution or suspension onto an inert substrate.

d) The addition of an outer controlled-release layer to drug-layered pellets.

2- Extruder/Spheroniser

The extrusion of a moist material followed by rounding on a rapidly rotating, roughened plate is known as spheronisation (Gamlen, 1985). This technique may be the only practical way of producing pellets with high drug content. In this process, the drug and other excipients are mixed in the dry state and then the binder solution,

is added to form a wet mass. The mass is then extruded and the extrudate is transferred to the spheroniser. Various types of extrusion devices are available.

3- Fluidized bed

The fluidized bed is ideal for the production of active-coated cores by layering, as well as for applying any type of controlled release coat (Story, 1989). The types of equipment include the top spray fluidized bed, the bottom spray fluidized bed and the tangential spray fluidized bed. The high evaporative efficiency and the ability to reproducibly control a wide range of process variables have resulted in the increased use of fluidized beds to produce pellets (Jones, 1989).

4- Microencapsulation

Microencapsulation is a process in which tiny particles or droplets are surrounded by a uniform coating (microcapsule) or held in a matrix of polymer (microsphere). A number of microencapsulation techniques, including aqueous phase separation, three-phase dispersion, organic phase separation and interfacial polymerization have been used to encapsulate pharmaceuticals (Chang and Robinson, 1990).

1.10 HYDROPHILIC MATRICES

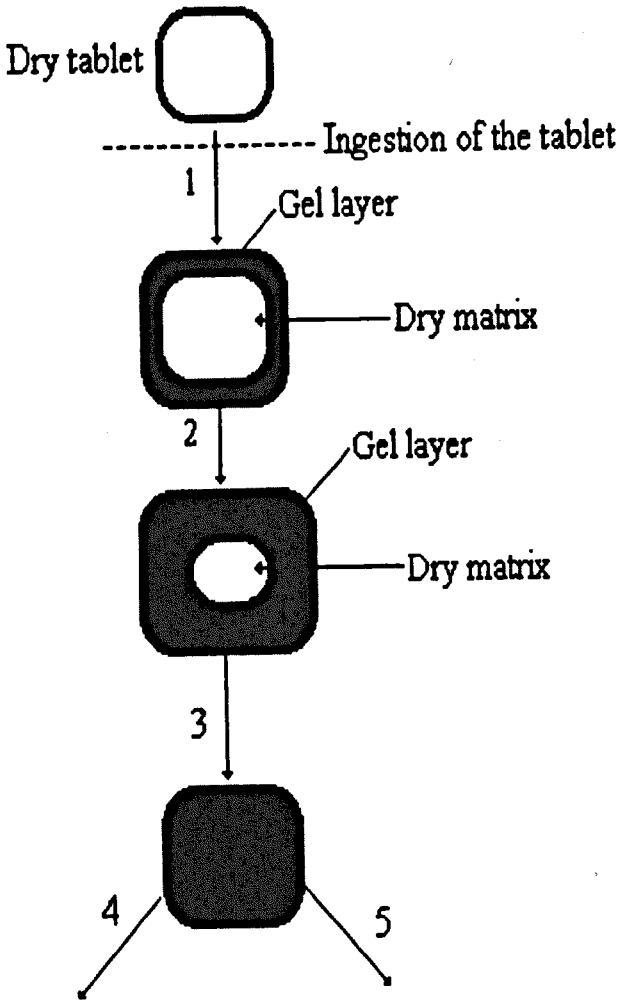
Matrices are widely used as the simplest and the cheapest way of producing oral sustained drug delivery systems. They are defined as a homogeneous dispersion of an active substance in a polymeric carrier (Alderman, 1984). Many polymers, waxes and gums have been used in the formulation of the matrix tablets using direct

compression, wet granulation or dry granulation. Drug diffusion through the polymer matrix is generally the rate-limiting step. The ease of fabrication of these systems and their lower cost are their advantages compared to reservoir devices (Langer and Peppas, 1981).

Hydrophilic polymer-based sustained release matrix tablets are well used in oral sustained release dosage forms (Timmins et al, 1991). The most widely used polymers in hydrophilic matrices are cellulose ethers due to their safety, acceptable cost, wide availability (Colombo, 1993), good compression properties and their ability to accommodate high drug loadings (Ranga Rao and Padmalatha Devi, 1988; Kawashima et al, 1993; Iannuccelli et al, 1995).

Among cellulose ethers, hydroxypropylmethylcellulose (HPMC) has been extensively used in hydrophilic matrices. The performance of HPMC in sustained release hydrophilic matrices is based on the rapid formation of a gel layer at the tablet surface which postpones hydration of the matrix core and prevents disintegration of the tablet (Alderman, 1984; Colombo, 1993). A schematic diagram of the performance of hydrophilic matrices is shown in Figure 1.7.

Generally two factors control the rate of drug release from hydrophilic matrices: one is the rate of aqueous infiltration into the matrix followed by a relaxation process (hydration, gelation or swelling) and the other is the rate of erosion of the matrix (Tahara et al, 1995). Initially, dissolution of the drug present at the surface of the



1- After contact with water hydrophilic polymer starts to form a protective gel layer and hydrates

2-Further water uptake by polymer increases the thickness of the gel layer. Soluble drug diffuses out of the gel layer

3-Outer gel layer becomes fully hydrated and dissolved. Water continues to enter into the tablet core

4- Soluble drug is released by diffusion through the gel layer

5- Insoluble drug is released by erosion of the gel layer

Figure 1.7. Schematic diagram of the performance of hydrophilic matrices (after Alderman, 1984).

matrix occurs which leaves some pores in the matrix. These pores facilitate the ingress of water into the matrix. As a result of polymer-solvent interactions the gel layer forms on the matrix periphery. The release of drug occurs by diffusion through the gel layer and/or by erosion of the swollen matrix depending on the solubility of the drug (Ford et al, 1987).

1.11 CELLULOSE DERIVATIVES

Cellulose derivatives are very popular in the production of controlled release dosage forms. As this thesis examines the application of cellulose ethers in oral controlled drug delivery systems, it is necessary to introduce some of the properties of these materials and their applications in pharmacy before discussing the factors controlling the drug release from coated pellets and hydrophilic matrices.

Cellulose, the starting source for all cellulose derivatives, is the most abundant natural polymeric raw material. Structurally, cellulose consists of repeating units of anhydro-β-D-glucopyranose units, linked together by β-1,4-glycoside bonds. The various chemically-modified cellulose products used in food, cosmetic, pharmaceutical, medical and related applications can be grouped into four classes, based on their method of preparation. These are: hydrocellulose, cellulose ethers, cellulose esters, and oxycelluloses (Kumar and Banker, 1993).

Cellulose ethers are the cellulose derivatives used most widely in the pharmaceutical industry. Some of the major applications of cellulose ethers include their use as:

i) Tableting aids (binders, fillers, disintegrants).

ii) Viscosity enhancing agents in the preparation of semi-solids, solutions and suspensions, shampoos, hair conditioners and food products.

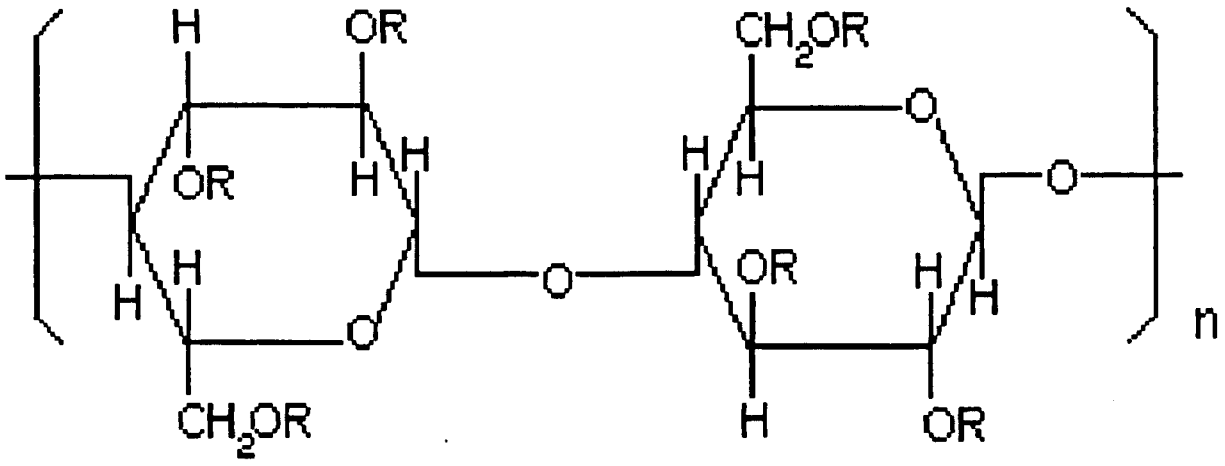
iii) Taste and odour masking agents.

iv) Coating materials for tablets and other dosage forms.

v) Carriers for cosmetic and topical formulations.

vi) Controlled and/or sustained release carriers for veterinary, agricultural and pharmaceutical preparations.

Cellulose is obtained from cotton linters or wood pulp. Cellulose is first converted into an alkali cellulose by reaction with sodium hydroxide and then treated with ethyl halide to produce ethylcellulose (EC) or with mixtures of methylchloride and propylene oxide to give hydroxypropylmethylcellulose (HPMC). For each anhydroglucose unit, three hydroxyl groups are available for nucleophilic substitution. The term "degree of substitution" (DS) is used to identify the average number of hydroxyl groups reacted per ring. The maximum DS is 3. The properties of cellulose ethers depend on the type, distribution and amount of the substitution groups (Greminger and Krumel, 1980). Some of the cellulose ethers are methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose. Their structures are shown in Figure 1.8.



Methylcellulose	R= -H, -CH3
Ethylcellulose	R= -H, $-C_2H_5$
Hydroxyethylcellulose	R=- H, $-CH_2CH_2OH$, $-CH_2CH_2OCH_2CH_2OH$
Hydroxypropylcellulose	R= -H, $-CH_2CH(OH)CH_3$
Hydroxypropylmethylcellulose	R= -H, $-CH_3$, $-CH_2CH(OH)CH_3$
Sodium carboxymethylcellulose	R= -H, $-CH_2COONa$

Figure 1.8. Structure of cellulose ethers (after Doelker, 1987).

1.11.1 HYDROXYPROPYLMETHYLCELLULOSE

Hydroxypropylmethylcellulose is a water soluble polymer and is available in various grades of molecular weights and viscosities. Various grades of HPMC are differentiated by the viscosities of their 2% w/w aqueous solutions at 20°C. The United States Pharmacopeia / National Formulary (1995) specifies the HPMCs of different substitution by four digits as HPMC 2208, HPMC 2906 and HPMC 2910. The first two digits refer to the approximate percentage content of the methoxyl group and the second two digits refer to the approximate percentage content of the hydroxypropoxyl group.

The low viscosity grades of HPMC are useful in low concentrations as tablet binders, whereas the high viscosity grades are used in preparing liquid formulations (e.g. creams, lotions, gels, ointments, and suspensions) and also in sustained release matrix tablets (Kumar and Banker, 1993).

The commercially-available brands of HPMC which are used widely for film coating are Pharmacoat 615, Pharmacoat 606 or Pharmacoat 603 (Shin-Etsu Chemical Co., Japan) and Methocel E15, Methocel E5 or Methocel E3 (Dow Chemical Co., USA). HPMCs of lower viscosities ($\leq$15 mPa.s) are commonly used in film coating and are produced by depolymerization of higher viscosity HPMCs. Although it is reported that HPMC of a higher viscosity grade may be used in film coating, this involves the use of organic solvents (Maffione et al, 1993). The viscosities required for aqueous film coating are commonly less than 100 mPa.s (Nagai et al, 1989).

As a film-coating material, HPMC has the characteristics of producing a transparent, tough, flexible, and non-tacky film when cast from an organic or aqueous solution. The film is stable to a wide range of biochemical or enzyme systems. The HPMC coat dissolves completely in the gastrointestinal tract at any biological pH and provides a good bioavailability of the active ingredients (Nagai et al, 1989).

Plasticizers are usually added to a film coating solution in order to decrease the minimum film formation temperature. Johnson et al (1991) showed that both polyethylene glycol 400 (water soluble) and triacetin (slightly soluble in water) were effective plasticizers for HPMC with PEG 400 being slightly more efficient. However, the presence of 15% or 20% w/w PEG 400 significantly increased the water vapour permeability while 20% w/w of the less hydrophilic triacetin lowered the ability of the film to absorb water (Johnson et al, 1991). In general, plasticizers with low water solubility are recommended for controlled drug release formulations (Chang and Robinson, 1990).

1.11.2 ETHYLCELLULOSE

Ethylcellulose (EC) is the most stable of the cellulose derivatives (Rekhi and Jambhekar, 1995) which is available as an aqueous dispersion as well as a dry powder. It is an inert film forming, hydrophobic polymer and has been used extensively in controlled drug delivery systems. It is used in the fabrication of sustained release dosage forms by addition to direct compression formulations (Upadrashta et al, 1993; Katikaneni et al, 1995; Dabbagh et al, 1996),

microencapsulation (Hasan et al, 1992; Tirkkonen et al, 1993), coating of tablets and multiparticulates (Miller and Vadas, 1984; Bianchini and Vecchio, 1987; Lippold et al, 1989; Dressman et al, 1995), or solid dispersions (Najib and Soleiman, 1985; Hernandez et al, 1994). Aqueous dispersions of ethylcellulose have also been used in matrix formulations using wet granulation to retard drug release (Klinger et al, 1990).

Ethylcellulose is insoluble in water but dissolves in a wide variety of organic solvents (e.g. esters, aromatic hydrocarbons, alcohol, chlorinated solvents). The solution viscosity increases with an increase in molecular weight and concentration. Ethylcellulose is available in three types of ethoxyl substitution from Hercules Inc. (USA) (Grade K: 46.1-47.2%; Grade N: 48.0-49.5%; Grade T: 49.6%) and Dow Chemical Co. (USA) (Trade name: Ethocel Grade M: 45.0-47.0%; Grade S: 48.0-49.5%; Grade HE: 49.5-52.0%). Because of its solubility characteristics, ethylcellulose has been applied mainly from organic solutions to generate film coating of various permeabilities. Due to the disadvantages of using organic solvents (e.g. high cost of solvent and solvent recovery, environmental pollution, explosion hazards and toxicity) the pharmaceutical industry has shifted towards aqueous film coating. As a result, extensive effort has been devoted to the development of water-based coatings and various aqueous polymeric dispersions (latexes and pseudolatexes) that have potential applications in enteric-coated and modified-release preparations are now available.

1.11.2.1 Latexes and pseudolatexes

A true latex is prepared by the polymerisation of a monomer or monomer blend, normally emulsified in an aqueous medium with the aid of anionic or nonionic surfactants. The polymerisation process requires addition of an initiator. In general, the particle size of the polymer produced in this way tends to be very small and there can be problems of toxicity associated with the presence of residual monomer. A pseudolatex, on the other hand, can be prepared from any existing thermoplastic, water-insoluble polymer. It is usually prepared by an emulsification-evaporation technique in which a polymer solution in a water-immiscible organic solvent is finely emulsified in an aqueous phase containing surfactants; the emulsion is subsequently heated to eliminate the solvent (de Labouret et al, 1995).

Recently, pseudolatex preparations or aqueous dispersions of EC have been manufactured under the trade names of Surelease (Colorcon Inc. USA) and Aquacoat (FMC Corp. USA) and are increasingly used in controlled release formulations. These are aqueous colloidal dispersions of solid and spherical particles with mean diameter of about 0.1-1 μm. They are characterized by low viscosity and a high (20-30% w/w) polymer concentration (de Labouret et al, 1995). Because ethylcellulose has a high glass-transition temperature (Onions, 1986b) it does not form flexible films under normal coating conditions and must be plasticised before application. Effective plasticizers that can be used with the Aquacoat aqueous dispersion are dibutylsebacate, diethyl phthalate and triethyl citrate (Harris and Ghebre-Sellassie, 1989). For Surelease, the plasticiser (dibutylsebacate) is incorporated into the

dispersion during the manufacture. A hot melt of the polymer, dibutylsebacate and a stabilizer (oleic acid) is created to form a homogenous mixture. The mixture is then diluted with ammoniated water to obtain a dispersion of the polymer (Iyer et al, 1990). The fumed silica acts as an anti-adherent, facilitating the application of Surelease during coating.

1.11.2.2 Advantages of latex or pseudolatex dispersions

Pseudolatex dispersions exhibit many advantages over polymer solutions. The low viscosities of pseudolatex dispersions and the high concentration of polymers they may contain in comparison to polymer solutions, gives them considerable advantages in use (Onions, 1986a). Thus,

a) Less water needs to be removed during drying and film formation,

b) Less water may be available to penetrate the tablet surface so that sealing of water sensitive tablets may not be necessary,

c) Less energy, particularly heat, is required to remove water during coating, and

d) Less time is required for coating.

1.11.2.3 The mechanism of the film formation from coating solutions and dispersions

The formation of a coat from polymer solutions involves the conversion of a viscous liquid into a visco-elastic solid (Porter, 1989a). In general, films from polymer solutions can be formed in three stages. Initially, the rapid evaporation of the solvent leads to an increase in polymer concentration. Secondly, further loss of solvent

immobilizes the polymer molecules. Lastly, additional loss of solvent, resulting from slow diffusion of residual solvent through the dry coating occurs. This latter stage is very time-dependent.

Film formation from latexes or psuedolatexes involves deposition of discrete polymer particles from water onto a tablet or pellet. In the first stage of film formation, the aqueous phase evaporates leaving the polymer particles in close proximity. Upon further evaporation of water, coalescence of the polymer particles into a continuous film commences. However, the complete coalescence to uniform film is only possible when the polymer chains are mobile enough to facilitate deformation and total fusion of the particles (Arwidsson et al, 1991).

Many theories purport to describe the mechanism of film formation from latexes. Dillon et al (1951) proposed that the main driving force for the coalescence of the polymeric spheres was the polymer-water interfacial tension. Later, Brown (1956) suggested that capillary forces generated by the water-air interfacial tension during the evaporation of water were responsible for the coalescence of the polymer particles. Voyutskii (1958) proposed an interdiffusion of the polymer chains through the particle/particle interface, without which the film would be inhomogeneous and not cohesive. Vanderhoff et al (1966) proposed that, in addition to surface tension and capillary forces, a phenomenon known as Further Gradual Coalescence (FGC) had a significant role in the formation of films which became more homogeneous upon aging.

Vanderhoff et al (1973) stated that film formation from latexes took place in three stages: an initial stage where the polymer particles are free to move and drying occurs at a constant rate; an intermediate stage in which the particles come into an irreversible contact with one another and start coalescing into a continuous film and a final stage in which the residual water evaporates at a very slow rate by diffusion either through capillary channels between the deformed polymer particles or through the polymer itself. It has been shown that a plasticised ethylcellulose latex film applied to non-pareils at 43°C requires approximately four weeks to complete the process (Onions, 1986b). If the same film is applied at a higher temperature, 60°C, or if it is dried for 1 h at 60°C after initial film formation, the FGC is essentially complete (Onions, 1986b).

1.12 FACTORS AFFECTING DRUG RELEASE FROM COATED PELLETS

Although ethylcellulose has been mainly used as a coating membrane, factors which affect other polymers are equally applicable and are discussed in this section.

The manufacturing of coated pellets products is a highly complex process influenced by at least the following parameters (Eskilson, 1985):

a) The active substance,

b) The core characteristics,

c) The coating technique and equipment, and

d) The membrane material and formulation.

1.12.1 THE ACTIVE SUBSTANCE

The physicochemical properties of an active substance play a crucial role in its release from coated pellets. The water solubility of a drug is important to the formulation. Ghebre-Sellassie et al (1988) investigated the release of diphenhydramine and theophylline as model drugs with high and low water solubility respectively, from pellets coated with Surelease (aqueous dispersion of ethylcellulose). It was shown that at a given level of coating, the rate of drug release from pellets was mainly a function of the drug solubilities. Similar results were reported by Iyer et al (1990) for the release of acetaminophen, guaifenesin and diphenhydramine hydrochloride from ethylcellulose coated pellets.

Ragnarsson et al (1992) investigated the impact of drug solubility on the in vitro release characteristics of ethylcellulose coated pellets for the sorbate, benzoate, succinate and fumarate salts of metoprolol. As the solubility of the salt increased, the rates of release became greater.

The faster release of drugs of higher water solubility than drugs of lower solubility was partly attributed to the different rates of migration of drug into the coat during film application (Ghebre-Sellassie et al, 1987). The migration process of a drug during film application is shown in Figure 1.9. When the first layer of film is applied (step 1) highly water soluble drugs are dissolved in the coating formulation to a greater extent and remain in the coat after evaporation of water. As more layers of film are applied (steps 2, 3 and 4), the extent of drug migration decreases until a film

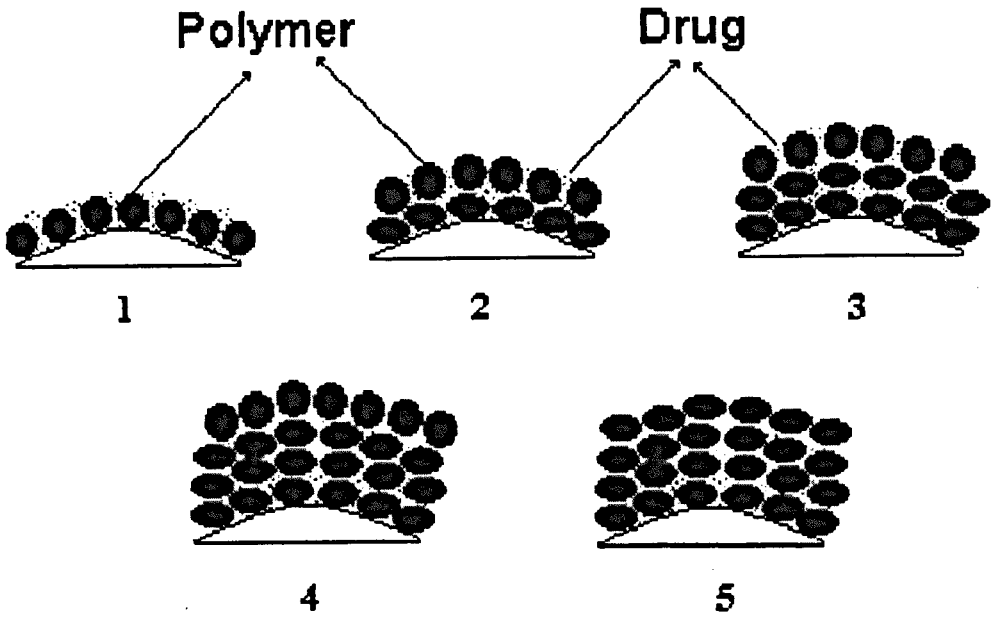


Figure 1.9. Schematic representation of drug migration into the coat during film application (after Porter and Ghebre-Sellassie, 1994).

layer free from drug is deposited (step 5). During dissolution, the drug present in the inner layer of a film dissolves and leaves some pores in the coat. These pores facilitate the ingress of dissolution medium into the core and consequently lead to a faster drug release. Therefore highly water soluble drugs require a thicker coat in order to show the same release profiles as a poorly water soluble drug.

1.12.2 CORE PROPERTIES

In order to obtain the desired drug release profiles from sustained release coated pellets, the core should have the following characteristics:

1. Sufficient mechanical strength and density to withstand the mechanical attrition

during coating (Eskilson, 1985).

2. A compact and smooth surface in order to minimize the defects in the coating due to the entrance of coating fluid into the pores (Iley, 1991).

3. Suitable shape and size to optimize the specific surface area for the applied coat (Iley, 1991).

4. Good flow properties to ensure uniform movement and also to alleviate packaging problems (Eskilson, 1985).

Ragnarsson and Johanson (1988) studied the influence of the size of barrier-coated beads on their release properties. They showed that the release rate was directly proportional to the surface area of the cores. Similar results were reported by Li et al (1989a) and El-Mahrouk et al (1993) for the release of indomethacin from non-pareil seeds having different particle size and coated with Eudragit polymers.

Porter (1989a) indicated that the release of chlorpheniramine maleate from Surelease coated pellets was faster for smaller sized beads than larger sized beads. Porter (1989a) postulated that geometry plays an important part in controlling drug release from coated dosage forms. The surface area to be covered by a coating would be affected by the particle size, resulting in a variation in coating thickness, when a fixed weight of coating fluid is used. Therefore, this would influence the rate at which the drug is released. Porter (1989a) also demonstrated that when rough or smooth surface beads were coated, drug release rate was affected. In other words, beads with rough surfaces demonstrated faster release of drug than beads with

smooth surfaces. This effect was attributed to the higher surface area of the beads with a rough surface (Porter, 1989a).

1.12.3 COATING TECHNIQUE AND EQUIPMENT

The morphological differences in the coating surface appeared to determine the rates at which a drug was released (Metha, 1986). It has been reported that the type of coating equipment (Mehta and Jones, 1985; Mehta, 1985; Porter and D'Andrea, 1985; Mehta, 1986; Jackson et al, 1989; Yang et al, 1992; Bertelsen et al, 1994) has a significant influence on the release of a drug by affecting the structure of the ultimate film coating. It is also well known that processing parameters of the coating process (Yang and Ghebre-Sellasie, 1990; Bodmeier and Paeratakul, 1991; Laicher et al, 1993) affect the quality of the film deposited onto the substrate and consequently the release of the drug. The effect of inlet air temperature, the amount of air introduced in the equipment and spray rate are important variables to be considered during the coating process (Chang et al, 1989).

The nozzle size, together with the atomizing air pressure determine the size of the coating droplet and as a general rule, the finer the droplet size the better the characteristics of the film (Mehta, 1986). As the atomizing air pressure increases it provides more energy to overcome the viscous and surface tension forces resisting droplet formation and facilitates movement of the coating fluid. Increasing the atomizing air pressure also improves the droplet spreading on the substrate. This in turn makes the drying process more efficient by enhancing the surface area exposed

to the drying air and also reduces the tendency of the substrate to stick (Twitchell et al, 1995). However the higher spreading of coating droplet reduces the extent of penetration of coating fluid into the substrate and therefore reduces the strength of the coat (Twitchell et al, 1995).

The effect of different spray rates on the in vitro release of granules coated with an aqueous polymeric dispersion has been investigated by Russo (1984). It was observed that granules coated under slower spraying conditions released drug more slowly than granules coated under faster spray rates. It was suggested that the slower spray rates allowed a warmer bed temperature, which in turn allowed more extensive coat curing and less coat permeability.

1.12.4 MEMBRANE MATERIAL AND FORMULATION

1.12.4.1 Polymer effect

The type of polymer used in coating multiparticulate systems can substantially alter the release of drug from the system (Dyer et al, 1995). Bianchini et al (1993) found that acrylic resin coatings were more suitable to reduce the release rate of d-Indobufen than Aquacoat. Several studies have also demonstrated differences in the release rates of drugs coated with different types of Eudragit polymers (Munday and Fassihi, 1989; Lehman and Petereit, 1994).

Significant differences can also be identified in the performance between various formulations of the same polymer type. In a comparative study on three forms of

ethylcellulose suitable for coating; Aquacoat, Surelease and ethylcellulose from an organic solvent solution, differences between the dissolution characteristics of their coated pellets have been reported (Iyer et al, 1990; Mathieu et al, 1995). Using a mixture of water and ethanol as the solvent for a ethylcellulose coating formulation, Narisawa et al (1994) reported that the porosity of the coating and consequently the drug release rates could be controlled by altering the ethanolic concentration.

In the case of aqueous dispersions of polymers, the solid concentration of the coating formulation also affects the release rate of the drug. Wagner and Keitel (1995) found that as the concentration of Eudragit NE 30D dispersion in a coating formulation was decreased, the amount of drug released also decreased. As water plays an important role in the process of film formation from aqueous dispersions, increasing the water fraction in a dispersion facilitated the coalescence of the particles to form a continuous film. Similar results were reported by Porter and Ghebre-Sellassie (1994). Water acts as a plasticizer during deposition of the film, so that the film coating process should be more complete when the water content is higher than when the water content is lower (Laicher et al, 1993).

Rowe (1986) showed that the molecular weight of the polymer used in coating could also affect the release process of the drug. When using low molecular weight ethylcellulose, the release was faster than when using high molecular weights of ethylcellulose. This was attributed to the formation of more flaws as a result of internal stresses that developed on drying in the coating containing low molecular

weight ethylcellulose. As the molecular weight of the polymer increased, the coating became more resistant to the effects of this stress, and above a certain molecular weight, any additional increase in molecular weight had no further effect (Rowe, 1986).

1.12.4.2 Coating thickness

As drug transport through a polymeric membrane is determined by Fick's first law of diffusion (Jambhekar et al, 1987), the quantity of drug released after a given time will be dependent on the thickness of the controlling membrane. Shah and Sheth (1972) showed that the passage of a dye solution through a membrane composed of ethylcellulose and hydroxypropylcellulose was dependent on the membrane thickness. The release rate increased as the membrane thickness decreased. This dependency of release on coating thickness has been subsequently reported by many authors (Ghebre-Sellassie et al, 1987; Jambhekar et al, 1987; Ghebre-Sellassie et al, 1988; Chang et al, 1989; Munday and Fassihi, 1989; Li et al, 1991).

Coating thickness is also an important factor in determining the mechanism of release of drug from coated pellets. Zhang et al (1991a) demonstrated that the release mechanism of acetaminophen changed from diffusion through pores to diffusion through intact polymer when the coating thickness of ethylcellulose increased. Similarly Dyer et al (1995) demonstrated the existence of a critical coating level for ibuprofen pellets coated with different polymers, above which the drug release kinetics changed from first-order to zero-order.

1.12.4.3 Additives

Several additives may be added to coating formulations in order to change the mechanical properties of the film, to change the permeability of the film, as anti-tack agents or to change the colour of the film. These additives include plasticizer, water soluble additives or water insoluble additives.

Plasticizer: Plasticizers play a crucial role in the formation of a film coat and its ultimate structure. They modify the mechanical properties of the polymers and improve their film forming ability. Plasticization in general refers to a change in the thermal and mechanical properties of a polymer (Guo, 1994). The ideal plasticizer used in film coating should not only be compatible with the polymer but also must:

a) be safe for use in pharmaceuticals.

b) be compatible with the drug and other components.

c) remain permanently in the resultant film.

To be effective, the plasticizer molecule must interpose between the polymer chains and interact with forces holding the chains together, thereby extending and softening the polymer matrix (Rowe, 1982). One of the theories that is used to explain changes in the mechanical properties of the films upon adding the plasticizer is the "gel theory" (Aulton et al, 1981). In this theory, there are some active centres along the polymer chain which bind the polymer molecules in solution. In solution, these bonds are in dynamic equilibrium, ie constantly forming and breaking. As they break, solvent (i.e., water) molecules compete for the active sites. Plasticizers

compete for the active sites and consequently decrease the number of polymer-polymer contacts, resulting in a decrease in the cohesive forces between the polymer chains. In summary, plasticizers act by preventing the aggregation of polymer molecules during gel formation as the solvent is evaporated (Aulton et al, 1981).

It is well known that not only the type of plasticizer but also its concentration are parameters which modify the release characteristics of an active substance. Goodhart et al (1984) reported that since the film forming process of the latex involves the fusion of individual polymer particles into a homogeneous film, particle coalescence is dependent upon the presence of enough plasticizer to soften the latex particles so that deformation can occur. Chang et al (1989) showed that the release rate of theophylline from pellets coated with 9% Eudragit RS was inversely proportional to plasticizer (dibutyl sebacate or triacetin) concentration. Schmidt and Niemann (1993) found that the release of theophylline from pellets coated with Eudragit RS30D was affected by the type and concentration of plasticizers. At a coating level of 4%, sustained release profiles were obtained from dispersions plasticized with 20% triethyl citrate or dibutyl phthalate but not for pellets plasticized with polyethylene glycol.

In general, by increasing the amount of plasticizer, the rate of drug release is reduced. However certain studies have revealed that release rates increased with higher plasticizer levels. Li et al (1991), examining the effect of plasticizer type and concentration on the release of pseudoephedrine from Eudragit RL coated pellets

pointed out that beads coated with lower levels of diethylphtalate showed slower release profiles than when higher levels of plasticizer were used. This was attributed to a higher degree of bead agglomeration, sticking and other problems related to the softer films which resulted from higher plasticizer levels. Hutchings and Sakr (1994) found that when the amount of dibutyl sebacate was increased from 30 to 35%, the release rate of propranolol hydrochloride increased for pellets coated with Aquacoat. These authors postulated that increasing the amount of plasticizer beyond a certain saturation point is associated with no further enhancement of film formation, but may result in detrimental effects on the film coating during processing.

Water soluble additives: Water soluble materials of high molecular weight or low molecular weight are added into the rate retarding films to enhance the permeability of that film towards the active agent. Muhammad et al (1991) investigated the influence of various additives, namely polyethylene glycol (PEG), mannitol, and HPMCP 50 (Hydroxypropylmethylcellulose phtalate 50) incorporated with Eudragit L30D on the release of a drug. It was shown that drug release from coated pellets was dependent on the type and the level of the additive. For example, at pH 1.5, PEG, regardless of its molecular weight, had no significant effect on drug release. At pH 5.5, however, the inclusion of PEG significantly decreased the drug release from coated pellets. This was attributed to the formation of a film which was not soluble at pH conditions where Eudragit L30D normally dissolves.

Porter (1989a) reported an increase in the release rate of chlorpheniramine maleate

from beads coated with Surelease when methylcellulose 15 mPa.s was added. The increase in release rate was attributed to the formation of pores upon dissolution of the water soluble methylcellulose (Porter, 1989a). Lindholm et al (1982) reported that the release rate of sodium salicylate from tablets coated with ethylcellulose was dependent on the water solubility of the solids which were added to the film (e.g. sodium chloride, sucrose, tetrabutylammonium chloride).

Water insoluble additives: Water insoluble materials are used in sustained release film coatings either to reduce the tackiness of the formulation or to change its colour (Porter, 1989a). Li et al (1989b) reported a decrease in the release rate of theophylline from pellets coated with Eudragit E30D on increasing the amount of talc in the formulation. This was attributed to an increase in thickness of the coating.

However Chang and Hiaso (1989) found that the addition of talc and silica to the coating dispersion of Eudragit RL or Eudragit RS pseudolatices increased the release of theophylline. Similar results were reported by Ghebre-Sellassie et al (1986; 1987), upon addition of talc, kaolin or magnesium trisilicate into Eudragit E30D formulations on the release of diphenhydramine hydrochloride from coated beads. Wan and Lai (1993) demonstrated the effect of various anti-tack additives such as magnesium stearate, stearic acid, talc and silicon dioxide, on the release of diphenhydramine hydrochloride from pellets coated with methylcellulose. These authors found that all the additives caused an increase in the release rate of drug from the coated granules with the effect being more in the case of magnesium

stearate. This was attributed to the uneven swelling of methylcellulose coated beads and also to the production of more interfacial voids in the film due to the uneven distribution of the hydrophobic magnesium stearate in the hydrophilic methylcellulose film.

1.12.5 RELEASE KINETICS OF COATED MULTIPARTICULATE DOSAGE FORMS

It is necessary to refer to the model of the reservoir device in which the active agent forms a core surrounded by a polymeric diffusion barrier in order to predict drug release from a coated solid dosage form. According to this model, the drug release rate will be either constant if the thermodynamic activity of the drug is maintained constant within the device with perfect sink conditions in the receptor medium (Jambhekar, 1987) or it will follow a first-order relationship if the core is not saturated with the drug or if sink conditions are not maintained (Friedman et al, 1979).

Many theoretical models have been used to describe drug release from controlled release devices. Theoretically, optimal release kinetics from a sustained release product should be zero-order (Kruger-Thiemer and Eriksen, 1966; Robinson and Eriksen, 1966; Robinson and Eriksen, 1970). Such a release follows equation 1.1:

$$W = W_o - Kt \qquad \textit{Equation 1.1}$$

where W is the amount remaining to be released at time t, W_o is the initial amount

of drug in the dosage form and K is the zero-order release rate constant.

In studies on microcapsules and coated granules, in addition to zero-order kinetics, Higuchian kinetics (Donbrow and Friedman, 1975; Alpar and Walters, 1981), first-order kinetics (Benita and Donbrow, 1982; Donbrow and Benita, 1982) and Hixon-Crowell equation kinetics (Benita and Donbrow, 1982) have been reported.

Higuchi (1963) developed kinetic equations for the release of active substances from inert matrices. The cumulative release per unit area, Q, versus time t, from a planar surface is determined by equation 1.2.

$$Q = \sqrt{DC_s \frac{\epsilon}{\tau}(2A - \epsilon C_s)t} \qquad \textit{Equation 1.2}$$

Here, ε is the porosity of the matrix and τ is a tortuosity factor which denotes the extra path to be taken by the diffusing drug molecules around the matrix particles. D and C_s are the diffusion coefficient and solubility in the dissolution medium respectively and A is the concentration of drug in the tablet.

If the release kinetics follow a first order relationship, then equation 1.3 applies,

$$W = W_o e^{-kt} \qquad \textit{Equation 1.3}$$

where k is a first-order release rate constant (Kruger-Thiemer and Eriksen, 1966). W and W_0 are the same as in equation 1.1.

Hixon and Crowell (1931) derived equation 1.4 to explain the dissolution rate of a single crystal under sink conditions.

$$W^{1/3} = W_o^{1/3} - Kt \qquad \textit{Equation 1.4}$$

W is the amount of drug remaining to be dissolved at time t, W_o is the initial amount and K is a constant. This equation has been applied to microcapsules by Benita and Donbrow (1982).

1.13 FACTORS AFFECTING DRUG RELEASE FROM HYDROXYPROPYLMETHYLCELLULOSE MATRICES

As the factors influencing drug release from hydrophilic matrices have been the focus of a vast number of studies, this section describes those which affect drug release from HPMC matrices.

1.13.1 POLYMER EFFECT

1.13.1.1 Polymer viscosity

The effect of viscosity grade of HPMC on the release of drugs has been the focus of many research articles. There are conflicting reports. Lapidus and Lordi (1968) stated that a lower molecular weight of HPMC with lower viscosity (the viscosity of its 2% solution at 20°C was 25 mPa.s) was more susceptible to erosion than the higher molecular weight with higher viscosity (15000 mPa.s). Alderman (1984) stated that the release of a drug would be slower if a higher viscosity grade of HPMC was used in the matrix. This was attributed to an increase in gel layer viscosity.

Ford et al (1985a) reported that HPMC K4M, HPMC K15M, HPMC K100M gave similar release profiles of promethazine hydrochloride while a lower viscosity grade (HPMC K100) behaved differently and gave the fastest release rates. Ford et al (1985a) claimed that the viscosities of the matrices containing hydrated higher molecular HPMC may be similar, in spite of differences in their viscosities. Ford et al (1985b) showed that both the lag time and release rate were not affected by the viscosity grade of HPMC for propranolol hydrochloride and aminophylline. However Ford et al (1985c) claimed that for poorly water soluble drugs, such as indomethacin, the viscosity grade plays a major role in controlling drug release.

Baveja et al (1988) reported that the release rate of a series of bronchodilators did not vary for matrices containing HPMC K4M, HPMC K15M, and HPMC K100M which was in agreement with the earlier studies of Ford et al (1985b). Similar results were reported by Mitchell et al (1993b) for the release of propranolol hydrochloride from matrices containing HPMC K4M or HPMC K15M.

Liu (1995) stated that the resistance of a gel layer is controlled by the viscosity grade of HPMC. Wan et al (1995a) claimed that the thickness of the swollen layer formed around the core was greater in compacts composed of HPMC of higher viscosity grade. Tahara et al (1995) demonstrated that the viscosity of HPMC had a great effect on the erosion rate of matrix tablets and consequently on the release rate of the drug.

1.13.1.2 Polymer substitution type

Alderman (1984) claimed that different levels of methoxyl and hydroxypropoxyl substitution in the HPMC affect the release of a drug from the matrices by influencing the hydration rates of the HPMC. Dahl et al (1990) examined different lots of HPMC 2208 from two suppliers and reported that the release of naproxen was dependent on the hydroxypropoxyl content in the polymer. Dahl et al (1990) claimed that suitable dissolution profiles were obtained only when the hydroxypropoxyl content was >7.5% in the HPMC. However Mitchell et al (1993a) and Rajabi-Siahboomi et al (1994b) showed that there was no differences in the hydration rates of HPMC E4M, HPMC F4M and HPMC K4M.

1.13.1.3 Polymer particle size

The polymer particle size affects its hydration rate and consequently the rate of drug release (Alderman, 1984). Alderman (1984) showed that the release of riboflavin was fast from matrices prepared of a coarse particle size of HPMC (>210 μm) while dissolution rates for tablets made from smaller particles (<150 μm) were sustained. Mitchell et al (1993d) reported that the role of particle size was dependent on the polymer concentration. At high polymer concentrations, coarse and fine fractions behaved similarly. However at low HPMC contents, drug release was faster from matrices prepared with coarser particles (>355 μm).

1.13.1.4 Polymer particle shape

Bonferoni et al (1995) stated that when HPMC E4M was sieved to give two different

shape fractions, matrices prepared from the fraction rich in fibrous particles showed drug release similar to the unsieved HPMC E4M. However, matrices prepared from the sieved fraction containing as low as 22.8% fibrous particles showed a lack of control of drug release. This was attributed to the better particle interlocking of fibrous particles which helped to strengthen the matrix structure.

1.13.2 EFFECT OF DRUG:POLYMER RATIO

Ford et al (1985a, b) demonstrated that the drug/HPMC ratio was the most important factor controlling the release of drug from HPMC matrices. Ford et al (1985a) found that a straight-line relationship existed between the Higuchian release rate ($\%min^{-1/2}$) of promethazine hydrochloride and the reciprocal of the polymer content in the matrix.

1.13.3 EFFECT OF DRUG

1.13.3.1 Effect of drug solubility and molecular size

The molecular size and water solubility of a drug are important factors which determine its release from swelling and erosion controlled polymeric matrices (Ranga Rao et al, 1990). Baveja et al (1988) examined the release of a series of structurally related water-soluble bronchodilators having almost identical solubilities from HPMC matrices. It was reported that the drugs showed different release rates from matrix tablets due to differences in the shape and size of the drug molecules (Ranga Rao et al, 1990).

Ford et al (1987) by studying 7 soluble and insoluble drugs, reported that the solubility of the drug plays an important role in its release from HPMC matrices. Skoug et al (1993) developed a method to measure polymer concentration in the dissolution medium and showed that the release of flurbiprofen (low solubility) from HPMC matrices was primarily by erosion whereas adinazelam mesylate (freely soluble) matrices exhibited diffusion controlled mechanisms. On the other hand, both diffusion and erosion contribute to the drug release from alprazolam (moderate solubility) matrices (Skoug et al, 1993).

1.13.3.2 Effect of drug particle size

Ford et al (1985a, 1985b) evaluated the effect of drug particle size on the release from HPMC matrices. The release of promethazine hydrochloride, propranolol hydrochloride and aminophylline was not dependent on their particle size except when the polymer/drug ratio was low and the particle size of the drugs was large. However, Ford et al (1985c) indicated that for insoluble drugs, the particle size plays an important role in controlling of release rate.

1.13.4 EFFECT OF EXCIPIENTS

Excipients are added to matrix tablets to provide enough volume for tableting, to modify the release rate of drug, to lubricate the formulation or to change the colour. As these materials may affect the release characteristics of a drug it is therefore necessary to study the effects which these excipients may have on release.

Lapidus and Lordi (1966) stated that the replacement of HPMC by insoluble or soluble excipients increased the rate of drug release. Lapidus and Lordi (1968) showed at only high excipient concentrations (>50%) that the release of chlorpheniramine maleate was faster when lactose was used than when an equivalent amount of dicalcium phosphate was used. Similar results were reported by Ford et al (1987) who found that differences between dicalcium phosphate and lactose were observed when tablets contained low amounts of HPMC (10 mg) and high amounts of excipients (30 mg). Ford et al (1985a) found that the presence or absence of lubricant did not have any effect on the release of promethazine hydrochloride from HPMC K15M matrices.

Daly et al (1984) observed that the release rates of chlorpheniramine maleate decreased in HPMC matrices containing the surfactant, sodium dodecyl sulphate. This was attributed to an increase in viscosity of the polymer due to its interaction with the surfactant. Feely and Davis (1988a) found that the release of chlorpheniramine maleate from HPMC matrices was decreased by the addition of anionic sodium alkyl sulphates and that was due to the formation of an insoluble complex. Ford et al (1991b) reported that the release of propranolol hydrochloride from HPMC matrices decreased in the presence of sodium dodecyl sulphate as a result of formation of propranolol dodecyl sulphate.

1.13.5 EFFECT OF COMPACTION FORCE

The effect of compaction force has been studied by many workers (Lapidus and

Lordi, 1968; Salomon et al, 1979; Conte et al, 1993). Generally, differences in compaction force have little effect on either tablet density or porosity of hydrophilic polymers such as HPMC and sodium carboxymethylcellulose (Huber and Christenson, 1968; Ford et al, 1985a; Dahl et al, 1990; Bettini et al, 1994; Sheskey et al, 1994).

However Korsmeyer et al (1983b) found that the release rate of potassium chloride from HPMC matrices compressed at forces ranging from 28 MPa to 280 MPa varied inversely with tablet porosity and mean pore diameter. They claimed that air trapped within the tablets acted as a transport barrier. Therefore as the porosity of the tablet increased, the initial air trapped in the tablet increased and this caused drug release to be reduced.

1.13.6 RELEASE KINETICS FOR MATRICES

Many mathematical models have been proposed to interpret drug release from matrices. Higuchi (1963) derived equation 1.2 to describe the release of dispersed drug from matrices. This equation predicts that the release of drug from a matrix is proportional to square root of time. The simple form of this equation is shown as equation 1.5 (Ford et al, 1991a).

$$Q = At^{0.5} + C \qquad \textit{Equation 1.5}$$

Q is the fraction of drug released, A is root time dissolution rate constant and C is a constant. The Higuchi equation can be applied if the mechanism of drug release

is diffusion. However diffusion is not always the only mechanism for release of drug from HPMC matrices. Erosion of the polymer also contributes to the process. Korsmeyer et al (1983a) used equation 1.6 to describe the release mechanism of hydrophilic matrices.

$$Q = Kt^n \qquad \textit{Equation 1.6}$$

In equation 1.6, Q is the percentage of drug released at time t, K is a constant relating to the structural and geometric characteristics of the controlled release device, t is the release time and n is the release exponent, indicating the mechanism of drug release. Peppas (1985) stated that equation 1.6 can be used to analyse the first 60% of a release curve. Peppas and Ritger (1987) gave the dependence of n on the diffusional mechanism as depicted in Table 1.1. Fickian diffusion involves the molecular diffusion of the drug due to a chemical potential gradient (Peppas and Sahlin, 1989) and is linearly related to the square root of time. In Case II transport (or relaxational release mechanism) the release rate is independent of time and zero order release can be observed. Non-Fickian or anomalous release is the coupling of diffusion and relaxation mechanisms. Super case II transport mechanism is a non-Fickian diffusion which is observed for systems exhibiting increased swelling at the relaxing front usually at long period of time (Langer and Peppas, 1981).

The effect of lag time was ignored in the equation 1.6. Later Ford et al (1987) stated that equation 1.6 was valid if the release occured as soon as the matrix was exposed to the dissolution fluid. Usually, however, a lag time prior to the release of a drug

Table 1.1. Analysis of diffusional release mechanism (after Peppas and Ritger 1987).

Diffusional exponent (n)			Drug release mechanism
Thin film	Cylindrical sample	Spherical sample	
0.5	0.45	0.43	Fickian diffusion
$0.5 < n < 1.0$	$0.45 < n < 0.89$	$0.43 < n < 0.85$	Non-Fickian diffusion
1.0	0.89	0.85	Case-II transport
>1.0	>0.89	>0.85	Super case II

was observed. Therefore equation 1.7 was proposed by Ford et al (1991a) to account for a lag time.

$$Q = K (t-l)^n \qquad \textit{Equation 1.7}$$

In this equation l is lag time and the other terms are the same as in equation 1.6. As both diffusion and erosion take part in release of drug from hydrophilic matrices, Catelani et al (1988) and Harland et al (1988) used equation 1.8 to analyse the release data. In this equation diffusion and polymer relaxation mechanisms are simultaneously considered.

$$Q = K_1 t^{0.5} + K_2 t \qquad \textit{Equation 1.8}$$

In equation 1.8, K_1 and K_2 are relative contribution of Fickian and relaxational mechanism respectively.

The fact that most systems have a value of n which is intermediate between the Fickian diffusion value and the zero-order release profile has led Peppas and Sahlin (1989) to describe an equation by which it was possible to calculate the contribution due to relaxation and that due to diffusion (equation 1.9). K and K′ in equation 1.9 are Fickian and relaxation release constants, respectively. They claimed that the exponent n for case II transport mechanism is twice that of the Fickian diffusional mechanism regardless of the geometric device used. Peppas and Sahlin (1989) considered that Fickian diffusion and relaxational mechanism were additive.

$$Q = Kt^{n} + K't^{2n} \qquad \textit{Equation 1.9}$$

Ford et al (1991a) derived equation 1.10 by adding a lag time correction to equation 1.9. In equation 1.10 K and K′ are the same as equation 1.9 and l is the lag time.

$$Q = K\,(t-l)^{n} + K'\,(t-l)^{2n} \qquad \textit{Equation 1.10}$$

1.14 AIMS AND OBJECTIVES

The aims and objectives of the work presented in this thesis were mainly to investigate the performance of cellulose ethers, namely hydroxypropylmethylcellulose and ethylcellulose in "coated pellets" and "matrices". Their performance was assessed by using two structurally different drugs with different solubilities (metoclopramide hydrochloride and diclofenac sodium). The study was performed:

(1) To examine the effect of hydroxypropylmethylcellulose (HPMC) of low viscosity

grades in the production of sustained release coated pellets. Chapter 4 deals with factors controlling drug release rate from pellets coated with the water soluble HPMC. The effect of coating load of polymer on drug release and the kinetics of drug release from coated pellets was assessed.

(2) To evaluate the effect of coating load of ethylcellulose aqueous dispersion (Surelease) on the release of drug. Chapter 5 investigates the factors controlling drug release from pellets coated with water insoluble ethylcellulose. The release kinetics were also characterized.

(3) To study the effect of inclusion of water soluble HPMC to water insoluble ethylcellulose on drug release profiles. Chapter 6 examines the effect of different ratios of HPMC:EC on drug release from coated pellets.

(4) To examine the release characteristics of drugs from HPMC matrices prepared by direct compression. Chapter 9 investigates the release kinetics and mechanism of drug release from HPMC matrices. The effect of polymer viscosity and polymer/drug ratio were studied.

(5) To explore the effect of incorporation of EC in HPMC matrices using wet granulation method on drug release and compare with matrices prepared by direct compression (chapter 10).

CHAPTER 2. MATERIALS AND GENERAL METHODOLOGY

2.1 MATERIALS

The following materials were used throughout this study:

2.1.1 HYDROXYPROPYLMETHYLCELLULOSE

Batches of hydroxypropylmethylcellulose USP types 2910 and 2208 manufactured by Dow Chemicals (Midland, Michigan, USA) and obtained from Colorcon Ltd (Orpington, Kent, UK) were used. The molecular structure and formula of HPMC were shown in Figure 1.8. The two HPMC grades which were used in this study were Methocel E (corresponds to USP type 2910) and Methocel K (corresponds to USP type 2208).

Methocel E has a methoxyl content of 28-30% and a hydroxypropoxyl content of 7-12%. Methocel E5 Premium (HPMC E5), Methocel E15-LV Premium (HPMC E15) and Methocel E4M Premium (HPMC E4M) were used in this study. The batch numbers and the nominal viscosities of their 2% solutions in water at 20°C are shown in Table 2.1.

Methocel K has a methoxyl content of 19-24% and a hydroxypropoxyl content of 7-12%. Methocel K100 LV Premium (HPMC K100) and Methocel K4M Premium (HPMC K4M) were used in this study. The batch numbers and the nominal viscosities of their 2% solutions in water at 20°C are shown in Table 2.1.

Table 2.1. The batch numbers and nominal viscosities of 2% w/w solutions of hydroxyproylmethylcellulose polymers used in this thesis.

Polymer	Batch number	Viscosity* (mPa.s)
HPMC E5	MM93051871E	5
HPMC E15	MM93042522E	15
HPMC E4M	MM91061011E	4000
HPMC K100	MM94051022K	100
HPMC K4M	MM92031903K	4000

*: Raw material specification supplied by Colorcon Ltd.

2.1.2 ETHYLCELLULOSE AQUEOUS DISPERSION (SURELEASE)

Throughout the study, pellets were coated mainly with a commercially available ethylcellulose aqueous dispersion (Surelease E-7-7050) obtained from Colorcon Ltd (Orpington, Kent, UK). The molecular structure and formula of ethylcellulose were shown in Figure 1.8. Surelease E-7-7050 has been described as an off white liquid (Raw material specification supplied by Colorcon Ltd.). It contains ethylcellulose 20 mPa.s (17.36% w/w), dibutyl sebacate (3.76% w/w), oleic acid (2.03% w/w), fumed silicon (1.85% w/w) and ammoniated water (75.00% w/w). The pH of dispersion is 9.5-11.5 (Moore, 1989). The solid content of the dispersion is 25% w/w and the average ammonia content in the liquid dispersion is 0.8-1.0% w/w (calculated as ammonia, not ammonium hydroxide). Its boiling point is about 95°C. Surelease was also used as a granulating agent (chapter 10) in the preparation of matrix tablets.

2.1.3 METOCLOPRAMIDE HYDROCHLORIDE

Metoclopramide hydrochloride (Figure 2.1) is a white odourless, crystalline powder, soluble 1 in 0.7 of water, 1 in 3 of ethanol, 1 in 55 of chloroform and practically insoluble in ether (Pitre and Stardi, 1987). It melts at about 182-183°C with decomposition and has a pK_a of 9.0. Its ultraviolet spectrum in aqueous acid has maxima at 273 nm and 309 nm (Moffat et al, 1986). Metoclopramide hydrochloride was obtained from Wilfrid Smith Limited (Edgware, Middlesex, UK).

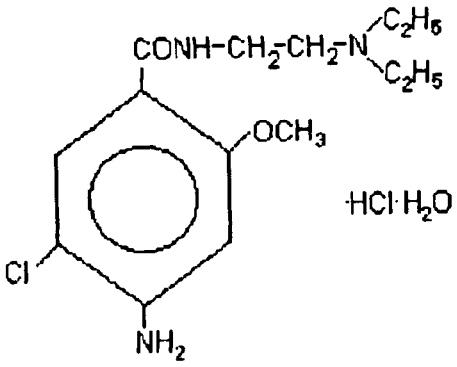


Figure 2.1. The molecular structure of metoclopramide hydrochloride.

2.1.4 DICLOFENAC SODIUM

Diclofenac sodium (Figure 2.2) is a white to slightly yellowish crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96%); slightly soluble in acetone, practically insoluble in chloroform and in ether (Adeyeye and Li, 1990). Its solubility is pH dependent (Navarro and Ballesteros, 1994). Diclofenac sodium melts at about 282-285°C with decomposition and has a pK_a of 4.0. Its ultraviolet spectrum in aqueous acid has a maximum at 273 nm and in

aqueous alkali has a maximum at 275 nm (Moffat et al, 1986). Diclofenac sodium was obtained from Industria Chimica Profarmaco (Milan, Italy).

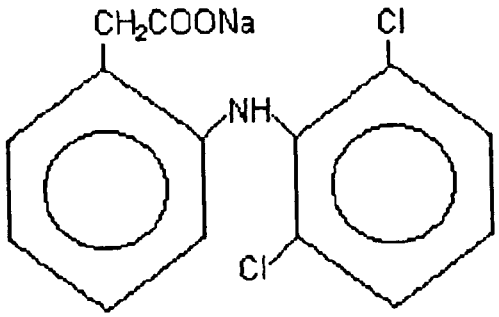


Figure 2.2. The molecular structure of diclofenac sodium.

2.1.5 NON-PAREILS

Non-pareil seeds (commercially available sugar spheres) were used as inert core in the formulations of pellets. Sugar spheres are prepared from crystalline sucrose which is coated using sugar syrup and a starch dusting powder. The United States Pharmacopeia / National Formulary (1995) describes sugar spheres as approximately spherical granules with a uniform diameter and containing not less than 62.5% and not more than 91.5% of sucrose, calculated on the dried basis. The rest of the formulation is mainly starch. Non-pareil seeds with size of 16/20 mesh (0.850-1.18 mm) and 20-25 mesh (0.710-0.850 mm) obtained from Edward Mendel Co. (Redhill, Surrey, UK) and were used as the base upon which the drugs were coated.

2.1.6 TRIACETIN

Triacetin (Figure 2.3) was obtained from Colorcon (Orpington, Kent, UK). It is a colourless and odourless liquid with specific gravity of about 1.15-1.16 $g.cm^{-3}$. It boils at 266°C and its solubility in water is about 6.1% at 25°C (raw material specification data supplied by Colorcon).

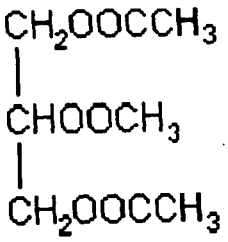


Figure 2.3. The molecular structure of triacetin.

2.1.7 TALC

Talc Fine Powder (Laboratory Reagent) was obtained from British Drug Houses (Poole, Dorset, UK) and used as an anti-adhering agent in coating formulations.

2.1.8 MAGNESIUM STEARATE

Magnesium stearate (General Purpose Reagent) was obtained from British Drug Houses (Poole, Dorset, UK) and used as lubricant in the preparation of tablets.

2.2 METHODS

2.2.1 UV CALIBRATION OF DRUGS

2.2.1.1 Metoclopramide hydrochloride

Solutions of metoclopramide hydrochloride in distilled water were prepared by

dissolving 4, 8, 12, 16 or 20 mg of metoclopramide hydrochloride, accurately weighed on an Oertling analytical balance (West Midlands, UK), in 1000 ml water. The UV absorbances of these solutions at 309 nm were determined using a spectrophotometer (Philips PU 8625, Cambridge, UK) and are shown in Figure 2.4. The best fit equation for the Beers's law plot of the UV absorbance versus drug concentration, is given by equation 2.1.

$$A = -0.0013 + 34.3\,C \qquad (r = 0.9998) \qquad \textit{Equation 2.1}$$

Where A is the absorbance of the solution and C is the concentration of metoclopramide hydrochloride (mg/ml). This equation was used to assay the drug content of pellets.

As the drug content of the pellets used in dissolution studies was 15 mg, solutions of metoclopramide hydrochloride in distilled water were prepared by dissolving 15 mg of metoclopramide hydrochloride, accurately weighed using an Oertling analytical balance (West Midland, UK), in 900 ml water. The UV absorbances of these solutions were determined at 309 nm using the Diode Array spectrophotometer (Hewlett Packard HP8452A, Waldbronn, Germany, coupled to the dissolution tester) and were 0.583 ± 0.008 (n=3). Its E 1%, 1 cm value, determined experimentally and used in dissolution studies, was 342.9.

2.2.1.2 Diclofenac sodium

Solutions of diclofenac sodium in distilled water were prepared by dissolving 4, 8, 12, 16 or 20 mg of diclofenac sodium, accurately weighed on an Oertling analytical balance (West Midlands, UK), in 1000 ml water. The UV absorbances of these solutions at 275 nm were determined using a spectrophotometer (Philips PU 8625, Cambridge, UK) and are shown in Figure 2.5. The best fit equation for the Beers's law plot of the UV absorbance versus drug concentration, is given by equation 2.2,

$$A = 0.0050 + 31.3\,C \qquad (r = 0.9997) \qquad \textit{Equation 2.2}$$

Where A is the absorbance of the solution and C is the concentration of diclofenac sodium (mg/ml). This equation was used to assay the drug content of pellets.

As the drug content of the pellets used for dissolution studies was 15 mg, solutions of diclofenac sodium in distilled water were prepared by dissolving 15 mg of diclofenac sodium, accurately weighed using an Oertling analytical balance (West Midland, UK), in 900 ml water. The UV absorbances of these solutions were determined at 275 nm using the Diode Array spectrophotometer (Hewlett Packard HP8452A, Waldbronn, Germany coupled to the dissolution tester) and were 0.535 ± 0.010 (n=3). Its E 1%, 1 cm value, determined experimentally and used in dissolution studies, was 314.1.

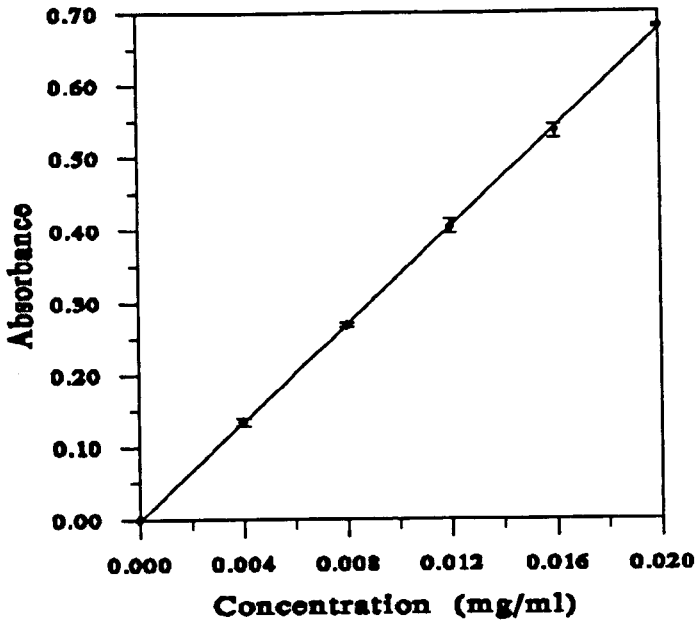


Figure 2.4. Calibration curve of metoclopramide hydrochloride in distilled water at 309 nm. (each point is the mean ± SD of three determinations).

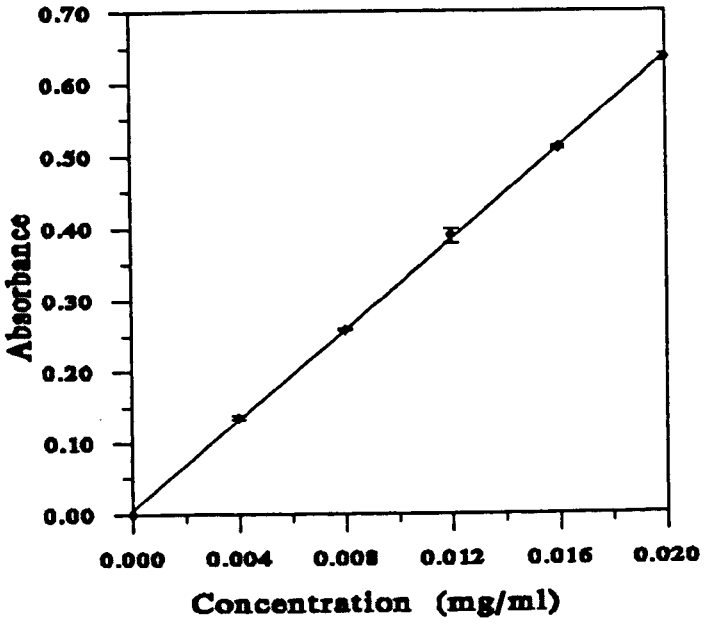


Figure 2.5. Calibration curve of diclofenac sodium in distilled water at 275 nm. (each point is the mean ± SD of three determinations).

2.2.2 DETERMINATION OF DRUG SOLUBILITY

2.2.2.1 Determination of solubility of metoclopramide hydrochloride

Because metoclopramide hydrochloride is a highly water soluble drug, in order to determine its solubility in water at 37°C, 2.5 g samples of metoclopramide hydrochloride were added into 5 ml test tubes containing 1 ml of distilled water. The test tubes were placed in a shaking water bath (Companstat 882942, UK), at 37°C. After complete dissolution of the drug, accurately weighed, additional amounts of drug in increments of 20 mg, were added and the test tubes were examined after 1 h for the occurrence of any crystals. The solubility of metoclopramide hydrochloride was reported at the point where the crystals of drug appeared in the tubes and remained for 48 h.

2.2.2.2 Determination of solubility of diclofenac sodium

Samples (500 mg) of diclofenac sodium powder were added into 10 ml test tubes containing 5 ml of distilled water. The test tubes were placed in a shaking water bath (Companstat 882942, UK), at 37°C for 48 h. Then the suspended solids were allowed to settle and the supernatants were filtered through a Whatman No. 1 filter paper (Whatman International Ltd., Maidstone, UK). The drug concentration was determined spectrophotometrically (Philips PU 8625 Cambridge, UK) at 275 nm after appropriate dilution. The mean of three determinations was used to calculate the solubility of diclofenac sodium in distilled water.

2.2.3 PREPARATION OF COATING FLUIDS

2.2.3.1 Preparation of coating fluids containing HPMC E5 or HPMC E15

Batches (8 kg) of coating fluids containing HPMC E5 or HPMC E15 were prepared at each time of coating. The composition of the coating suspensions for HPMC E5 and HPMC E15 are shown in Tables 2.2 and 2.3 respectively. The concentrations of HPMC E5 and HPMC E15 in the coating fluids were around the values (6% and 4% w/w respectively) needed to achieve uniform coating (Nagai et al, 1989). The amount of plasticizer (triacetin) added was 25% of the polymer weight on the basis of a study performed by Johnson et al (1991).

Solutions of HPMC E5 or HPMC E15 were prepared by initially heating one third of the total amount of water to 80-90°C. The desired amount of HPMC powder was added while stirring with a paddle stirrer. The mixtures were stirred until all agglomerates had disappeared and the particles were thoroughly wetted. Whilst stirring, the remaining water was added as cold water. The talc and plasticizer (triacetin) were added at this stage. The coating fluids were prepared 24 h before use to ensure uniform solvation of the polymer.

Table 2.2. The composition of the coating suspensions of HPMC E5.

Ingredient	% w/w
HPMC E5	5.76
Triacetin	1.44
Talc	2.13
Water	90.67

Table 2.3. The composition of the coating suspensions of HPMC E15.

Ingredient	% w/w
HPMC E15	3.76
Triacetin	0.94
Talc	1.39
Water	93.91

2.2.3.2 Preparation of coating suspension of Surelease

The commercial ethylcellulose aqueous dispersion (Surelease E-7-7050 which contains 25% w/w solids) was diluted to a solid content of 15% w/w with distilled water. This was based on the recommendation of Colorcon Ltd. The suspension was stirred for approximately 30 min. The composition of the diluted coating suspension of Surelease is shown in Table 2.4. The coating dispersion was prepared 30 min before use.

Table 2.4 The composition of coating suspensions for Surelease.

Ingredient	% w/w
Surelease	60
Distilled water	40

2.2.4 EVALUATION OF PELLETS

2.2.4.1 Coating efficiency

The solid contents of each polymeric suspension (HPMC E5, HPMC E15 or Surelease) were determined by drying aliquots (20 g) of the suspensions in an oven

at 60°C until constant weights were obtained. The amounts of dry substance were calculated after weighing the solid contents which remained following drying.

The amount of dry substance applied in each coating process was calculated based on the amount of the coating suspension that had been consumed for coating, as a theoretical weight gain (%A) for each coating process. The increase in pellet weight after each coating process, which was determined by weighing the pellets before and after the coating process was used as the experimental weight gain (%B). Then, the coating efficiencies were calculated using equation 2.3.

$$\textit{Coating efficiency} = \frac{B}{A} \times 100 \qquad \textit{Equation 2.3}$$

This procedure was used in the optimization of the coating conditions (chapter 3) that were used to apply the polymeric films.

2.2.4.2 Degree of aggregation of the pellets

The degree of aggregation of placebo pellets (see section 3.4) was evaluated by mechanical sieving using a series of 20 cm diameter sieves (Endcotts Ltd., London, UK) with aperture sizes 1.4 mm, 1 mm, 0.850 mm, and 0.710 mm. A sample load of 100 g of coated pellets was sieved using the nest of sieves which were shaken on a mechanical shaker (Pascal Engineering, Sussex, UK) continuously for 10 min. A visual analysis showed that the pellet fraction retained on the 1.4 mm sieve consisted of aggregated pellets. Therefore, the percentages of the final product that was retained on the 1.4 mm sieve were used as an indicator of the degree of aggregation.

Duplicate samples were used to calculate the degree of aggregation. This procedure was used in optimization of coating conditions that were used to apply the polymeric film.

2.2.4.3 Scanning Electron Microscopy (SEM)

Coated pellets were examined under a scanning electron microscope (SEM) (Jeol model JSM-T200, Tokyo, Japan) to study the surface morphology of the pellets. This study was used in evaluating the coating conditions and also to investigate the surface of the drug-loaded pellets coated with polymers before and after dissolution. Dry samples were mounted onto stubs using double sided adhesive tape and vacuum coated with gold in an argon atmosphere in the coating chamber of a Polaron E500 diode sputter coating unit (Holywell Industrial Estate, Watford, UK). The coated samples were individually placed on the specimen holder of the scanning electron microscope in a vacuum chamber. The chamber was evacuated and a voltage of 25 kV was selected for accelerating the electrons from electron gun onto the specimen. The image formed was viewed directly via a screen or recorded photographically.

2.2.4.4 Assay of drug content of the drug layered pellets

From each batch, 400 mg of pellets was weighed accurately, ground to fine powder with the use of a glass pestle and mortar and transferred into a 1000 ml volumetric flask using water. The flask was shaken for a period of 1 hour and then brought to volume with water. An aliquot of this solution was filtered and assayed spectrophotometrically at 309 nm and 275 nm for metoclopramide hydrochloride and

diclofenac sodium respectively using a spectrophotometer (model Phillips PU 8625, Cambridge, UK). All the assays were carried out in triplicate and the mean value reported. The concentration of metoclopramide hydrochloride or diclofenac sodium in the each batch of pellets was calculated from the calibration curves (Figures 2.4 and 2.5).

2.2.5 PREPARATION OF MATRICES

Matrices prepared by direct compression of blends containing metoclopramide hydrochloride <90 μm or diclofenac sodium <90 μm, polymers (HPMC E15, HPMC E4M, HPMC K100 or HPMC K4M) in drug:polymer ratios of 1/3, 1/4, 1/5 and 1/10 and 0.5% magnesium stearate as lubricant. The blends were mixed for 15 minutes using a tumbler mixer. Flat-faced tablets, 7.14 mm diameter, were directly compressed on a Manesty F3 single punch tabletting machine (Manesty Machines Ltd., Liverpool, UK) at 20 kN compression force.

2.2.6 DISSOLUTION TESTING

Dissolution was measured by a Pharmatest (GMbH, Hainburg, Germany) dissolution tester coupled with a Diode Array spectrophotometer (Hewlett Packard HP8452A, Waldbronn, Germany). The USP XXII (apparatus I) was used, rotating at 50 rpm in 900 ml distilled water at 37 ± 0.5°C and maintained at this temperature. The media were automatically sampled using an Ismatec peristaltic pump (ISP 8/B, Carshalton, UK) at 50 $ml.min^{-1}$ flow rate. Metoclopramide hydrochloride and diclofenac sodium were monitored at 309 and 275 nm respectively. The mean of six determinations was

used to calculate the drug release for each formulation.

2.2.7 RELEASE KINETICS

In order to determine drug release rates, data were fitted to various kinetic models discussed in chapter 1 (equations 1.1-1.4) using statistical software (Minitab, Standard Release 9.1). Regression analyses were used to obtain the release constants (K) and correlation coefficients (r) for each model. The correlation coefficients for the best statistical fit were used as the principal criteria to evaluate the models. The equation with the highest correlation coefficient was judged to be the most appropriate model for each system. Lag times were also defined as the X intercept when the fitted curve of each model was extrapolated to 0% drug release.

The release data were also analyzed using equations 1.6 and 1.7 in order to evaluate the mechanism of drug release. The data were fitted to equations 1.6 and 1.7 using a privately produced "Curfit" (Philip Rowe: Liverpool John Moores University) computer program. This program calculates the optimum values for n, K, and l using a non-linear, least-squares fitting method (Ford et al, 1991). The understanding of the release mechanism is possible by fitting the release data to these equations and comparing the value of n to the semi-empirical values for various geometries (Table 1.1) reported by Ritger and Peppas (1987). The sums of squares of errors and Schwartz information criterion (Schwartz, 1978) were used as the basis for the best fit.

Sums of squares of errors indicate the discrepancies between the observed data and the values which were predicted by a particular model. Information criteria are used to asses the best model for a set of data and they are calculated using sums of squares of errors and the number of parameters used by a particular model. As a general rule the higher the sums of squares the poorer the model (Ford et al, 1991). The lower the Schwartz information criterion the better the model.

For comparative purposes, release data between 15-60% were used for modelling drug release. This range also corresponded to the limits of applicability of equations 1.6 and 1.7.

2.2.8 THERMAL ANALYSIS

Thermal analysis is a method which can be used to characterize the alterations of physical or chemical properties of substances induced by temperature changes. The most common types of thermal analysis are differential scanning calorimetry, differential thermal analysis, thermogravimetric analysis and thermomechanical analysis (Ford and Timmins, 1989).

2.2.8.1 Thermomechanical analysis

Thermomechanical analysis (TMA) may be used to measure the dimensional changes in a solid sample (such as expansion or contraction) as a function of temperature (Ford and Timmins, 1989). It may also be used to measure deformation of a sample under a constant load. Properties such as the glass transition temperature (T_g),

softening temperature (T_s), tensile modulus, compression modulus, expansion coefficient and shrinkage temperature can be determined by TMA (Masilungan and Lordi, 1984). A Perkin Elmer Model TMA7 (Beaconsfield, UK) was used to measure the glass transition temperature of the polymeric films.

In the penetration mode, the polymeric film initially exhibits resistance to penetration due to the limited movement of the individual molecules. As the temperature increases, the amount of thermal energy in the polymer chains increases and this makes the immobilized chains more flexible (Ford and Timmins, 1989). Near the glass transition temperature, there is a corresponding increase in void volume in the polymers, allowing the polymer to become penetrable (Masilungan and Lordi, 1984). As the polymer softens the position of the probe will change and this position is accurately monitored as a function of temperature.

2.2.8.1.1 Calibration of TMA

The thermal analyzer was calibrated before use. Four different calibrations were performed. These were furnace calibration, two standard temperature calibration, height calibration and force calibration. Furnace calibration linearizes the furnace response by matching the program temperature to the thermocouple temperature over the temperature range which had been selected. In practice this was from 30°C to 200°C. This calibration was performed automatically by the analyzer. A two standard calibration was performed after the furnace calibration using indium (melting temperature 156.60°C) and zinc (melting temperature 419.47°C) as calibrants to

correct for differences in temperature between the sample and the thermocouple. The samples were scanned at a heating rate of 10°C/min and the onset temperatures which were obtained by the instrument were programmed into the TMA. Height calibration was used to calibrate the ordinate axis of the TMA7 using a displacement standard supplied by Perkin Elmer with a defined height accurately measured with a micrometer (Mitutoyo, Japan). Force calibration was performed to calibrate the force which the analyzer applied on the sample using a force calibration standard with weight of 50 g, supplied by Perkin Elmer.

2.2.8.1.2 Thermomechanical analysis measurement

A flat faced quartz probe with 3.66 mm radius was applied with 15 mN force on free films while they were heated at 10°C/min from 30°C to 160°C for Surelease films and from 30°C to 200°C for HPMC films. The experiments were performed in duplicate to obtain the T_g or T_s of the polymer films.

2.2.8.2 Differential scanning calorimetry (DSC)

Differential scanning calorimetry measures the heat gain resulting from physical or chemical changes within a sample as a function of temperature (Fiese and Hagen, 1986). DSC measurements were carried out using a Perkin Elmer (Beaconsfield, UK) Differential Scanning Calorimeter (Model DSC7) controlled by a Perkin Elmer TAC7.

2.2.8.2.1 Calibration of DSC

Calibration of DSC was performed at ambient conditions. Indium (onset of melting temperature: 156.60°C, enthalpy of fusion (ΔH_f) = 28.45 J/g) and Zinc (onset of melting temperature: 419.47°C) were used as calibrants. Samples (2-3 mg) were heated at 10°C/min in crimped aluminium pans under a nitrogen atmosphere. A similar empty pan was used as the reference. Melting points and enthalpies of fusion of samples were automatically calculated by the instrument. The calculated peak area of indium and the melting temperatures of indium and zinc were programmed into the calorimeter as calibrant data.

2.2.8.2.2 DSC measurements

DSC measurements were performed in order to characterize the drug substances and to investigate the interaction between metoclopramide hydrochloride and Surelease. Samples of 2-3 mg of drug was sealed in aluminium pans and scanned at 10°C/min over the range of 50-220°C for metoclopramide hydrochloride and 80-320°C for diclofenac sodium.

CHAPTER 3. DEVELOPMENT OF COATING CONDITIONS FOR APPLICATION OF POLYMERIC FILMS ON PELLETS

The application of a uniform coating is necessary in order to achieve sustained drug released from coated pellets. As the coating conditions in which polymeric films are applied, could influence both the surface characteristics of the pellets (and consequently the release rate) and the efficiency of the coating, the optimization of their coating conditions is therefore necessary. The aims and objectives of the studies outlined in this chapter are to optimize the process conditions used to apply the coats and to describe the coating equipment which was used.

3.1 DESCRIPTION OF COATING EQUIPMENTS

An Accela-cota 10 (Manesty, Liverpool, UK) equipped with an air-borne spray unit (Walther Pilot model WAXVU, Germany) was used for coating. It has an angular pan that rotates on the horizontal axis. The periphery of the pan is completely perforated. The drying air enters from above and is exhausted through a stationary plenum that almost covers the entire bed. The temperature of the inlet air can be adjusted with a thermostat. The pan is equipped with 8 baffles. The maximum working capacity of Accela-cota 10 is approximately 18 kg. A schematic diagram of Accela-cota 10 is shown in Figure 3.1.

3.1.1 MODIFICATION OF THE COATING MACHINE

For this study, the circumference of the pan was meshed with gauze (aperture size

of 450 μm) in order to prevent pellets escaping through the perforations during coating.

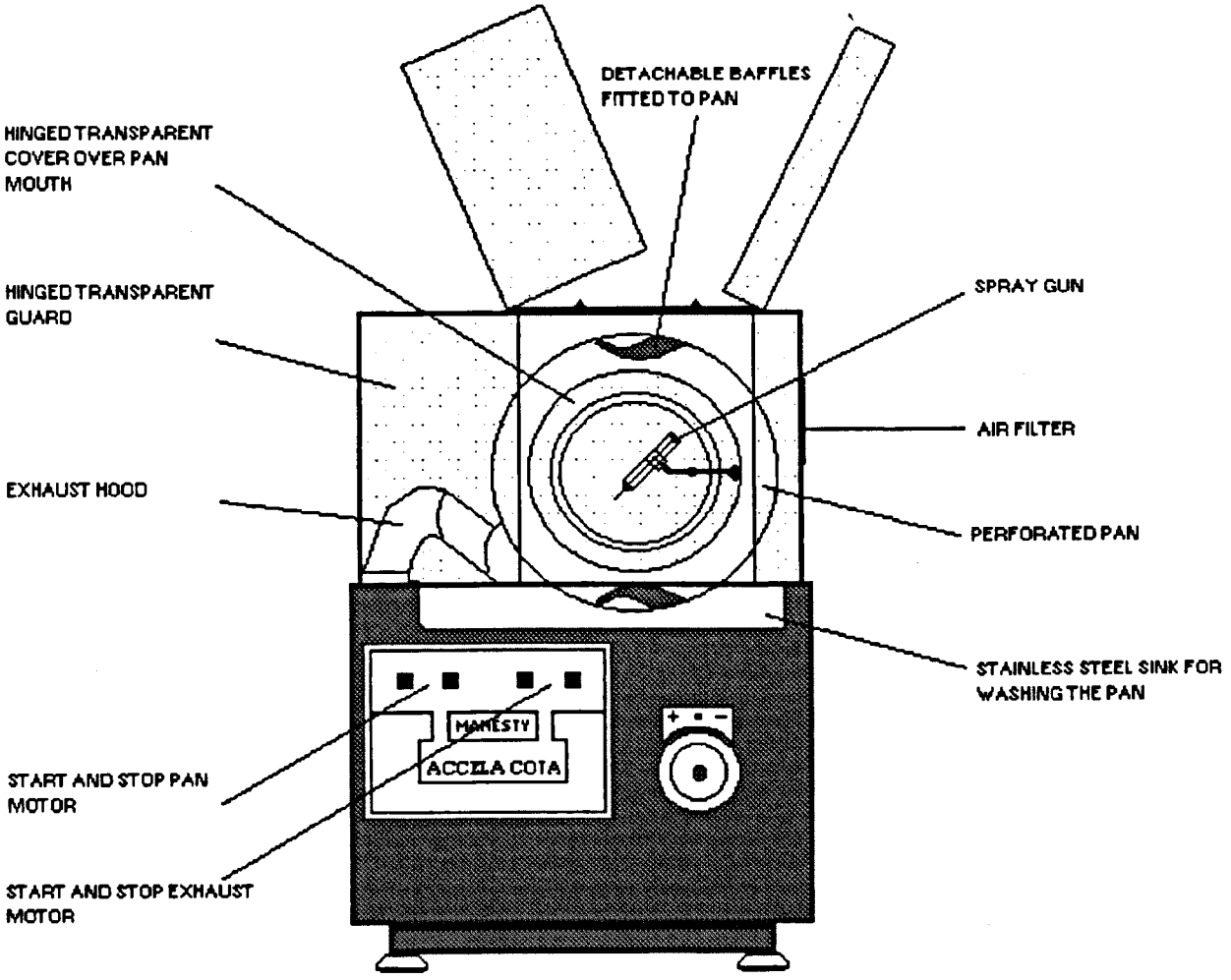


Figure 3.1. Schematic diagram of Accela-Cota 10.

3.2 DETERMINATION OF GLASS TRANSITION TEMPERATURE OF THE POLYMERIC FILMS

It is necessary to characterize the coating of film coated products in order to optimize the coating formulation or process (Masilungan and Lordi, 1984). One of the properties of a film-coating material is its glass transition temperature (T_g) which is the key to film formation (Ghebre-Sellassie et al, 1986). In film formation, during the drying stage, either the solvent evaporates from the solution or, if water, evaporates from the dispersion or solution. Initially, the polymers are present as isolated coils (Osterwald, 1985). If the solvent evaporates slowly the coils approach until, at a certain polymer concentration, they begin to penetrate each other. A film is formed provided the sprayed droplets are able to coalesce and penetrate each other. It is necessary that at least segments of the polymer be mobile, i.e. they must be present above the glass transition temperature in order to penetrate each other (Osterwald, 1985).

At temperatures above the T_g, the polymer chains have appreciable mobility and are conducive to film formation. Below the T_g, the polymer chains are immobile, except for movement around the equilibrium position, making it very difficult for the polymer particles to coalesce (Ghebre-Sellassie et al, 1986). In other words, below the T_g the polymer is said to exist in the glassy state and is characterized by a somewhat ordered structure in which there is minimal polymer chain movement. Another property of the polymer is the thermal softening point (T_s) which indicates the point at which the polymer softens prior to melting. Usually, the T_s lies between

the T_g and the melting point (Johnson et al, 1991). Since most polymers have a high T_g and T_s which can not be achieved during coating, they need to be plasticized. A plasticizer is added in order to reduce the T_g of a polymer (section 1.12.4.3).

Goodhart et al (1984) stated that when the inlet air temperature during coating approached the T_g of the polymer, smoother surfaces and faster coalescing of the film resulted. In film coating, the drying air must be able to provide enough energy to soften the polymeric chains in order to achieve a uniform film. Therefore knowledge of the T_g or the T_s of a polymer can be used as a guideline for selecting the inlet air temperature for the coating process (Chang et al, 1987). Thermomechanical analysis was used in this study to determine the T_g or T_s of the polymeric film.

3.2.1 MATERIALS

HPMC E5, HPMC E15, Surelease, triacetin and talc, as described in section 2.1, were used.

3.2.2 METHODS

3.2.2.1 Preparation of free films

The coating fluids of HPMC E5, HPMC E15 and Surelease (prepared as described in sections 2.2.3.1 and 2.2.3.2) were used to prepare free films. The polymeric films were prepared by intermittently spraying the coating suspensions, using the Accela-Cota spray unit, onto the flat surface of a teflon coated pan. This was accommodated

in the Accela-Cota pan which had been prewarmed by means of the hot air unit. The films were dried at about 70°C. The dried films were carefully removed from the pan using a spatula and stored over silica gel in a desiccator and used within 24 h of preparation.

3.2.2.2 Thermomechanical analysis measurements

The thermal transitions of the polymeric films were measured using a TMA Perkin Elmer Model TMA7, as described in section 2.2.8.1.

3.3 RESULTS AND DISCUSSION

3.3.1 TRANSITION TEMPERATURES OF THE HPMC E5 OR HPMC E15 FILMS

Figure 3.2 is a TMA scan of the free film of HPMC E5. There are two inflections. According to Johnson et al (1991), who used TMA to measure the T_g of HPMC 6 mPa.s films, the first inflection in the scan could be related to the T_g and the second inflection may be taken as the T_s. Therefore the glass transition temperature of HPMC E5 film plasticized with 25% triacetin probably was around 70°C and the softening point of the polymer was around 161°C. The values of T_g and T_s reported by Johnson et al (1991) for HPMC 6 mPa.s films plasticized with 20% w/w triacetin were about 99°C and 179°C respectively.

The TMA scans of the HPMC E15 films (Figure 3.3) were similar to those of HPMC E5. There was a sudden shift between 60°C and 86°C. Therefore the T_g was probably around 77°C.

3.3.2 TRANSITION TEMPERATURES OF THE SURELEASE FILM

A TMA scan of the film prepared from Surelease is shown in Figure 3.4. There was a change in the resilience of the film between 40 and 60°C. A similar shift for Surelease films was reported by Ghebre-Sellassie et al (1988) and attributed to softening of the film. Iyer et al (1990) found that the softening temperature of Surelease films was approximately 35°C.

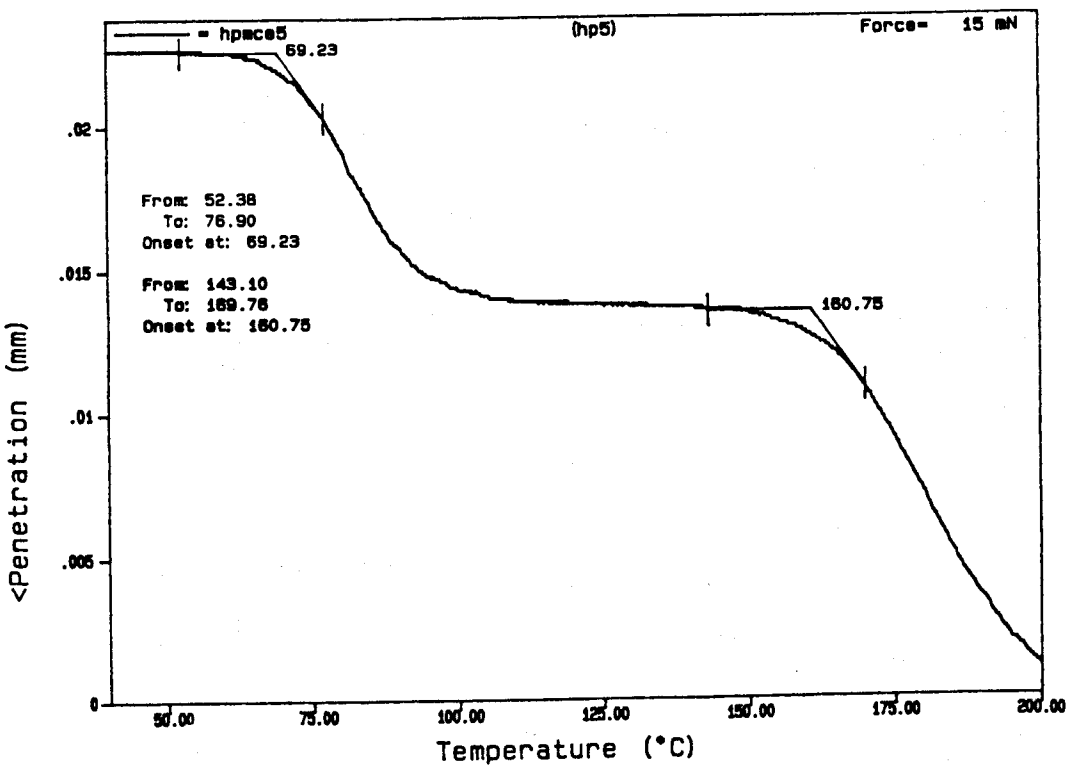


Figure 3.2. TMA scan of HPMC E5 film using a penetration probe at a force of 15 mN.

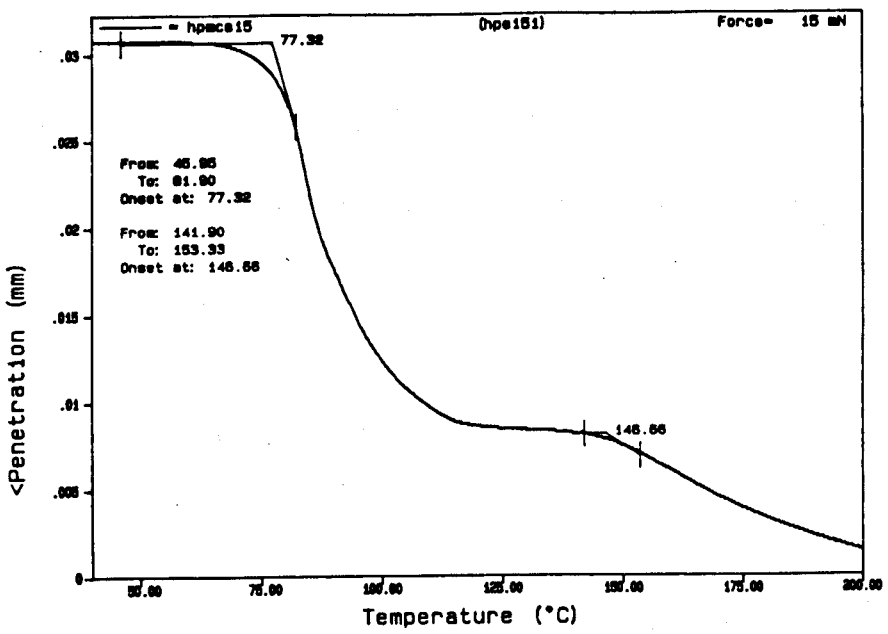


Figure 3.3. TMA scan of HPMC E15 film using a penetration probe at a force of 15 mN.

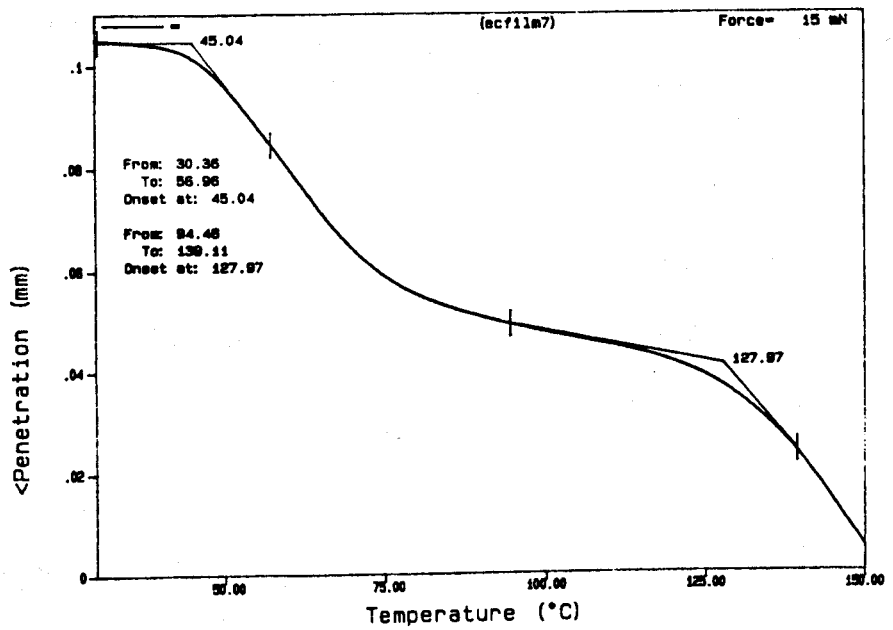


Figure 3.4. TMA scan of Surelease film using a penetration probe at a force of 15 mN.

3.4 DEVELOPMENT OF COATING CONDITIONS

The coating conditions were investigated in order to optimize the coating process. The pan speed (10 rpm), the position of spray gun (central and 20 cm above the bed of seeds) and the flow rate of inlet air (approximately 290 cuft/min) were not varied. The inlet air temperature, spray rate and atomizing air pressure were varied.

The following criteria were taken into consideration when choosing the coating conditions:

1. The surface morphology of the coated pellets. This parameter has a tremendous effect on the release rate of a coated drug (Mehta and Jones, 1986).
2. The degree of aggregation of the coated pellets.
3. Coating efficiency. This can be used as an indication of the extent of loss of coating material.

3.4.1 MATERIALS

Non-pareil seeds (0.850-1.18 mm), HPMC E5, HPMC E15, Surelease, talc and triacetin, as described in section 2.1, were used in this study.

3.4.2 METHODS

3.4.2.1 Preparation of coating fluids

The formulations that were employed for coating the pellets with HPMC E5, HPMC E15 or Surelease are listed in Tables 2.2, 2.3 and 2.4 respectively.

3.4.2.2 Coating procedure

The coating fluids for HPMC E5 or HPMC E15 were stirred for 1 h before and throughout the coating process. The surelease coating suspension was stirred for at least 30 min before coating and throughout the coating process. Batches of 4500 g non-pareils (0.850-1.18 mm) were pre-warmed for 10 min prior to coating. The variations in the parameters of the coating process that were used to coat the non-pareils with HPMC E5, HPMC E15 or Surelease are shown in Tables 3.1, 3.2 and 3.3 respectively. The amount of coating suspension applied in each experiment was calculated on the basis of a theoretical 4% increase in pellet weight.

3.4.2.3 Evaluation of coating process

Coating efficiency, degree of aggregation of the pellets and surface morphology of the coated pellets were used in evaluating the coating process. Coating efficiency was measured as described in section 2.2.4.1, the degree of aggregation of the pellets was determined as described in section 2.2.4.2 and SEM of the surface of uncoated and coated non-pareils was carried out as described in section 2.2.4.3.

3.5 RESULTS AND DISCUSSION

3.5.1 COATING CONDITIONS FOR HPMC E5

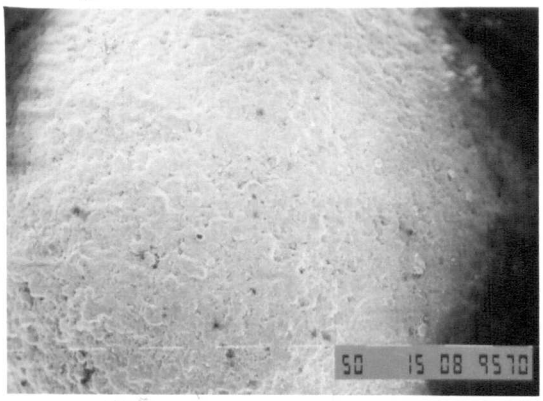
A summary of the results obtained from coating pellets with HPMC E5 under the various conditions are shown in Table 3.1. Although higher temperatures (80-85°C) reduced the incidence of aggregated pellets to 6% w/w and ensured film formation because it is above T_g of the HPMC E5 film (in condition C) the coating efficiency

Table 3.1. Process conditions used to apply the coating fluid of HPMC E5 onto non-pareils and the results of degree of aggregation ± SD and coating efficiency of the coated pellets.

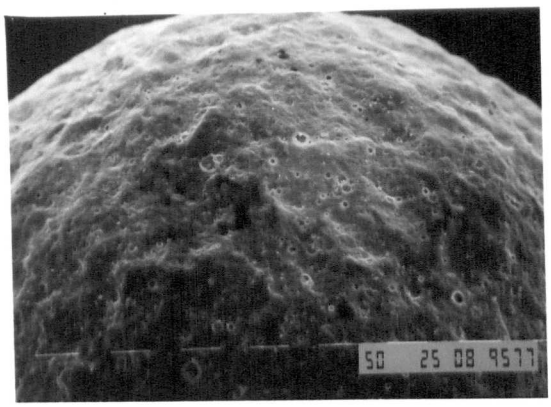
Condition	A	B	C	D	E
Inlet air temperature (°C)	60-63	72-74	80-85	72-74	72-74
Outlet air temperature (°C)	47-49	53-55	60-65	56-59	57-59
Atomizing air pressure (psi)	30	30	30	40	40
Spray rate (g/min)	27	27	27	27	20
Results of degree of aggregation ± SD and coating efficiency					
Degree of aggregation	15% ± 3	10% ± 1.5	6% ± 2	5% ± 1.5	1% ± 0.5
Coating efficiency	91%	91%	70%	91%	91%

decreased to 70%. This may indicate that spray drying of the coating liquid droplets and consequent loss of coating material had occurred. The inlet air temperatures in conditions A (60-63°C) and B (72-74°C) were also close to the T_g (about 70°C) of the HPMC E5 coat. Scanning electron micrographs of pellets coated at these conditions (Figure 3.5) show the formation of film without any cracks. However, due to the lower degree of aggregation of pellets in condition B the inlet air temperature for coating process was therefore, selected to be 72-74°C.

The atomizing air pressure was increased (condition D) and consequently the finer atomized fluid droplets were produced. This increased the drying efficiency of the coating droplets and resulted in a lower degree of aggregation (Table 3.1). The spray rate was lowered to 20 g/min (condition E). This reduced the degree of aggregation. Therefore the condition E was chosen to apply the coating fluid containing HPMC E5 (chapter 4).



(a)



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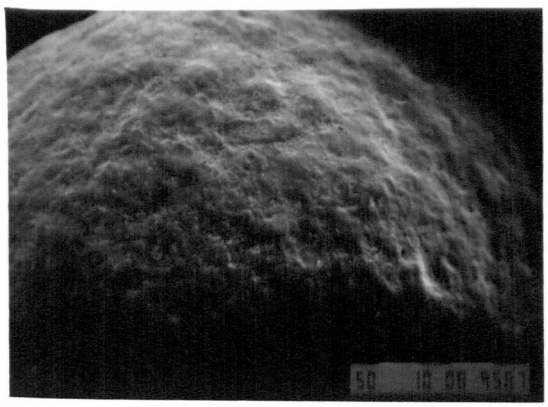
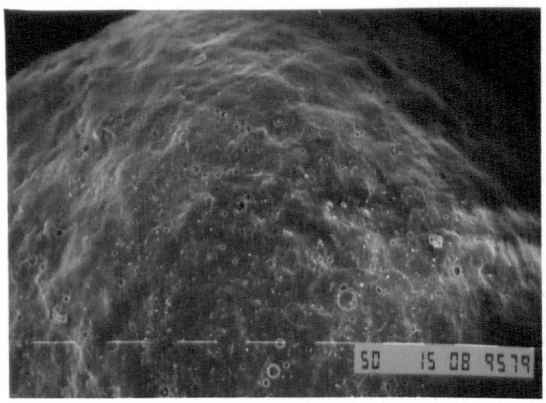


(c)



(d)

Figure 3.5. Micrographs of the surface of non-pareils of: (a) uncoated and non-pareil coated with HPMC E5 using conditions; (b) A, (c) B, (d) C, described in table 3.1. (Magnification × 100).

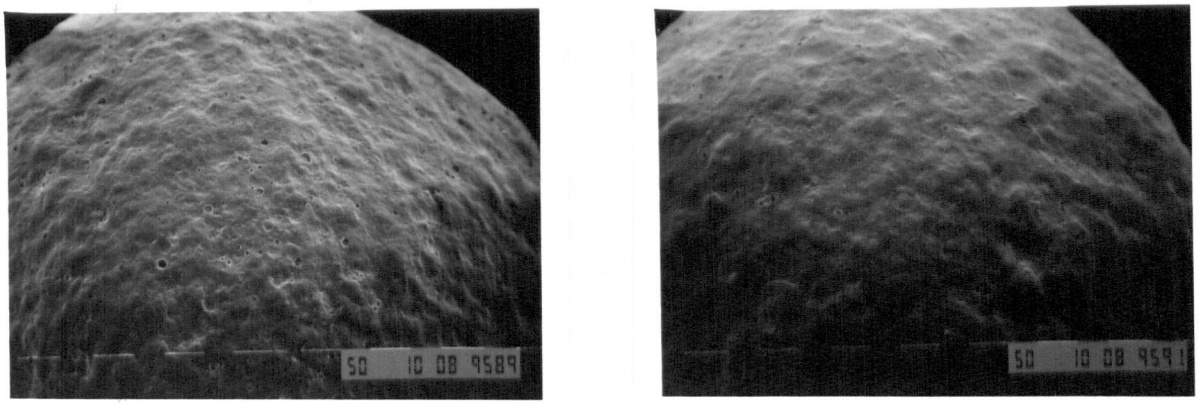
3.5.2 COATING CONDITIONS FOR HPMC E15

The Summary of results obtained from pellets coated with HPMC E15 are shown in Table 3.2.

Table 3.2 Process conditions used to apply the coating fulid of HPMC E15 onto non-pareils and the results of degree of aggregation ± SD and coating efficiency of the coated pellets.

Condition	**F**	**G**	**H**
Inlet air temperature (°C)	72-74	80-85	72-74
Outlet air temperature (°C)	52-54	60-62	56-58
Atomizing air pressure (psi)	40	40	40
Spray rate (g/min)	28	28	21
Results of degree of aggregation ± SD and coating efficiency			
Degree of aggregation	5% ± 2	1.5% ± 1	1% ± 0.2
Coating efficiency	90%	83%	90%

Although higher temperatures of 80-85°C (Table 3.2 condition G) reduced the formation of aggregated pellets to 1.5% and ensured the formation of homogenous films, the coating efficiency decreased to 83%. Again this indicates that spray drying of the coating liquid droplets and consequent loss of coating material have occurred. Therefore the inlet air temperature selected for coating HPMC E15 was 72-74°C (condition F). Scanning electron micrographs of pellets coated under conditions F and G are shown in Figure 3.6. This indicates the deposition of a film without cracks. In all cases the inlet air temperature was then able to soften the polymer to form a film. Lowering the spray rate to 21 g/min (condition H), further reduced the degree of aggregation.

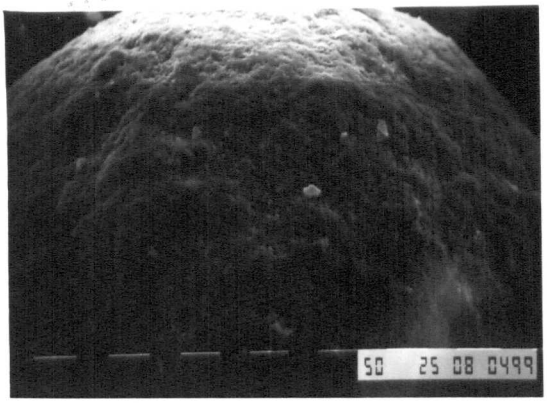


(a) (b)

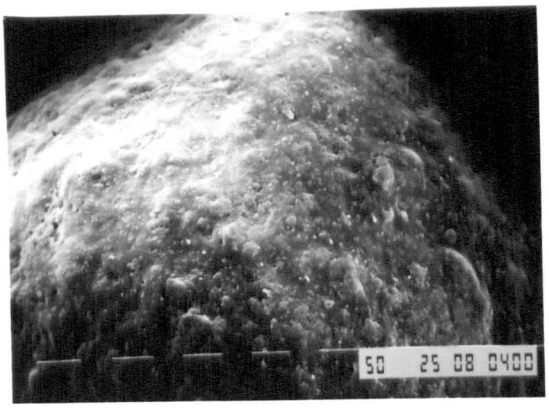
Figure 3.6. Micrographs of the surface of non-pareils coated with HPMC E15 using conditions; (a) F, (b) G described in table 3.2. (Magnification × 100).

3.5.3 COATING CONDITIONS FOR SURELEASE

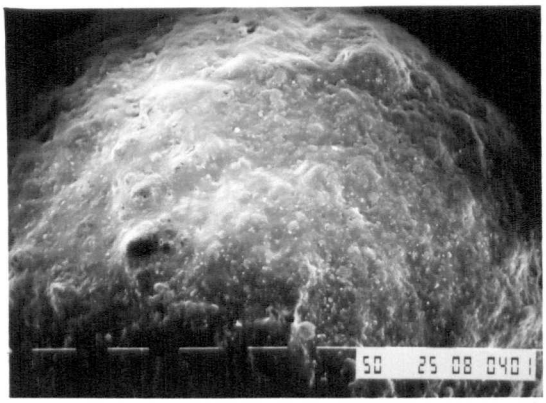
Table 3.3 summarizes the results obtained from pellets coated with Surelease. The transition observed in Surelease film at 45°C (Figure 3.4) is probably related to the T_g of Surelease. Therefore, the inlet air temperatures for all conditions (I to M) were high enough to promote coalescence of the polymer chains to form a film. The scanning electron micrographs of pellets coated under conditions I, J and K are shown in Figure 3.7. The surfaces show the formation of the film without any cracks. The results in Table 3.3 show that there was no aggregation of the pellets in condition K but the efficiency of coating decreased in comparison with conditions I and J. When the atomizing air pressure was increased and spray rate was lowered to 16 g/min (condition M) the formation of aggregated pellets reduced to 0.5%.



(a)



(b)



(c)

Figure 3.7. Micrographs of the surface of non-pareils coated with Surelease using conditions; (a) I, (b) J, (c) K described in table 3.3. (Magnification × 100).

Therefore, due to the lower degree of aggregation and higher coating efficiency in condition M, these conditions were chosen to apply the Surelease coat onto pellets (chapters 5, 6 and 7).

Table 3.3 Process conditions used to apply the coating fluid of Surelease onto non-pareils and the results of degree of aggregation ± SD and coating efficiency of the coated pellets.

Condition	I	J	K	L	M
Inlet air temperature (°C)	45-50	60-62	70-73	60-62	60-62
Outlet air temperature (°C)	38-40	51-53	66-68	50-53	51-53
Atomizing air pressure (psi)	30	30	30	40	40
Spray rate (g/min)	20	20	20	20	16
Results of degree of aggregation ± SD and coating efficiency					
Degree of aggregation	7% ± 1.5	5% ± 0.9	0%	1% ± 0.4	0.5% ± 0.3
Coating efficiency	92%	92%	88%	92%	92%

3.6 CONCLUSIONS

The results were used to optimize conditions which were used to apply HPMC E5, HPMC E15 or Surelease coating fluids. The conditions are summarized in Table 3.4 and were used as the basis of coating in chapters 4 to 7.

Table 3.4 The optimized conditions which were used to apply HPMC E5, HPMC E15 or Surelease coating fluid.

Condition	HPMC E5	HPMC E15	Surelease
Inlet air temperature (°C)	72-74	72-74	60-62
Outlet air temperature (°C)	57-59	56-58	51-53
Atomizing air pressure (psi)	40	40	40
Spray rate (g/min)	20	21	16

CHAPTER 4. EFFECT OF HPMC E5 OR HPMC E15 ON THE DRUG RELEASE FROM PELLETS

4.1 INTRODUCTION

Water-soluble polymers, are often used in film coating to protect the dosage form from environmental influence and to improve its appearance, ingestion, taste, etc (Osterwald, 1985). HPMC-based aqueous films are the first choice for tablet coatings that are designed to mask bitter taste, make tablets easy to swallow, impart aesthetic appearances and identify product (Dansereau et al, 1993). Low viscosity grades of HPMC are commonly used in film coating. High viscosity grades of HPMC are unsuitable for film coating because they present some technical problems related mainly to the need for organic solvents to make sprayable dispersions (Gazzaniga et al, 1995). Aqueous solutions of high viscosity grades of HPMC can be used but only at very low concentrations, in order to achieve sprayability. This results in a long processing time (Maffione et al, 1993). On the other hand, Chang et al (1987) reported that water soluble polymers which yield solutions of low viscosities are not suitable for controlled drug release. However these authors have not given empirical evidence of the unsuitability of low viscosity polymers to control drug release.

4.1.1 AIMS OF THE STUDY

This study was carried out to evaluate the viscosity effect and coating load on the release of metoclopramide hydrochloride or diclofenac sodium from pellets coated with low viscosity, water soluble HPMC polymers.

4.2 MATERIALS AND METHODS

4.2.1 MATERIALS

Metoclopramide hydrochloride, diclofenac sodium, HPMC E5, HPMC E15, talc, non-pareils (0.710-0.850 mm) and triacetin, as described in section 2.1, were used.

4.2.2 METHODS

4.2.2.1 Drug layering of non-pareils

4.2.2.1.1 Preparation of coating suspension of metoclopramide hydrochloride

The composition of the coating suspension used to apply metoclopramide hydrochloride to the non-pareils is shown in Table 4.1. The HPMC E15 solution was prepared by dissolving 40 g HPMC E15 in 600 ml water as described in section 2.2.3.1. Metoclopramide hydrochloride was separately dissolved in 400 ml of water and then mixed with the HPMC E15 solution. The talc, which was dispersed in 100 ml of water, was then added as a suspension.

Table 4.1. Composition of metoclopramide hydrochloride suspension used for drug layering.

Ingredient	Amount
Metoclopramide hydrochloride	200 g
HPMC E15	40 g
Talc	60 g
Water	1100 ml

4.2.2.1.2 Preparation of coating suspension of diclofenac sodium

The composition of the coating suspension used to apply diclofenac sodium to the non-pareils is shown in Table 4.2. Initially a solution of 40 g HPMC E15 in 600 ml of water was prepared as described in section 2.2.3.1. Diclofenac sodium was dispersed in 500 ml of water. The dispersion was passed through a 105 μm sieve with the aid of an additional 100 ml water to remove any large aggregates of drug. The HPMC solution was then added to the drug suspension.

Table 4.2. Composition of diclofenac sodium suspension used for drug layering.

Ingredient	Amount
Diclofenac sodium	200 g
HPMC E15	40 g
Water	1200 ml

4.2.2.1.3 Coating of non-pareil seeds with drug

Batches of 4500 g of non-pareil seeds were prewarmed (10 minutes) and coated with drug suspensions using the conditions shown in Table 4.3. The drug suspensions were stirred for 1 h before and throughout the coating process. Drug layering produced pellets with a metoclopramide hydrochloride load of 3.94 ± 0.03% w/w for HPMC E5 and 3.98 ± 0.05% w/w for HPMC E15 coated pellets. Diclofenac sodium loaded pellets were coated only with HPMC E15 (section 4.3.2) and the percent of drug loading was 3.93 ± 0.08% w/w.

Table 4.3. The conditions used for drug layering.

Condition	Metoclopramide hydrochloride	Diclofenac sodium
Inlet air temperature (°C)	60-63	60-63
Spray rate (g/min)	15	18
Atomizing air pressure (psi)	40	40

4.2.2.2 Assay of drug content

The drug content of the drug-loaded non-pareil seeds was determined using the method described in section 2.2.4.4.

4.2.2.3 Coating of drug loaded non-pareils with HPMC E5 or HPMC E15

Batches of 4500 g drug-loaded pellets were coated with HPMC E5 or HPMC E15 under the conditions shown in Table 3.4 (section 3.6). By taking into consideration the coating efficiency, samples of 50 g of coated pellets were removed from the coating pan when the coating loads had reached 4%, 8%, 12%, 16% and 20% w/w.

4.2.2.4 Scanning electron microscopy

Scanning electron microscopy was performed as described in section 2.2.4.3.

4.2.2.5 Dissolution testing

Dissolution studies were carried out as described in section 2.2.6 with modifications. The pellets were put in small bags (with major dimensions of 2 cm × 3 cm) made

from metal gauze (25 μm) to prevent the pellets coming out of the baskets during dissolution tests. These metal bags were placed inside the dissolution baskets.

4.2.2.6 Release kinetics for coated pellets

The kinetics of drug release was studied as described in section 2.2.7.

4.2.2.7 Determination of drug solubility

The solubility of either drug in water at 37°C was determined as described in section 2.2.2.

4.3 RESULTS AND DISCUSSION

4.3.1 EFFECT OF COATING LOAD ON THE RELEASE OF METOCLOPRAMIDE HYDROCHLORIDE FROM PELLETS COATED WITH HPMC E5 OR HPMC E15

The release profiles of metoclopramide hydrochloride from pellets coated with HPMC E5 or HPMC E15 are shown in Figures 4.1 and 4.2 respectively. All dissolution data were plotted as percent dissolved against time. As the coating load increased the drug release decreased for pellets coated with either HPMC E5 or HPMC E15. Although using a different system, similar results were reported by Wan and Lai (1991). Wan and Lai (1991) demonstrated that the release of diphenhydramine hydrochloride from lactose granules coated with an HPMC E15 film was dependent, to a large extent, on the total content of the polymer present in the coat.

Tables 4.4 and 4.5 summarize the rate constants and the correlation coefficients for different kinetic models of the release for metoclopramide hydrochloride coated with HPMC E5 or HPMC E15 respectively. The increase in the coating load for both HPMC E5 and HPMC E15 was accompanied by a decrease in the release rate. For example, the square-root release rate for HPMC E15 coated pellets was halved as the coating load increased from 4% to 20% w/w.

Comparison of release rates for HPMC E5 or HPMC E15 coated pellets indicates that slower release rates were obtained from HPMC E15 coated pellets. For example, at the 20% coating load the square-root release rate of drug was one and half times faster for HPMC E5 coated pellets than for HPMC E15 coated pellets.

All the pellets disintegrated during the dissolution test and no gel like structure remained, indicating complete erosion of the membrane and pellets, even at the 20% w/w coating load.

4.3.2 EFFECT OF COATING LOAD ON THE RELEASE OF DICLOFENAC SODIUM FROM HPMC E15 COATED PELLETS

Since the use of HPMC E5 or HPMC E15 as coatings, produced similar release profiles for metoclopramide hydrochloride from pellets, it was decided to investigate only the HPMC E15 coat on the release of diclofenac sodium loaded pellets. Figure 4.3 shows the effect of HPMC E15 coating load on the release of diclofenac sodium. Similarly to metoclopramide hydrochloride, the drug released decreased as the coating

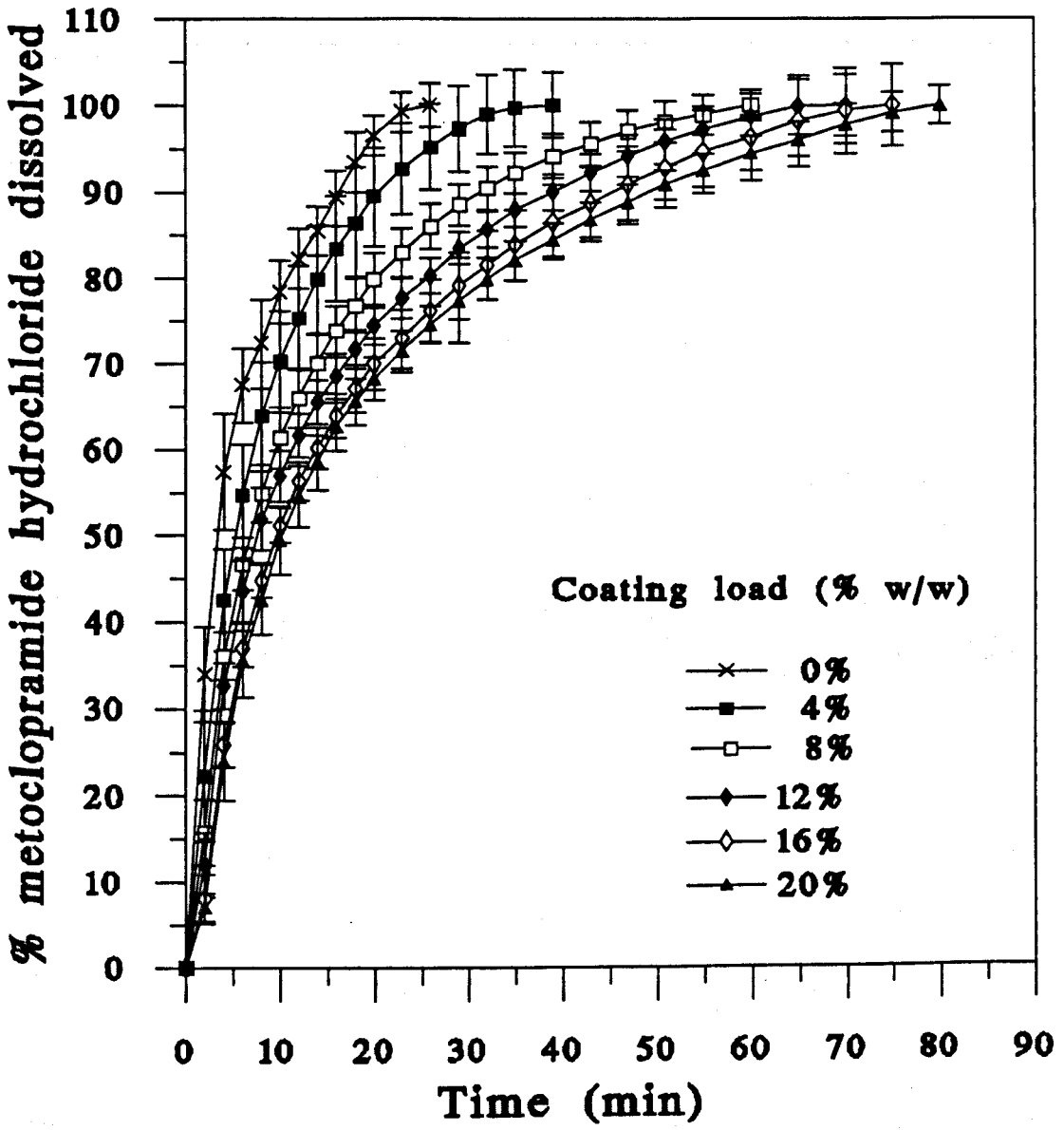


Figure 4.1. Effect of coating load on the release of metoclopramide hydrochloride from HPMC E5 coated pellets.

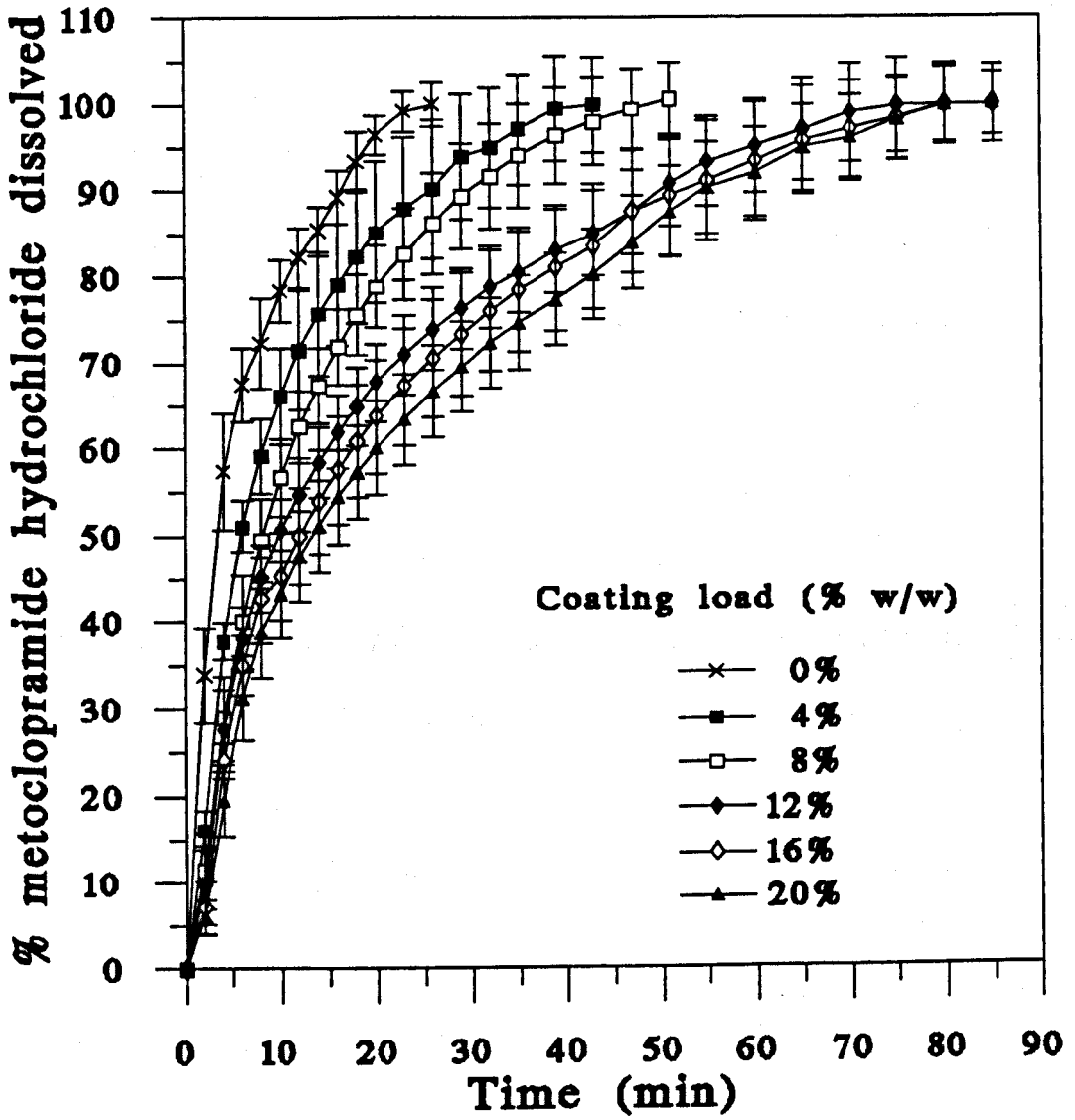


Figure 4.2. Effect of coating load on the release of metoclopramide hydrochloride from HPMC E15 coated pellets.

load increased. The release rates of diclofenac sodium from HPMC E15 coated pellets (Table 4.6) decreased as the coating load increased. The pellets disintegrated during the dissolution test indicating that erosion of the polymeric membrane and dissolution of the pellets had occurred.

4.3.3 RELEASE KINETICS FOR METOCLOPRAMIDE HYDROCHLORIDE RELEASE FROM HPMC E5 OR HPMC E15 COATED PELLETS

The correlation coefficients for the best statistical line (Tables 4.4 and 4.5) revealed that square-root kinetics were probably the most applicable to the release data for pellets coated with HPMC E5 or HPMC E15.

Release data were also analysed by equations 1.6 and 1.7. Tables 4.7 and 4.8 shows the values of K, n and l for the release data which corresponded to 15-60% of drug released from HPMC E5 and HPMC E15 coated pellets, respectively. Considering the sums of squares (ss) and Schwartz information criterion the equation 1.7 which included the lag time in calculation of n gave the best fit for release data.

According to Ritger and Peppas (1987) the value of $0.43 < n < 0.85$ represents non-Fickian release mechanism. The mean values of n (equation 1.7) were 0.45 ± 0.03 for HPMC E5 and 0.46 ± 0.04 for HPMC E15 coated pellets indicating non-Fickian release mechanism.

Generally the values of n were similar for HPMC E5 and HPMC E15 coated pellets

Table 4.4. Values of release constants (K) and correlation coefficients (r) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from pellets coated with HPMC E5, using equations 1.1-1.4.

Model	*	Percent of coating				
		4%	8%	12%	16%	20%
Zero-order (Equation 1.1)	K_1	7.5 ± 2.1	5.3 ± 0.8	4.6 ± 0.5	3.9 ± 0.3	3.9 ± 0.4
	r	0.989	0.976	0.965	0.972	0.969
	P<	0.1	0.1	0.01	0.01	0.001
Square-root (Equation 1.2)	K_2	30.4 ± 7.5	25.4 ± 3.1	23.8 ± 2.2	21.6 ± 1.2	20.9 ± 1.4
	r	0.997	0.992	0.988	0.993	0.993
	P<	0.1	0.01	0.01	0.001	0.001
First-order (Equation 1.3)	K_3	0.131 ± 0.032	0.092 ± 0.011	0.078 ± 0.009	0.060 ± 0.005	0.024 ± 0.007
	r	0.996	0.990	0.986	0.991	0.990
	P<	0.1	0.01	0.01	0.001	0.001
Hixon-Crowell (Equation 1.4)	K_4	0.168 ± 0.040	0.119 ± 0.017	0.103 ± 0.010	0.087 ± 0.007	0.084 ± 0.008
	r	0.995	0.987	0.980	0.986	0.985
	P<	0.1	0.01	0.01	0.001	0.001

* Key: The units of rate constants are: K_1 ($\%min^{-1}$), K_2 ($\%min^{-1/2}$), K_3 (min^{-1}), K_4 ($\%^{1/3}min^{-1}$)
P is the degree of significance.

Table 4.5. Values of release constants (K) and correlation coefficients (r) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from pellets coated with HPMC E15, using equations 1.1-1.4.

Model	*	Percent of coating				
		4%	8%	12%	16%	20%
Zero-order (Equation 1.1)	K_1	6.4 ± 1.2	5.1 ± 0.8	3.8 ± 0.3	2.9 ± 0.3	2.1 ± 0.3
	r	0.977	0.980	0.957	0.949	0.956
	P<	0.1	0.01	0.01	0.001	0.001
Square-root (Equation 1.2)	K_2	29.1 ± 3.9	25.3 ± 2.8	19.3 ± 0.8	18.1 ± 1.4	14.6 ± 1.2
	r	0.993	0.997	0.986	0.982	0.987
	P<	0.01	0.001	0.001	0.001	0.001
First-order (Equation 1.3)	K_3	0.113 ± 0.021	0.087 ± 0.011	0.057 ± 0.007	0.048 ± 0.005	0.034 ± 0.005
	r	0.992	0.995	0.983	0.979	0.983
	P<	0.01	0.001	0.001	0.001	0.001
Hixon-Crowell (Equation 1.4)	K_4	0.145 ± 0.03	0.112 ± 0.017	0.075 ± 0.008	0.064 ± 0.007	0.048 ± 0.006
	r	0.989	0.994	0.976	0.971	0.975
	P<	0.1	0.001	0.001	0.001	0.001

* Key: See table 4.4.

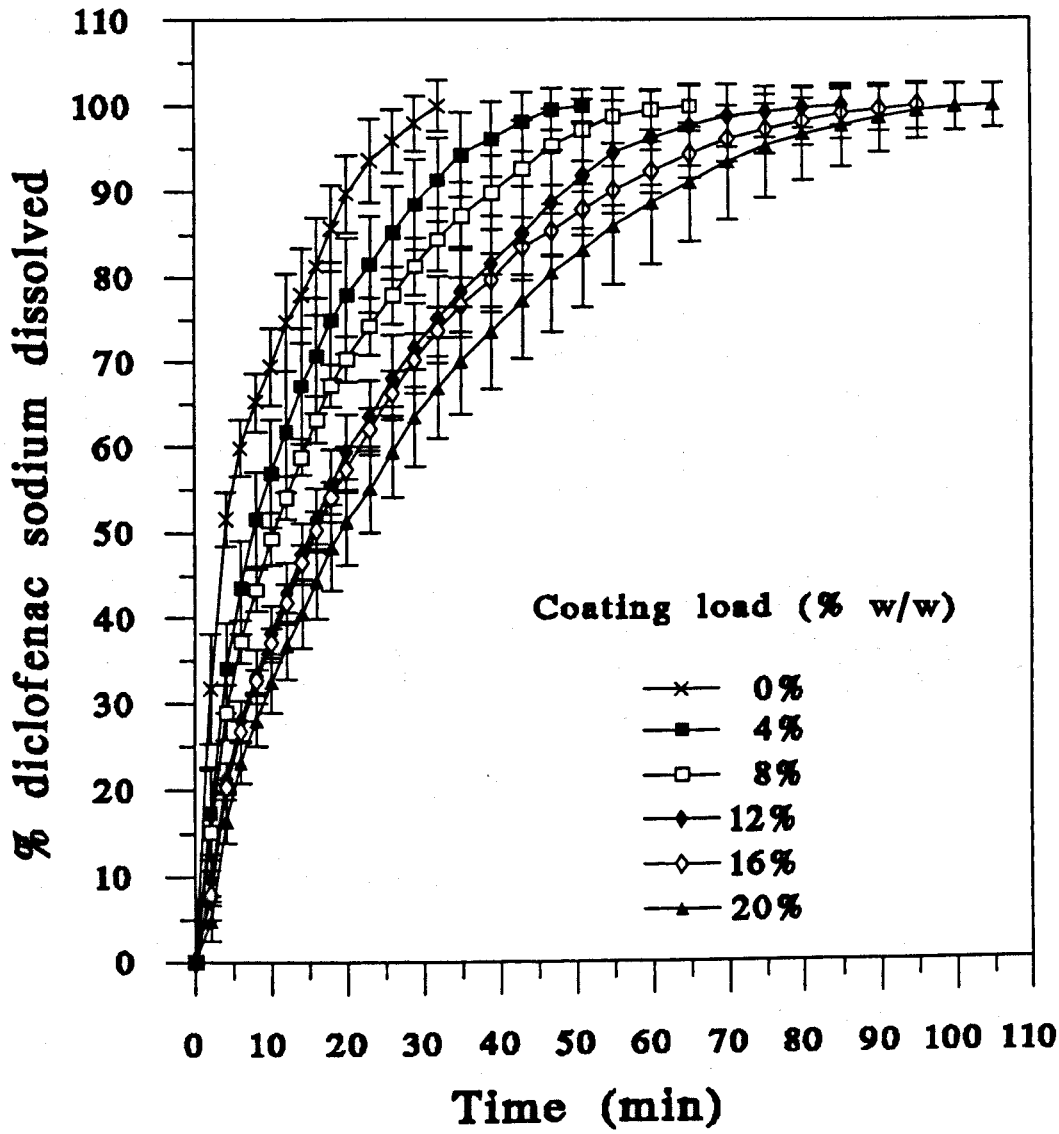


Figure 4.3. Effect of coating load on the release of diclofenac sodium from HPMC E15 coated pellets.

Table 4.6. Values of release constants (K) and correlation coefficients (r) obtained from data corresponding to 15-60% release of diclofenac sodium from pellets coated with HPMC E15, using equations 1.1-1.4.

Model	*	Percent of coating				
		4%	**8%**	**12%**	**16%**	**20%**
Zero-order (Equation 1.1)	K_1	4.4 ± 1.2	3.6 ± 0.4	2.7 ± 0.3	2.1 ± 0.07	2.0 ± 0.3
	r	0.976	0.979	0.986	0.982	0.979
	P<	0.001	0.001	0.001	0.001	0.001
Square-root (Equation 1.2)	K_2	21.9 ± 4.4	19.2 ± 2.1	17.0 ± 0.4	14.6 ± 0.5	14.4 ± 1.4
	r	0.994	0.997	0.999	0.998	0.998
	P<	0.001	0.001	0.001	0.001	0.001
First-order (Equation 1.3)	K_3	0.078 ± 0.021	0.062 ± 0.005	0.046 ± 0.005	0.037 ± 0.016	0.034 ± 0.004
	r	0.992	0.995	0.998	0.996	0.996
	P<	0.001	0.001	0.001	0.001	0.001
Hixon-Crowell (Equation 1.4)	K_4	0.077 ± 0.03	0.080 ± 0.006	0.059 ± 0.007	0.047 ± 0.002	0.045 ± 0.006
	r	0.988	0.991	0.995	0.993	0.992
	P<	0.001	0.001	0.001	0.001	0.001

* Key: See table 4.4.

indicating that viscosity of HPMC had no apparent effect on the mechanism of drug release from coated pellets.

Table 4.7 The values of K_1, n, based on equation 1.6, K_2, l, n, based on equation 1.7 calculated in the range of 15-60% metoclopramide hydrochloride release from HPMC E5 coated pellets. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	l*	n	ss	Schwartz
4%	13.70	0.78	6.64	7.87	28.00	1.40	0.44	0.00	-137.44
8%	11.10	0.78	26.40	15.86	25.30	1.67	0.42	0.01	-14.61
12%	10.30	0.76	58.60	23.57	23.80	1.80	0.42	1.03	4.96
16%	8.06	0.80	59.50	28.09	18.00	1.81	0.49	1.05	5.64
20%	8.14	0.77	76.80	34.28	17.10	1.87	0.50	3.60	14.81

* Key: The units of K_1 and K_2 are $\%min^{-n}$ and the unit of l is min.

Table 4.8 The values of K_1, n, based on equation 1.6, K_2, l, n, based on equation 1.7 calculated in the range of 15-60% metoclopramide hydrochloride release from HPMC E15 coated pellets. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	l*	n	ss	Schwartz
4%	11.30	0.81	33.30	16.78	26.30	1.67	0.44	0.90	3.74
8%	8.51	0.84	25.40	19.39	18.00	1.57	0.54	0.17	-3.92
12%	10.40	0.67	79.60	34.53	20.70	1.83	0.42	2.86	13.20
16%	9.59	0.66	108.0	41.64	18.90	1.90	0.42	8.40	23.27
20%	8.39	0.68	107.0	46.44	15.80	1.88	0.47	14.90	30.91

* Key: See table 4.7.

4.3.4 RELEASE KINETICS FOR DICLOFENAC SODIUM RELEASE FROM HPMC E15 COATED PELLETS

The correlation coefficient for the best statistical fit (Table 4.6) revealed that the drug release was again probably best described by the square-root kinetic model.

The values of K, n and l obtained using equation 1.6 and 1.7 are listed in Table 4.9. Again equation 1.7 gave the lower sums of squares (ss) and Schwartz information criterion, indicating the better fit for data. The mean value of n (equation 1.7) was 0.50 ± 0.05 indicating non-Fickian diffusion control. The obtained value of n for release of diclofenac sodium was different from those reported by Liu et al (1993) for the release of diclofenac sodium from HPMC 50 mPa.s (0.65-0.73) and HPMC 100 mPa.s (0.77-0.87) matrices. Other values of n for the release of diclofenac sodium from HPMC E15 and HPMC 100 mPa.s matrices were 0.83 (Bain et al, 1991) and 0.82 (Sheu et al, 1992), respectively.

Table 4.9 The values of K_1, n, based on equation 1.6, K_2, l, n, based on equation 1.7 calculated in the range of 15-60% diclofenac sodium release from HPMC E15 coated pellets. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	l*	n	ss	Schwartz
4%	13.00	0.65	19.80	18.14	23.30	1.51	0.42	0.34	-0.55
8%	11.90	0.61	15.90	23.34	18.50	1.35	0.45	0.26	-3.58
12%	8.17	0.66	14.00	31.00	11.17	1.25	0.55	1.86	13.11
16%	7.62	0.68	24.60	36.65	12.00	1.53	0.53	1.37	10.05
20%	6.42	0.69	40.40	49.36	10.30	1.74	0.55	1.04	7.92

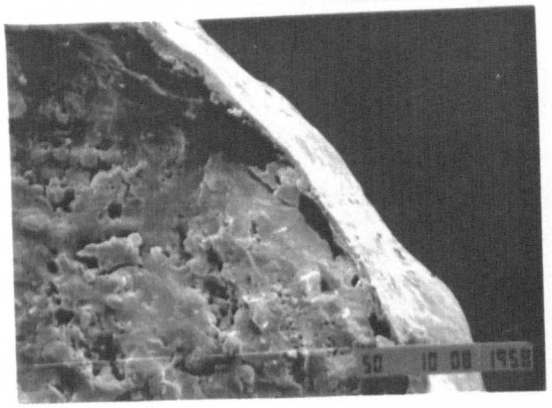
* Key: See table 4.7.

4.4. GENERAL DISCUSSION

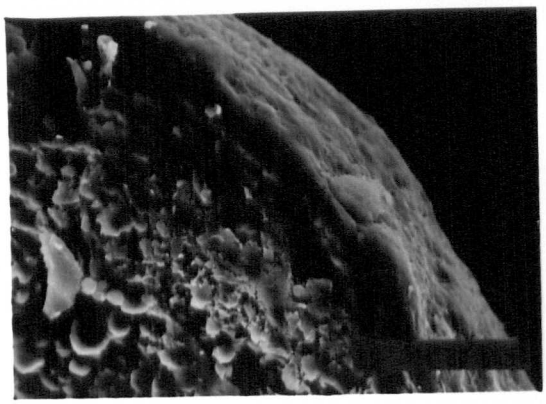
As described earlier, the increase in coating load of HPMC resulted in the slower release of both drugs. The reduction in release rate with increasing coating load may be attributed to the increased diffusional path length with increase in the coating load. This was confirmed by scanning electron micrographs of the cross section of the metoclopramide hydrochloride loaded pellets at 4% and 20% w/w coating load of HPMC E15 (Figure 4.4) where increase in the thickness of the applied coat lengthened the diffusional path. On the other hand, as proposed by Wan and Lai (1991), HPMC hydrates and gels when in contact with water. As the coat thickness increases, the resulting gel could become thicker and therefore its resistance to penetration by water and to erosion increases. This would lead to a decrease in the release rate of the drug out of the gelled coat.

Although the coating load of HPMC E5 or HPMC E15 had a great effect on the release rate constants of metoclopramide hydrochloride or diclofenac sodium from coated pellets (Tables 4.4-4.6) the overall release was fast and the majority of either drug (> 90%) was released within approximately 1 h, even with a coating load of 20% w/w. This indicates that the pellets coated with HPMC had no sustained release properties. Rapid release of either drug from the pellets coated with HPMC E5 or HPMC E15 may be attributed to the pellet disintegration and rapid dissolution of the polymeric membrane.

The release exponent n indicated although both diffusion and erosion contributed to



(a)



(b)

Figure 4.4. Micrographs of cross sections of metoclopramide hydrochloride pellets coated with HPMC E15 a) 4% w/w coating load b) 20% w/w coating load. (Magnification × 350).

the release mechanisms of drugs, diffusion was the predominant mechanism. Drug solubility did not seem to affect the release mechanism as the values of the exponent n were similar for the release of both metoclopramide hydrochloride and diclofenac sodium from pellets coated with HPMC E15. It was observed that pellets coated with HPMC E15 released the drug slightly slower than pellets coated with HPMC E5. This may be due to the fact that increase in the viscosity grade of HPMC in the coat increased the gel layer viscosity and consequently slowed the erosion of the polymer and drug diffusion.

Comparison of the release data for metoclopramide hydrochloride and diclofenac sodium pellets coated revealed that the diclofenac sodium released slightly slower than metoclopramide hydrochloride at equivalent coating load. As the molecular weights of both drugs are similar but slightly bigger for metoclopramide hydrochloride (354.3) than diclofenac sodium (318.13) then the faster release of metoclopramide hydrochloride may be ascribed to its higher water solubility (> 2.6 g in 1 ml water at 37°C compared to 30 ± 0.3 mg in 1 ml water for diclofenac sodium at this temperature).

4.5 CONCLUSIONS

Overall, the drug release from HPMC E5 and HPMC E15 coated pellets (upto 20% w/w) was fast and completed within 1 h. It was found that the release of metoclopramide hydrochloride decreased as the coating load of HPMC E5 or HPMC E15 increased. In fact, small differences were observed for performance of HPMC

E5 and HPMC E15 in release of metoclopramide hydrochloride at equivalent coating loads. A similar relationship between coating load and diclofenac sodium release was observed for pellets coated with HPMC E15. However, diclofenac sodium released slightly slower than metoclopramide hydrochloride at equivalent coating load.

CHAPTER 5. EFFECT OF SURELEASE ON THE DRUG RELEASE FROM PELLETS

5.1 INTRODUCTION

Many studies have concentrated on developing a method for preparing sustained release peroral drug products. Film coating is an ideal process for the production of sustained release dosage forms (Rowe 1985a). For application in controlled-release delivery systems, film coats with well-characterized permeability properties are essential. Ethylcellulose is the most widely used water-insoluble polymer in film-coating (Rowe, 1985a). This polymer is tasteless, odourless and has the ability to form tough, flexible coatings. Optimization of coating formulations containing ethylcellulose can easily be achieved due to characteristics of this polymer including (Porter, 1989a):

a) Availability in a wide range of viscosity (or molecular weight) grades,

b) Solubility in a variety of organic solvents and their mixtures, and

c) Miscibility with various water-soluble materials which cause a change in the permeability of the resultant film.

While ethylcellulose was initially used in organic solvent-based solutions (Kannikoski, 1984), the pharmaceutical industry has been shifting towards aqueous film coating methods (Hogan, 1982) and as a result some water-based dispersions of ethylcellulose such as Surelease and Aquacoat have been introduced which are widely used in film coating. The use of ethylcellulose is common in the development

of controlled drug delivery systems (Benita and Donbrow, 1982; Miller and Vadas, 1984; Najib and Suleiman, 1985; Porter and D'Andrea, 1985; Bianchini and Vecchio, 1987; Iyer et al, 1993).

5.1.1 AIMS AND OBJECTIVES

The present study was undertaken to determine the effect of coating load on the release of metoclopramide hydrochloride or diclofenac sodium from pellets coated with Surelease.

5.2 MATERIALS AND METHODS

5.2.1 MATERIALS

Metoclopramide hydrochloride, diclofenac sodium, Surelease, HPMC E15, Talc, non-pareils (0.710-0.850 mm), as described in section 2.1, were used.

5.2.2 METHODS

5.2.2.1 Coating of non-pareils with drug

Batches of 4500 g non-pareils were loaded with metoclopramide hydrochloride or diclofenac sodium as described in section 4.2.2.1. The drug layering process produced pellets with a metoclopramide hydrochloride load of 3.96 ± 0.02% w/w and diclofenac sodium load of 3.93 ± 0.04% w/w.

5.2.2.2 Coating of drug-loaded non-pareils with Surelease

Batches of 4500 g drug-loaded non-pareils were coated with Surelease under the

conditions shown in Table 3.4 (section 3.6). By taking into consideration the coating efficiency, samples of 50 g of coated pellets were removed from the coating pan when the coating loads had reached 4%, 8%, 12%, 16% and 20% w/w.

5.2.2.3 Scanning electron microscopy

SEM was performed as described in section 2.2.4.3.

5.2.2.4 Dissolution testing

Dissolution studies on pellets coated with Surelease were performed as explained in section 2.2.6.

5.2.2.5 Release kinetics for coated pellets

In order to determine the kinetics of drug release, data were fitted to different equations as explained in section 2.2.7. The data corresponding drug release < 15% clearly did not concur with controlled drug release. Therefore, the data between 15-60% were fitted to all equations.

5.3 RESULTS AND DISCUSSION

5.3.1 EFFECT OF SURELEASE COATING LOAD ON THE RELEASE OF METOCLOPRAMIDE HYDROCHLORIDE

The effect of coating load on the release of metoclopramide hydrochloride from pellets coated with Surelease is shown in Figure 5.1. Uncoated metoclopramide hydrochloride pellets disintegrated rapidly in the dissolution medium and released

their drug content in less than 5 min. The percent of drug released dramatically decreased as coating loads were increased. For instance at higher coating loads, such as 20% coating, only about 7% of the drug was released in 2 h, whereas those pellets coated to weight increases of 10% and 4%, released 51% and 97% of drug respectively in 2 h. In addition, as the level of coating increased, the release profiles showed biphasic pattern where there was a phase which showed low slope followed by a phase with a steep slope. The change in release pattern was achieved after a longer period (which here is named as lag time) as the coating load increased. It is evident from the results that the coating load had a major effect on the ultimate rate of drug release and the duration of the lag times. All the pellets remained intact during dissolution test indicating that the Surelease membrane controls the drug release.

Table 5.1 shows the release constants (K) and lag times (t) of the fits of release data to different kinetic models. Due to insufficient data points for release of metoclopramide hydrochloride from pellets with a 4% coating load of Surelease, it was not possible to perform regression analysis for these pellets and therefore no results are reported for 4% coating load. A dramatic decrease in the release rate of metoclopramide hydrochloride with increasing coating load of Surelease can be observed. For instance the first-order release rate was more than five times faster at the 8% coating load than the 20% load. The calculated lag times increased as the coating load increased irrespective of the kinetic model used.

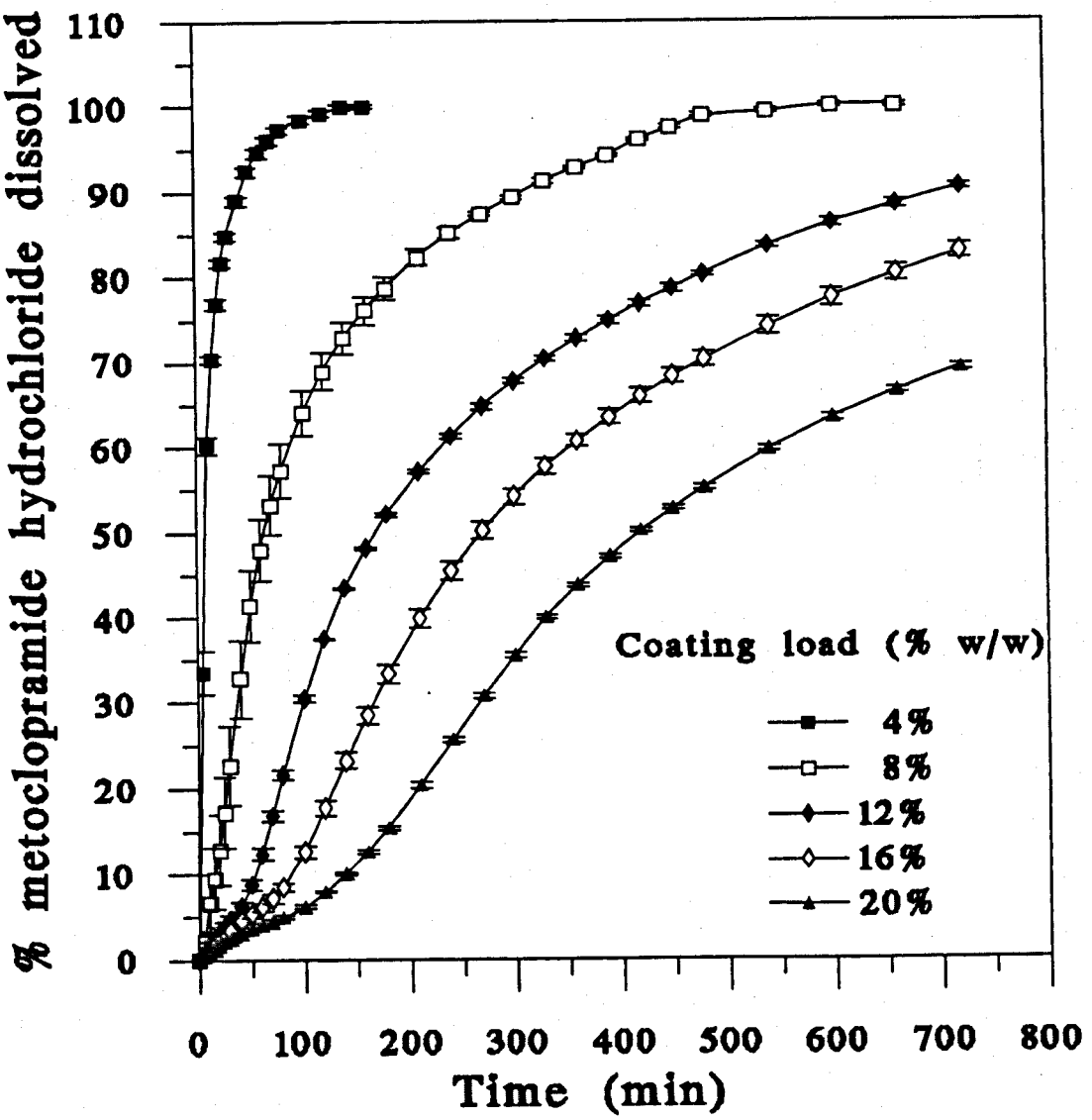


Figure 5.1. Effect of coating load on the release of metoclopramide hydrochloride from Surelease coated pellets.

Table 5.1. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from pellets coated with Surelease, using equations 1.1-1.4.

Model	*	Percent of coating			
		8%	12%	16%	20%
Zero-order (Equation 1.1)	K_1	0.71 ± 0.04	0.28 ± 0.01	0.19 ± <0.01	0.12 ± <0.01
	r	0.983	0.978	0.988	0.985
	P<	0.001	0.001	0.001	0.001
	t1	2.0 ± 3.2	-2.3 ± 3.3	12.97 ± 5.06	32.96 ± 3.4
Square-root (Equation 1.2)	K_2	9.8 ± 0.2	6.5 ± 0.1	5.5 ± 0.1	4.5 ± 0.1
	r	0.995	0.993	0.996	0.996
	P<	0.001	0.001	0.001	0.001
	t2	9.5 ± 3.0	30.3 ± 1.6	56.4 ± 2.6	92.9 ± 1.8
First-order (Equation 1.3)	K_3	0.0117 ± 0.0007	0.0046 ± 0.0001	0.0032 ± 0.0001	0.0020 ± 0.0000
	r	0.996	0.995	0.998	0.998
	P<	0.001	0.001	0.001	0.001
	t3	6.8 ± 3.6	23.3 ± 1.9	51.5 ± 0.83	90.10 ± 1.1
Hixon-Crowell (Equation 1.4)	K_4	0.0153 ± 0.0009	0.0060 ± 0.0001	0.0040 ± 0.0000	0.0027 ± 0.0000
	r	0.993	0.990	0.996	0.995
	P<	0.001	0.001	0.001	0.001
	t4	4.5 ± 2.8	16.7 ± 2.1	41.1 ± 3.4	72.8 ± 4.0

* Key: The units of release constants are: K_1 ($\%min^{-1}$), K_2 ($\%min^{-1/2}$), K_3 (min^{-1}), K_4 ($\%^{1/3}min^{-1}$) and the units of the lag times corresponding to different equations (1.1-1.4) t1, t2, t3 and t4 are (min). P is the degree of significance.

5.3.2 EFFECT OF SURELEASE COATING LOAD ON THE RELEASE OF DICLOFENAC SODIUM

The effect of Surelease coating load on the release of diclofenac sodium is depicted in Figure 5.2. Similar to metoclopramide hydrochloride loaded pellets, uncoated diclofenac sodium loaded pellets disintegrated rapidly and 100% of drug was released from pellets in the first 5 min. As the coating load increased the release rate considerably decreased. For example, increasing the coating load from 12 to 20% decreased the percent of drug released from 40% to 8% after 2 h. Scanning electron micrographs of diclofenac sodium pellets coated with 12% Surelease before and after dissolution are depicted in Figure 5.3. The pellets remained intact after the dissolution test suggesting that the membrane controlled the release of drug. The lag time prior to change in release pattern was also observed for diclofenac sodium pellets coated with Surelease (Figure 5.2). Its duration increased with increasing coating load. Table 5.2 summarizes the release constants (K) and lag times (t) of the fits of release data for diclofenac sodium to different kinetic models. The release rates considerably decreased as the coating load increased. For example the first-order release rate was four times faster at 8% coating load than 20% coating load. The calculated lag times were also increased as the coating load increased.

5.3.3 RELEASE KINETICS FOR METOCLOPRAMIDE HYDROCHLORIDE PELLETS COATED WITH SURELEASE

The correlation coefficients (r) for the best statistical fit (Table 5.1) revealed that first-order kinetics are probably most applicable model to all the release data.

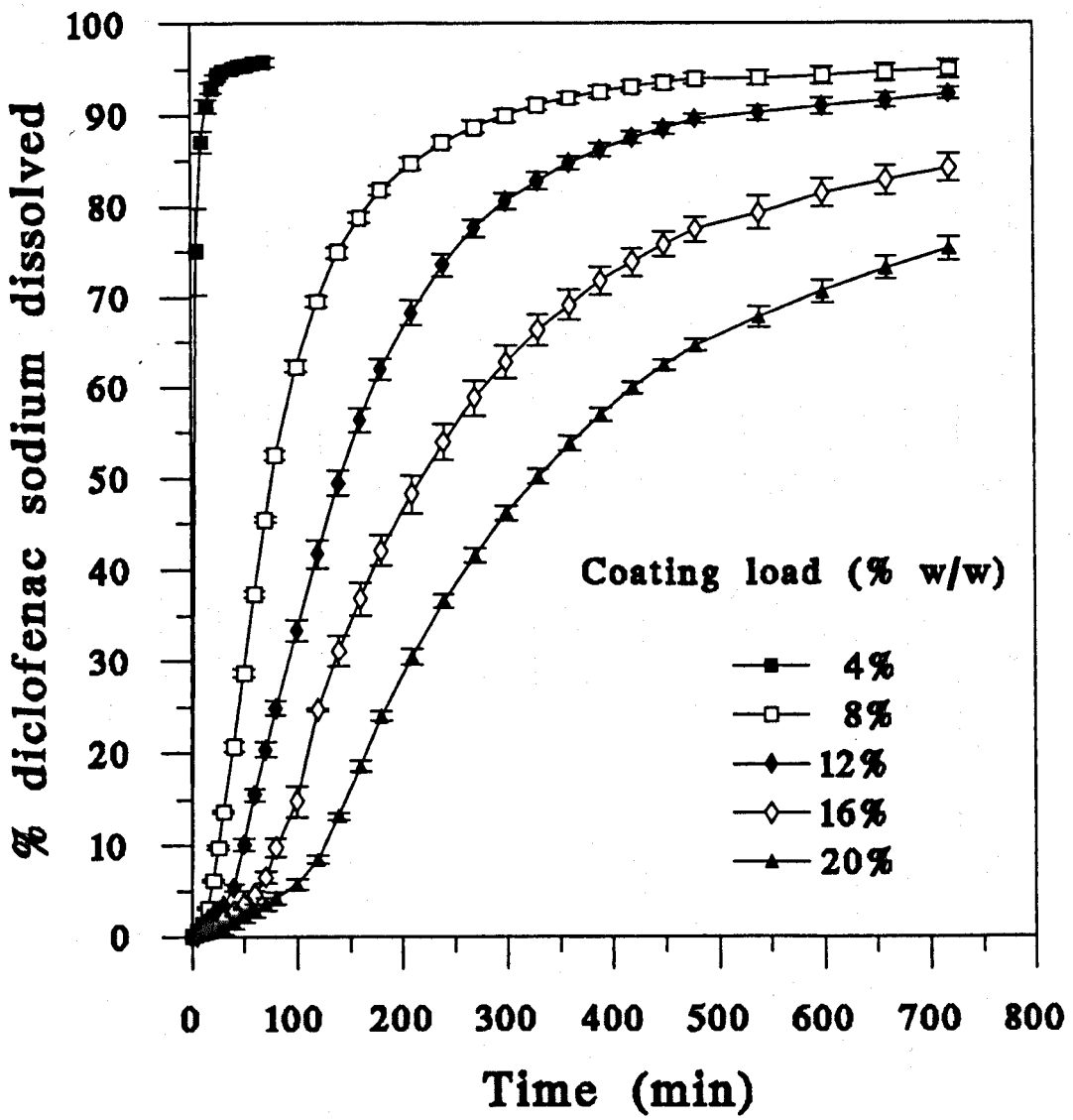
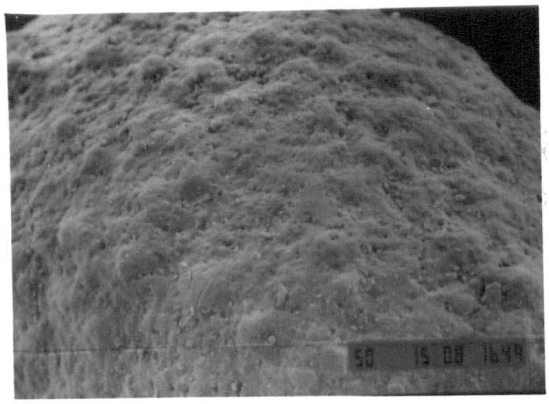


Figure 5.2. Effect of coating load on the release of diclofenac sodium from Surelease coated pellets.

Table 5.2. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of diclofenac sodium from pellets coated with Surelease, using equations 1.1-1.4.

Model	*	Percent of coating			
		8%	12%	16%	20%
Zero-order (Equation 1.1)	K_1	0.73 ± 0.01	0.40 ± 0.01	0.24 ± 0.01	0.16 ± <0.01
	r	0.996	0.997	0.985	0.985
	P<	0.001	0.001	0.001	0.001
	t1	10.5 ± 0.2	19.9 ± 1.5	18.3 ± 5.1	25.3 ± 4.3
Square-root (Equation 1.2)	K_2	10.9 ± 0.1	8.3 ± 0.1	6.4 ± 0.1	5.3 ± 0.1
	r	0.997	0.998	0.996	0.995
	P<	0.001	0.001	0.001	0.001
	t2	18.0 ± 0.1	34.8 ± 0.8	50.7 ± 2.7	78.5 ± 2.1
First-order (Equation 1.3)	K_3	0.0119 ± 0.0002	0.0067 ± 0.0002	0.0039 ± 0.0002	0.0028 ± 0.0001
	r	0.996	0.999	0.999	0.998
	P<	0.001	0.001	0.001	0.001
	t3	18.9 ± 0.72	36.1 ± 1.0	51.3 ± 2.3	78.3 ± 2.3
Hixon-Crowell (Equation 1.4)	K_4	0.0155 ± 0.0002	0.0086 ± 0.0002	0.0052 ± 0.0001	0.0035 ± <0.0001
	r	0.998	0.998	0.996	0.995
	P<	0.001	0.001	0.001	0.001
	t4	16.2 ± 0.14	31.3 ± 0.98	40.3 ± 2.8	61.6 ± 3.1

* Key: See table 5.1.



(a)

(b)

Figure 5.3. Micrographs of diclofenac sodium pellets coated with 12% Surelease a) before dissolution b) after 12 h dissolution (Magnification × 150).

Table 5.3 shows the values of K, n and l obtained from equations 1.6 and 1.7. Considering the sums of squares and Schwartz information criterion, equation 1.7 which included the lag time in calculation of n gave the best fit for release data. The importance of inclusion of lag time in calculation of n has been discussed by Ford et al (1991a). The mean value of n based on equation 1.7 was 0.60 ± 0.03 indicating that diffusion is the predominant mechanism controlling drug release. It was also observed that the coating load had no apparent effect on the mechanism of release of metoclopramide hydrochloride as the values of n were similar for all coating loads.

Table 5.3. The values of K_1, n based on equation 1.6, K_2, l, n based on equation 1.7 calculated in the range of 15-60% metoclopramide hydrochloride release from Surelease coated pellets. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1*	n	ss	Schwartz	K_2*	l*	n	ss	Schwartz
8%	0.869	0.971	42.5	34.14	4.740	15.40	0.604	8.46	23.32
12%	0.252	1.030	71.8	42.85	3.720	52.00	0.543	6.29	23.14
16%	0.110	1.090	51.20	43.96	1.950	81.40	0.618	5.27	23.53
20%	0.060	1.110	84.00	60.34	1.480	133.00	0.619	11.80	39.75

* Key: The units of K_1 and K_2 are $\%min^{-n}$ and the unit of l is min.

5.3.4 RELEASE KINETICS FOR DICLOFENAC SODIUM PELLETS COATED WITH SURELEASE

The correlation coefficient for the best statistical fit (Table 5.2) revealed that the

first-order kinetics are possibly most applicable to all the release data at all coating loads except 8% coating which Hixon-Crowell model gave the best fit.

The values of K and n obtained from equations 1.6 and 1.7 are presented in table 5.4 at different coating loads. Again equation 1.7 gave the lowest sums of squares and Schwartz information criterion indicating better fit of data with this equation. The mean value of n (equation 1.7) is 0.70 ± 0.20. It seems that diclofenac sodium release mechanism was dependent on the coating load of Surelease. The higher value of n for 8 and 12% coating load may be due to contribution of the dissolution of the drug to the overall release mechanism. While at high coating loads the predominant mechanism is the diffusion of the drug.

5.4 GENERAL DISCUSSION

It was shown that the release rate of either drug decreased considerably as the coating load of Surelease increased. These results are in agreement with the findings of Ghebre-Sellassie et al (1988) and Porter (1989b) who showed that the release of drug (diphenhydramine hydrochloride or chlorpheniramine maleate) from pellets coated with Surelease was related to the weight of coating material deposited on the pellets. The dependency of the release of drugs on the thickness of ethylcellulose membranes has been reported by many authors (Ozturk et al, 1990; Bianchini et al, 1993; Maganti and Celik, 1994; Sarisuta and Punpreuk, 1994).

Scanning electron micrographs of coated pellets with 8% and 20% coating levels

Table 5.4. The values of K_1, n based on equation 1.6, K_2, l, n based on equation 1.7 calculated in the range of 15-60% diclofenac sodium release from Surelease coated pellets. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	l*	n	ss	Schwartz
8%	0.154	1.330	3.07	10.32	0.715	12.40	1.02	0.930	4.94
12%	0.146	1.160	16.10	26.41	1.590	39.40	0.735	1.01	6.28
16%	0.129	1.100	58.00	36.64	4.360	88.50	0.501	0.241	-5.14
20%	0.074	1.120	78.60	52.80	2.620	123.00	0.552	2.56	17.52

* Key: See table 5.3.

before and after dissolution tests are shown in Figures 5.4 and 5.5. The presence and distribution of the pores are more apparent on the surface of pellets with a low coating load (8%), than that of the higher coating level (20%). These pores may exist through the full thickness of the coating and act as points of entry for dissolution fluid into the pellets and as points of exit for the release of dissolved drug into the dissolution medium. On the other hand, coating layer was thicker as the load increased (Figure 5.4b and 5.5b). Therefore, the diffusion path length for the dissolution medium to enter the core and the dissolved drug to come out through the core could be increased. This also would account for the much lower release rates for pellets with higher coating levels.

Generally in dosage forms which have a water insoluble polymer as the rate controlling membrane, since the release rate through the membrane controls the overall release rate of the drug, the membrane properties and geometry, such as membrane porosity, internal structure (tortuosity) and the membrane thickness may

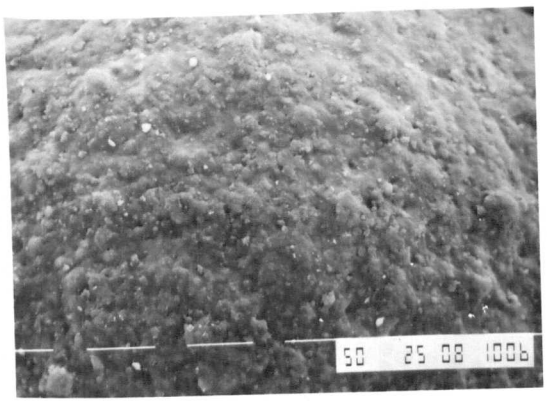
be critical factors in determining the release rate of the drug (Tojo and Miyanami, 1983). During film application, the pellets are continuously layered with additional coating material, the film formed in the coating pan or fluid bed apparatus therefore, consists of segments which overlap each other (Wouessidjewe et al, 1991). As more layers of film is applied the holes from overlapping films are gradually blocked. Hence this reduces the dissolution rate and therefore, the higher the coating level the longer the lag time and the lower the apparent drug dissolution rate.

Diffusion through membranes is usually described by Fick's first law:

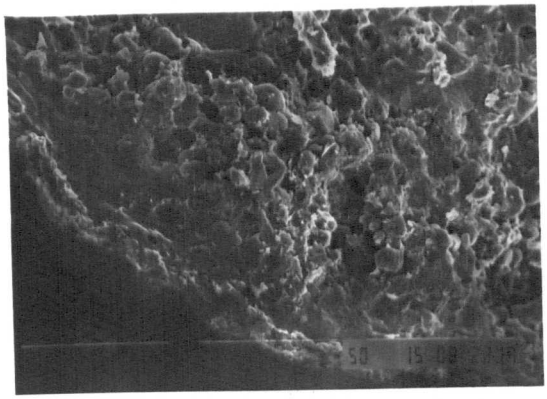
$$\frac{dM_t}{dt} = \frac{ADK\Delta c}{L} \qquad \textit{Equation 5.1}$$

where dm_t/dt is drug diffusion rate, A is surface area of the device, D is the diffusion of the drug in the barrier membrane, K is the partition coefficient of the drug between the coating and the medium, Δc is the drug concentration gradient across the membrane and L is the membrane thickness (Jambhekar et al, 1987). A delivery system which follows this model would display zero-order release kinetics as long as the concentration gradient is kept constant.

However, the kinetic studies for metoclopramide hydrochloride or diclofenac sodium release showed that the release of either drug from Surelease coated pellets was probably best described by the first-order kinetic model and not the zero-order model. First-order release of drugs from ethylcellulose membranes have been reported previously (Friedman et al, 1979; Najib and Suleiman, 1985; Singh and



(a)



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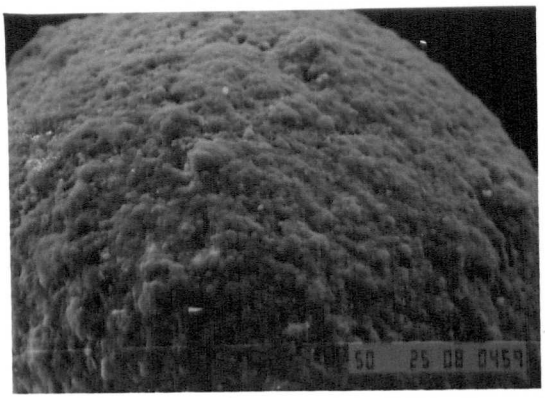
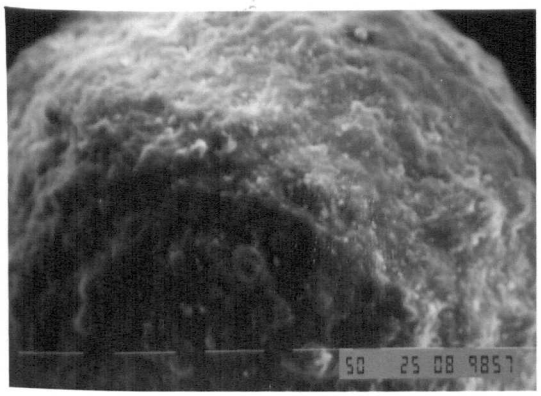
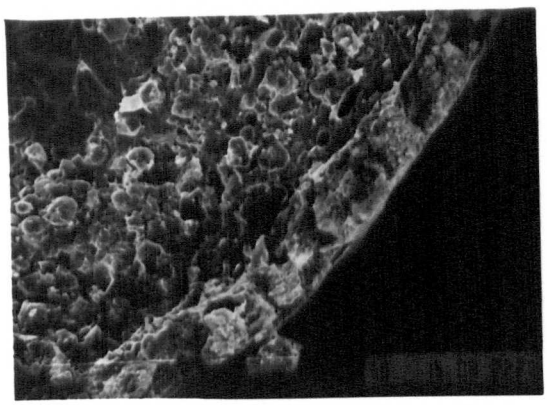


(c)

Figure 5.4. Micrographs of metoclopramide hydrochloride pellets coated with 8% Surelease coating level a) Surface structure of the pellet before dissolution (Magnification × 150) b) Cross section of the coated pellets (Magnification × 350) c) Surface structure of the coated pellets after 6 h dissolution (Magnification × 150).



(a)



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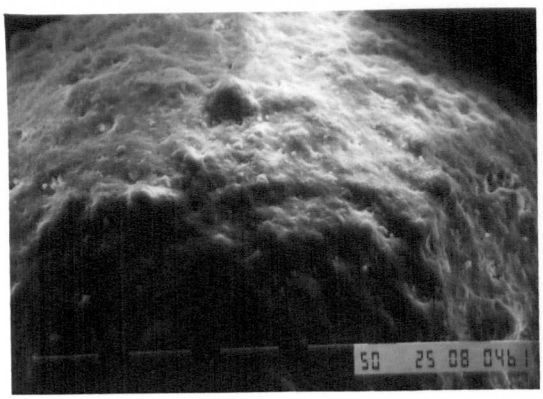


(c)

Figure 5.5. Micrographs of metoclopramide hydrochloride pellets coated with 20% Surelease coating level a) Surface structure of the pellet before dissolution (Magnification × 150) b) Cross section of the coated pellets (Magnification × 350) c) Surface structure of the coated pellets after 12 h dissolution (Magnification × 150).

Robinson, 1988; Sarisuta and Sirithunyalug, 1988; Yang and Ghebre-Sellassie, 1990). Factors such as dialysis (diffusion through pores) and osmotic effects tend to influence release through a barrier and as a result deviations from zero-order release are usually seen (Haluska et al, 1992). In addition, after the initial stages of dissolution, if the active material within the device is present as an unsaturated solution, its concentration will fall as the agent is released, and release rate declines exponentially producing a first-order release profile (Baker, 1987).

One hypothesises suggested to describe the first-order release of drugs from multiparticulate systems has been given by Griffin and Grattan (1994) who showed that the release data of dextromethorphan hydrobromide from pellets coated with mixtures of EC and HPMC fitted the first-order kinetic model. It was shown that individual beads released their drug at variable zero-order rates (Griffin and Grattan, 1994). This lead to a nett first-order release profile.

The results of the kinetic studies presented in this chapter showed that the coating load had no effect on the mechanism of drug release. However Zhang et al (1991a) reported that the release of acetaminophen from beads coated with Aquacoat was dependent on the levels of the coating. A change in the release mechanism from diffusion through water filled pores (for 2-10% w/w coating load) to diffusion through the membrane (for 12-20% w/w coating load) was reported. Similar results were observed by Dyer et al (1995) who claimed that at low coating levels, the membrane is relatively more porous and the drug takes the route of least resistance

for release. As the coating thickness increases, fewer pores are available for drug transport, thus retarding drug release and it is probable that drug release occurs by diffusion across the polymeric membrane rather than diffusion through pores or imperfections within the film coat.

A comparison of the release profiles for metoclopramide hydrochloride and diclofenac sodium coated with Surelease revealed that despite of its lower solubility diclofenac sodium (30 mg in 1 ml water at 37°C; chapter 4) showed faster release rates than metoclopramide hydrochloride (>2.5 g in 1 ml water at 37°C; chapter 4) at equivalent coating loads (Tables 5.1 and 5.2). It has been claimed that the aqueous solubility of the drug plays an important role in release rate of the drug from coated pellets (Ghebre-Sellassie et al, 1988; Iyer et al, 1990). Highly water soluble drugs generally release faster than poorly water soluble compounds.

Since several factors clearly contributed to the faster release of diclofenac sodium, the aims of next chapters were to elucidate the cause of this differences.

5.5 CONCLUSIONS

The results presented in this study indicate that Surelease is suitable coating system for preparing sustained-release dosage forms, especially at high coating levels for metoclopramide hydrochloride and diclofenac sodium. The coating load had a major effect on drug release rate. As the coating load increased release rates dramatically

decreased. The kinetics of the release of either drug were best described by the first order kinetic model. Diclofenac sodium (with lower aqueous solubility) formulations showed faster release than metoclopramide hydrochloride (with higher aqueous solubility) at each coating load.

CHAPTER 6. EFFECT OF INCLUSION OF HPMC E15 IN SURELEASE ON THE DRUG RELEASE FROM COATED PELLETS

6.1 INTRODUCTION

Coats consisting of low viscosity hydroxypropylmethylcellulose did not control the release of metoclopramide hydrochloride or diclofenac sodium from pellets (chapter 4). The majority of either drug was released in less than 1 h, even at the highest coating load (20% w/w). Drug release from Surelease coated pellets (chapter 5) was rapid at low coating loads while drug release was sustained over 12 h at high coating loads. However the release of either drug was incomplete at high coating loads. For example, only about 70% of either drug was released from pellets coated with 20% w/w Surelease after 12 h. In addition, the duration of lag times before establishing controlled release profiles increased at higher coating loads of Surelease. Therefore, the inclusion of an additional substance into the Surelease film was needed to permit the drug to be released not too quickly but would allow all of the drug to be released before the end of the dissolution test.

It has been reported that the drug release from systems coated with insoluble polymers may be modified by additives that dissolve on exposure to biological fluids and thus render the coating porous (Lindholm and Juslin, 1982). It is well known that addition of suitable hydrophillic substances such as methylcellulose (Colletta and Rubin, 1964; Fites et al, 1970; Yuen et al, 1993), hydroxypropylmethylcellulose (Ghebre-Sellassie et al, 1988; Li et al, 1990; Govender et al, 1995),

hydroxypropylcellulose (Borodkin and Tucker, 1974; 1975, Donbrow and Samuelov, 1980) polyethylene glycol (Donbrow and Friedman, 1975) to hydrophobic polymer films is one method of increasing the permeability of that film.

6.1.1 AIMS AND OBJECTIVES

The aims and objectives of the study presented in this chapter were to modify the permeability of Surelease films by the addition of low viscosity HPMC E15. Release of metoclopramide hydrochloride or diclofenac sodium was investigated as a function of coating load and level of the HPMC E15 in the coat.

6.2 MATERIALS AND METHODS

6.2.1 MATERIALS

Metoclopramide hydrochloride, diclofenac sodium, HPMC E15, Surelease, talc, non-pareils (0.710-0.850 mm), as described in section 2.1, were used.

6.2.2 METHODS

6.2.2.1 Coating of non-pareils with drug

Batches of 4500 g non-pareils were coated with metoclopramide hydrochloride or diclofenac sodium as described in section 4.2.2.1. The drug layering process produced pellets with a metoclopramide hydrochloride load of 3.95 ± 0.08% w/w and diclofenac sodium load of 3.93 ± 0.01% w/w.

6.2.2.2 Preparation of the coating suspension containing mixtures of Surelease and HPMC E15

The amounts of HPMC E15 needed for 1200 g Surelease (solid weight) to make films containing 5%, 7.5% or 10% w/w HPMC E15, were 60, 90 or 120 g respectively. Solutions of HPMC (5% w/w) were prepared as described in section 2.2.3.1 and kept overnight. The Surelease was diluted with water to 15% w/w. Then 5% HPMC solution was added to the diluted Surelease to produce the required HPMC contents and stirred.

6.2.2.3 Coating of drug loaded non-pareils with mixtures of Surelease and HPMC E15

Batches of 4500 g drug-loaded pellets were coated with Surelease/HPMC under the conditions used to apply Surelease (Table 3.4). By taking into consideration the coating efficiency, samples of 50 g of coated pellets were removed from the coating pan when the coating loads had reached 4%, 8%, 12%, 16% and 20% w/w.

6.2.2.4 Dissolution testing

Dissolution studies on coated pellets were performed as explained in section 2.2.6.

6.2.2.5 Release kinetics for coated pellets

The release data between 15-60% were fitted to the different kinetic models described in section 2.2.7.

6.2.2.6 Scanning electron microscopy

The micrographs of the pellets before and after dissolution were taken as described in section 2.2.4.3.

6.2.2.7 Determination of HPMC release from free films of Surelease containing 7.5% HPMC

To examine the effect of HPMC E15 on the Surelease films, Surelease/HPMC films containing 7.5% HPMC were prepared as described in section 3.2.2.1. Films of 64 ± 10 μm thickness (measured by micrometer Mitutoyo, Japan) were cut into strips of 5 cm × 5 cm using scissors and weighed precisely using an Oertling analytical balance (West Midlands, UK). The films were placed in stoppered glasses containing 50 ml of distilled water at 37°C and shaken in a shaker bath (Companstat 882942, UK) for 30 min. After this period the content of each stoppered glass was passed through Whatman No.1 filter papers (Whatman International Ltd. Maidston, UK) to remove undissolved particles and films and the filter papers were washed with 20 ml additional water. The aqueous extracts of the films were collected in previously tared 100 ml beakers and heated to reduce their water content. The beakers were kept in oven at 60°C until the contents were dry and then weighed. The increase in the weight of beakers was taken as the amount of HPMC E15 released. The same procedure was performed, as a reference, for Surelease films without HPMC. The procedure was repeated three times for each type of film.

6.3 RESULTS AND DISCUSSION

6.3.1 EFFECT OF INCLUSION OF HPMC E15 ON THE RELEASE OF METOCLOPRAMIDE HYDROCHLORIDE

Figures 6.1-6.3 show the plots of release of metoclopramide hydrochloride from pellets coated with Surelease containing 5, 7.5 and 10% HPMC E15, respectively. As the coating loads increased, the percent of metoclopramide hydrochloride released at each time interval decreased at each coating composition. The amount of drug released increased with increase in the HPMC content of the coats.

The release rates (K) and lag times (t) of the fits of release data to the different kinetic models are shown in Tables 6.1-6.3. No results are reported for the 4% coating load due to insufficient data points for regression analysis. The release rates decreased as the coating loads increased, irrespective of the kinetic model used. On the other hand increasing the HPMC content in the coats increased the release rates at equivalent coating loads. For example, the first-order release rate was more than three times faster when the HPMC content was 10% than when the HPMC content was 5% at the coating load of 20%. Therefore the ratio of HPMC/Surelease had a major effect on the release rate of the drug. Similar to Surelease coated pellets (chapter 5) a lag time was observed before establishing the controlled release profiles. The durations of this lag time increased with increasing coating load but were reduced as the amount of HPMC in the coats increased.

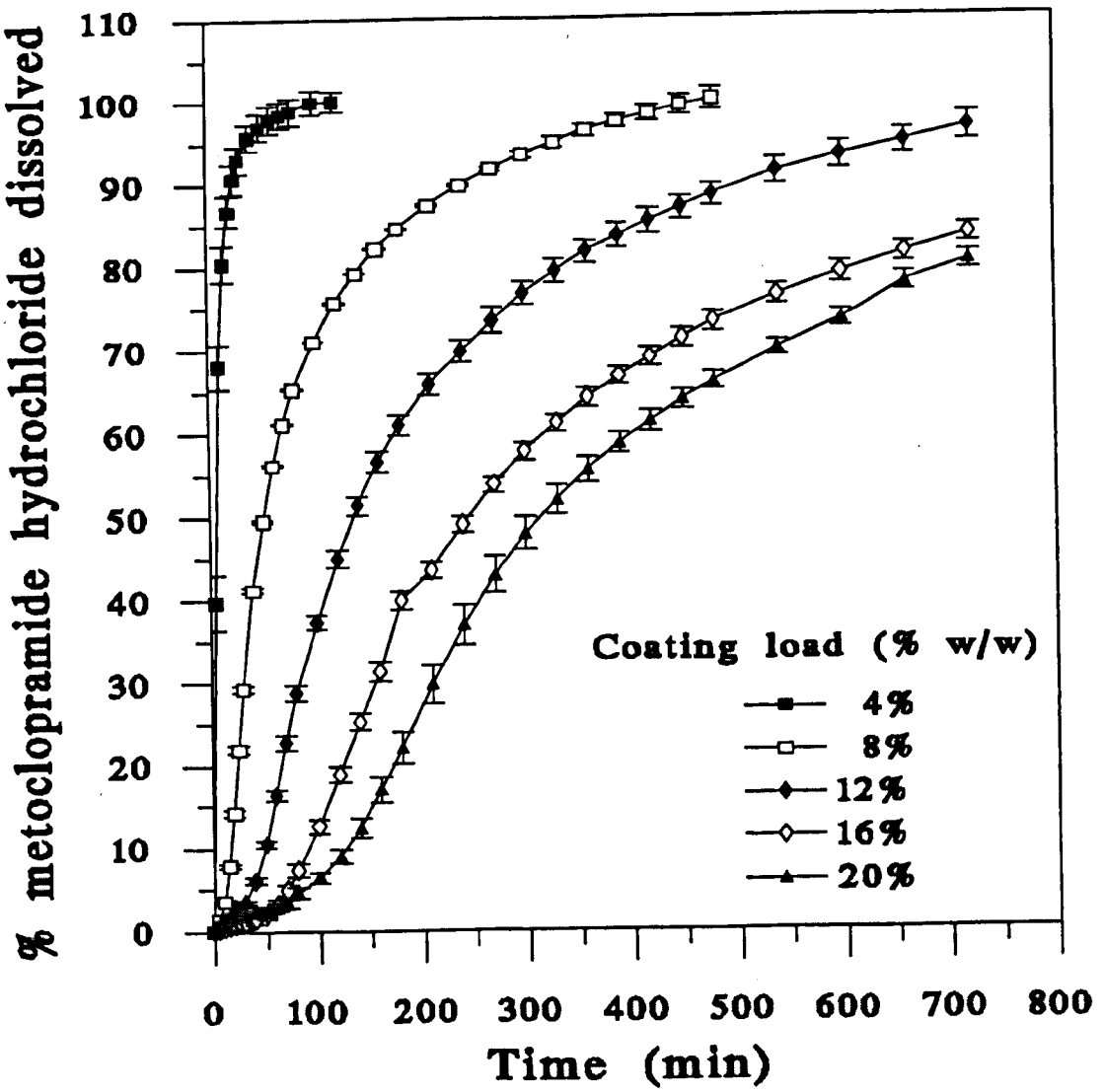


Figure 6.1. Effect of coating load on the release of metoclopramide hydrochloride from pellets coated with Surelease containing 5% HPMC E15.

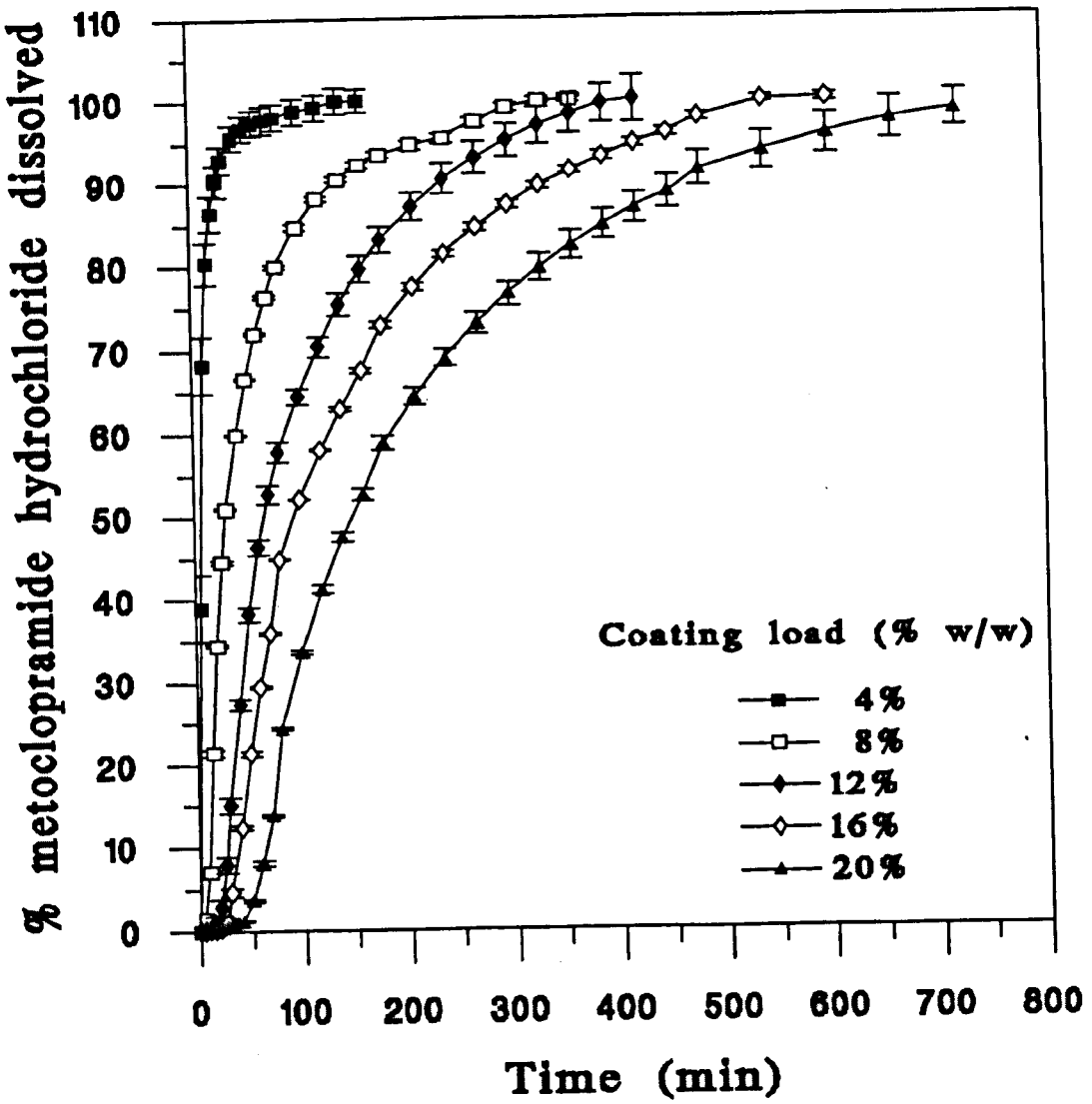


Figure 6.2. Effect of coating load on the release of metoclopramide hydrochloride from pellets coated with Surelease containing 7.5% HPMC E15.

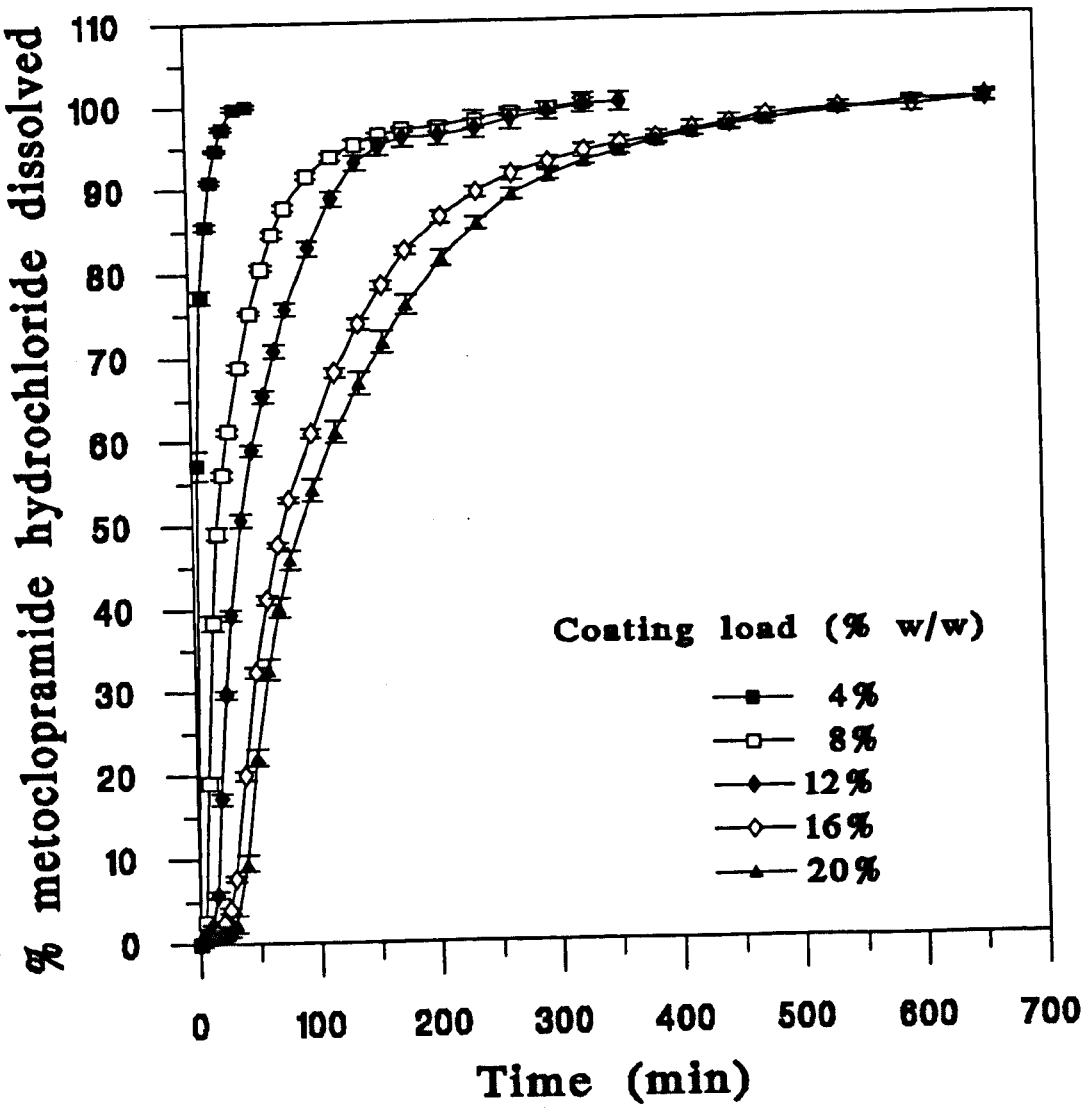


Figure 6.3. Effect of coating load on the release of metoclopramide hydrochloride from pellets coated with Surelease containing 10% HPMC E15.

Table 6.1. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from pellets coated with Surelease containing 5% HPMC E15, using equations 1.1-1.4.

Model	*	Percent of coating			
		8%	12%	16%	20%
Zero-order (Equation 1.1)	K_1	0.85 ± 0.01	0.33 ± <0.01	0.20 ± 0.0	0.16 ± <0.01
	r	0.977	0.980	0.981	0.985
	P<	0.001	0.001	0.001	0.001
	t1	-3.2 ± 0.6	-4.9 ± 1.6	9.5 ± 4.5	43.1 ± 9.4
Square-root (Equation 1.2)	K_2	11.5 ± 0.1	7.4 ± 0.1	5.8 ± <0.1	5.6 ± 0.2
	r	0.992	0.993	0.987	0.995
	P<	0.001	0.001	0.001	0.001
	t2	9.1 ± 0.3	26.7 ± 0.6	52.2 ± 2.4	95.1 ± 9.6
First-order (Equation 1.3)	K_3	0.0152 ± 0.0002	0.0059 ± 0.0001	0.0034 ± 0.0001	0.0028 ± 0.0001
	r	0.995	0.997	0.997	0.998
	P<	0.001	0.001	0.001	0.001
	t3	7.6 ± 0.1	25.5 ± 1.1	53.2 ± 0.9	101.0 ± 11.2
Hixon-Crowell (Equation 1.4)	K_4	0.0192 ± 0.0001	0.0076 ± 0.0002	0.0044 ± <0.0001	0.0036 ± <0.0001
	r	0.991	0.993	0.993	0.995
	P<	0.001	0.001	0.001	0.001
	t4	4.4 ± 0.2	16.3 ± 0.7	40.8 ± 2.8	84.3 ± 12.6

* Key: The units of release constants are: K_1 ($\%min^{-1}$), K_2 ($\%min^{-1/2}$), K_3 (min^{-1}), K_4 ($\%^{1/3}min^{-1}$) and the units of the lag times corresponding to different equations (1.1-1.4) t1, t2, t3 and t4 are (min). P is the degree of significance.

Table 6.2. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from pellets coated with Surelease containing 7.5% HPMC E15, using equations 1.1-1.4.

Model	*	Percent of coating			
		8%	12%	16%	20%
Zero-order (Equation 1.1)	K_1	1.22 ± 0.02	0.70 ± 0.01	0.40 ± <0.01	0.31 ± 0.00
	r	0.961	0.969	0.950	0.979
	P<	0.002	0.001	0.001	0.001
	t1	-7.9 ± 0.5	-0.01 ± 1.2	3.2 ± 2.5	18.1 ± 1.7
Square-root (Equation 1.2)	K_2	13.7 ± 0.2	11.1 ± 0.2	8.4 ± 0.1	7.7 ± <0.1
	r	0.981	0.987	0.979	0.992
	P<	0.001	0.001	0.001	0.001
	t2	4.0 ± 0.1	14.6 ± 0.6	25.5 ± 0.6	45.7 ± 0.9
First-order (Equation 1.3)	K_3	0.0239 ± 0.0001	0.0126 ± 0.0001	0.0074 ± 0.0001	0.0055 ± 0.0001
	r	0.989	0.992	0.996	0.997
	P<	0.001	0.001	0.001	0.001
	t3	2.4 ± 0.5	13.9 ± 0.6	24.7 ± 0.3	46.1 ± 0.5
Hixon-Crowell (Equation 1.4)	K_4	0.0293 ± 0.0002	0.0159 ± 0.0003	0.0093 ± 0.0001	0.0069 ± <0.0001
	r	0.963	0.986	0.991	0.973
	P<	0.001	0.001	0.001	0.001
	t4	-0.7 ± 0.3	9.6 ± 0.7	18.2 ± 0.8	38.7 ± 1.7

* Key: See table 6.1.

Table 6.3. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from pellets coated with Surelease containing 10% HPMC E15, using equations 1.1-1.4.

Model	*	Percent of coating			
		8%	12%	16%	20%
Zero-order (Equation 1.1)	K_1	2.04 ± 0.02	1.15 ± 0.0	0.66 ± 0.01	0.53 ± <0.01
	r	0.965	0.971	0.973	0.975
	P<	0.01	0.001	0.001	0.001
	t1	-1.9 ± 0.6	-0.3 ± 0.5	2.7 ± 1.1	0.4 ± 1.3
Square-root (Equation 1.2)	K_2	18.0 ± 0.2	14.3 ± 0.0	11.0 ± 0.1	9.7 ± 0.1
	r	0.982	0.985	0.987	0.987
	P<	0.01	0.001	0.001	0.001
	t2	3.7 ± 0.2	8.8 ± 0.2	17.8 ± 0.5	19.8 ± 0.6
First-order (Equation 1.3)	K_3	0.0361 ± 0.0001	0.0212 ± 0.0002	0.0119 ± 0.0001	0.0096 ± 0.0001
	r	0.987	0.993	0.993	0.993
	P<	0.01	0.001	0.001	0.001
	t3	2.8 ± 0.3	8.7 ± 0.1	16.9 ± 0.7	20.3 ± 0.9
Hixon-Crowell (Equation 1.4)	K_4	0.0461 ± 0.0002	0.0267 ± 0.0002	0.0150 ± 0.0002	0.0122 ± 0.0001
	r	0.981	0.987	0.987	0.988
	P<	0.01	0.001	0.001	0.001
	t4	1.3 ± 0.4	6.0 ± 0.4	13.1 ± 1.1	13.6 ± 1.1

* Key: See table 6.1.

6.3.2 EFFECT OF INCLUSION OF HPMC E15 ON THE RELEASE OF DICLOFENAC SODIUM FROM PELLETS

Figures 6.4-6.6 show the release of diclofenac sodium from pellets coated with Surelease containing 5%, 7.5% and 10% HPMC E15, respectively. At each coat composition, as the coating load increased, the release of diclofenac sodium decreased.

The release rates (K) and lag times (t) of the fits of diclofenac sodium release data to different kinetic models are shown in Tables 6.4-6.6. Due to insufficient data points for regression analysis no results were obtained for 4% coating load for all pellets and also for the 8% coating containing 7.5% or 10% w/w HPMC E15. Release rates decreased as the coating loads increased. Similarly to metoclopramide hydrochloride pellets, inclusion of HPMC in the coat increased the release rates of diclofenac sodium compared to those coated with only Surelease. Release rates were similar for pellets coated with Surelease/5% HPMC E15 and Surelease/7.5% HPMC E15. Increasing the HPMC content in the film to 10% increased release rates. Addition of 5% HPMC into Surelease film increased the first-order release rate by a factor of four compared to those coated with Surelease solely at the 20% coating load (Table 5.2). When the HPMC content in the film reached 10% the first-order release rate (Table 6.6) was one and half times faster than from pellets containing 5% HPMC (Table 6.4) at the 20% coating load. Here again the inclusion of HPMC decreased the lag times before the release profiles were established. Contrary to metoclopramide hydrochloride loaded pellets, the inclusion of 5% HPMC considerably increased the release rate of diclofenac sodium. Additionally the lag

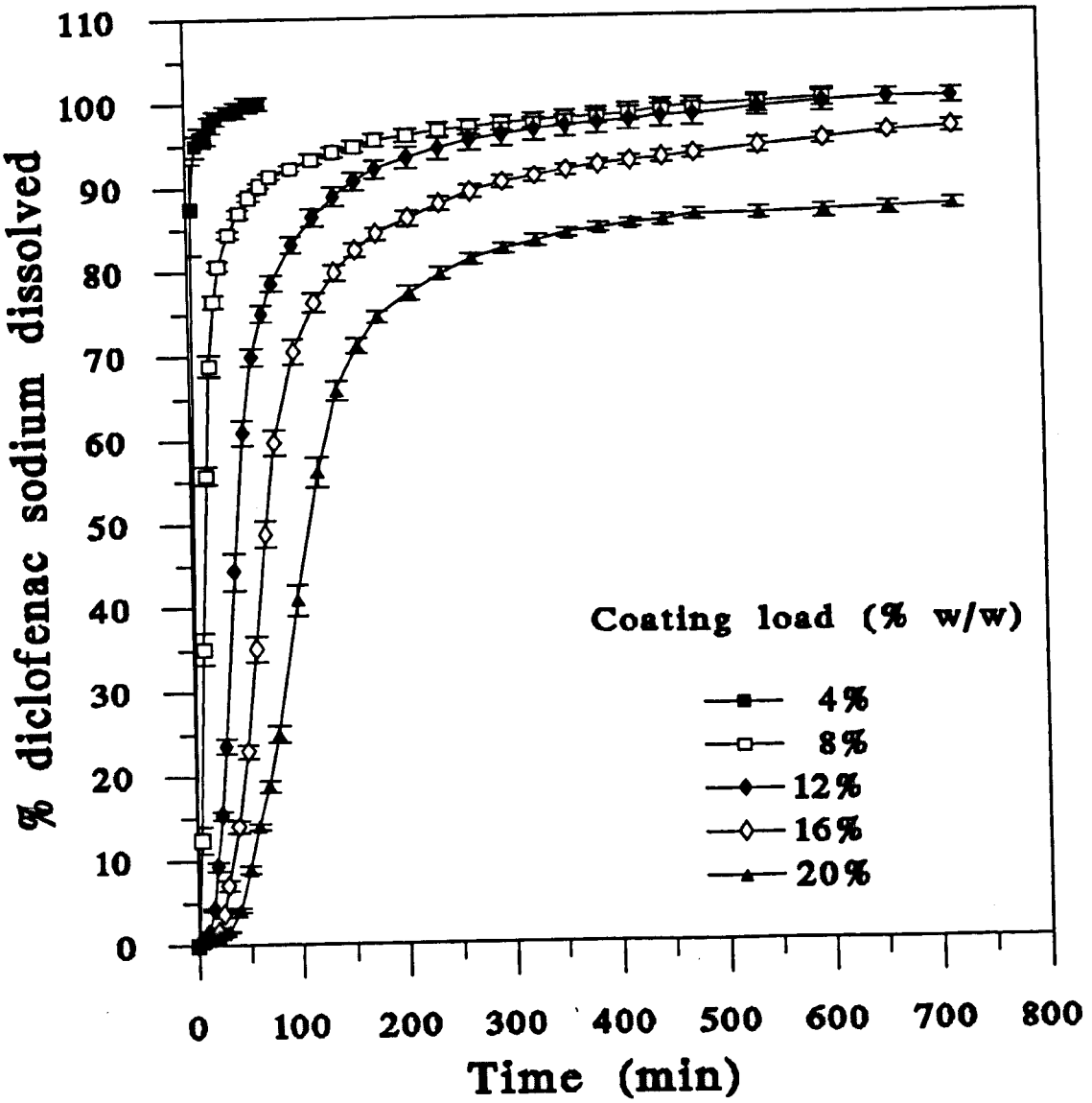


Figure 6.4. Effect of coating load on the release of diclofenac sodium from pellets coated with Surelease containing 5% HPMC E15.

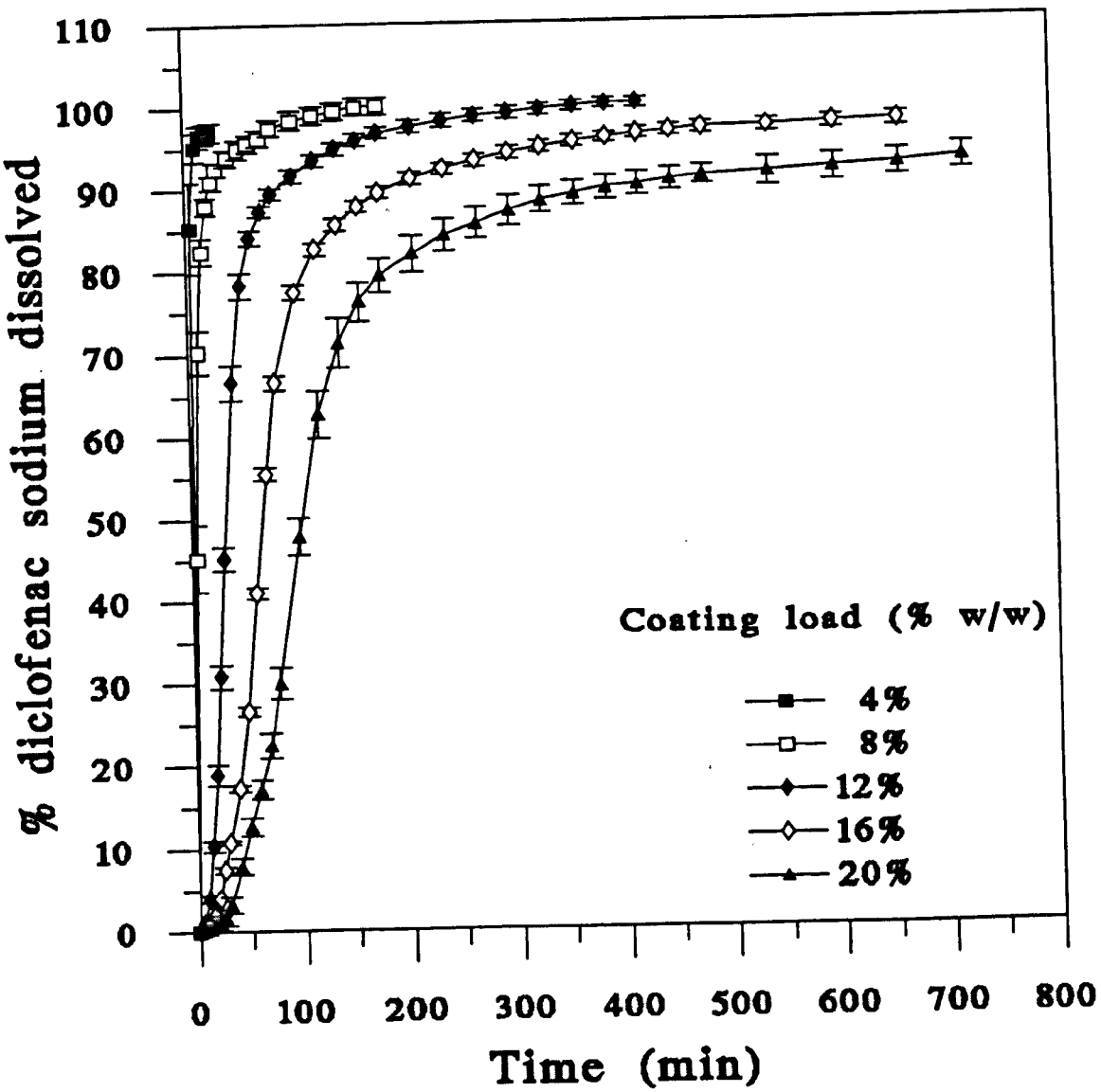


Figure 6.5. Effect of coating load on the release of diclofenac sodium from pellets coated with Surelease containing 7.5% HPMC E15.

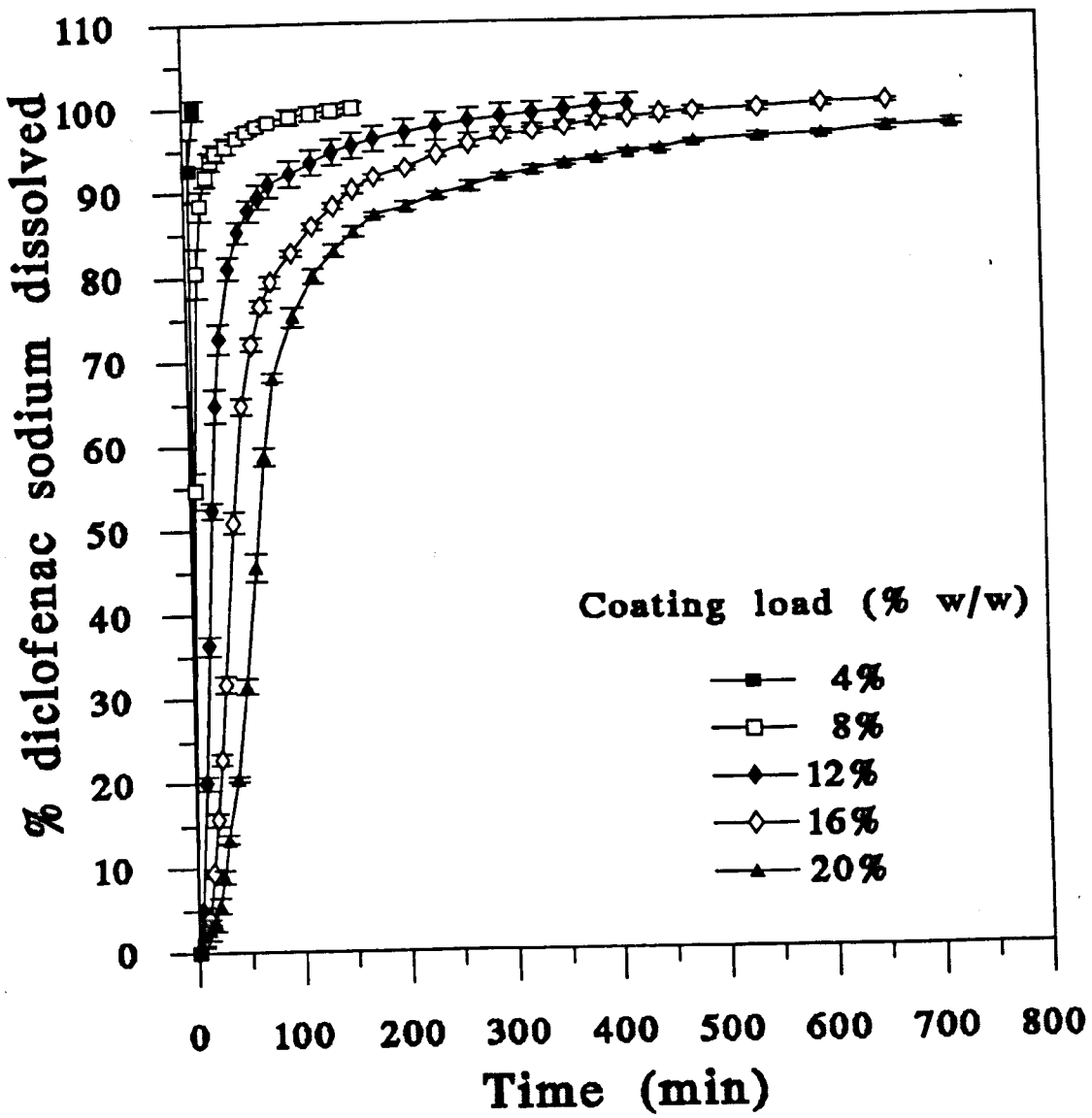


Figure 6.6. Effect of coating load on the release of diclofenac sodium from pellets coated with Surelease containing 10% HPMC E15.

Table 6.4. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of diclofenac sodium from pellets coated with Surelease containing 5% HPMC E15, using equations 1.1-1.4.

Model	*	Percent of coating			
		8%	12%	16%	20%
Zero-order (Equation 1.1)	K_1	3.8 ± 0.1	1.9 ± 0.1	1.2 ± <0.1	0.68 ± 0.01
	r	0.993	0.998	0.998	0.997
	P<	0.01	0.01	0.001	0.001
	t1	1.2 ± 0.4	16.7 ± 0.2	29.3 ± 0.6	40.9 ± 0.7
Square-root (Equation 1.2)	K_2	25.6 ± 0.6	22.3 ± 0.8	17.9 ± 0.4	13.4 ± 0.3
	r	0.990	0.997	0.994	0.996
	P<	0.01	0.01	0.001	0.001
	t2	3.1 ± 0.2	18.9 ± 0.1	32.3 ± 0.5	47.3 ± 0.4
First-order (Equation 1.3)	K_3	0.0697 ± 0.0021	0.0313 ± 0.0016	0.0191 ± 0.0009	0.0119 ± 0.0005
	r	0.988	0.996	0.989	0.994
	P<	0.01	0.01	0.001	0.001
	t3	3.4 ± 0.3	20.6 ± 0.3	34.9 ± 0.3	52.1 ± 0.6
Hixon-Crowell (Equation 1.4)	K_4	0.0874 ± 0.0020	0.0404 ± 0.0020	0.0251 ± 0.0010	0.0151 ± 0.0005
	r	0.991	0.997	0.993	0.996
	P<	0.001	0.01	0.001	0.001
	t4	2.7 ± 0.3	19.4 ± 0.2	33.3 ± 0.4	48.9 ± 0.4

* Key: See table 6.1.

Table 6.5. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of diclofenac sodium from pellets coated with Surelease containing 7.5% HPMC E15, using equations 1.1-1.4.

Model	*	Percent of coating		
		12%	16%	20%
Zero-order (Equation 1.1)	K_1	2.3 ± 0.1	1.2 ± <0.1	0.74 ± 0.05
	r	0.998	0.992	0.995
	P<	0.001	0.001	0.001
	t1	11.2 ± 0.3	23.9 ± 0.3	36.6 ± 1.3
Square-root (Equation 1.2)	K_2	23.7 ± 0.5	16.7 ± 0.2	13.3 ± 0.9
	r	0.994	0.983	0.987
	P<	0.001	0.001	0.001
	t2	12.8 ± 0.2	26.5 ± 0.3	41.3 ± 1.1
First-order (Equation 1.3)	K_3	0.0370 ± 0.0069	0.0202 ± 0.0005	0.0124 ± 0.0011
	r	0.988	0.975	0.982
	P<	0.01	0.001	0.001
	t3	14.3 ± 0.2	29.5 ± 0.2	45.2 ± 1.1
Hixon-Crowell (Equation 1.4)	K_4	0.0516 ± 0.0021	0.0256 ± 0.0005	0.0161 ± 0.0015
	r	0.993	0.983	0.988
	P<	0.001	0.001	0.001
	t4	13.3 ± 0.2	28.1 ± 0.5	42.8 ± 1.4

* Key: See table 6.1.

Table 6.6. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of diclofenac sodium from pellets coated with Surelease containing 10% HPMC E15, using equations 1.1-1.4.

Model	*	Percent of coating		
		12%	16%	20%
Zero-order (Equation 1.1)	K_1	3.0 ± 0.1	1.7 ± <0.1	1.2 ± <0.1
	r	0.999	0.998	0.996
	P<	0.001	0.001	0.001
	t1	2.8 ± 0.4	10.9 ± 0.3	20.5 ± 0.3
Square-root (Equation 1.2)	K_2	24.7 ± 0.8	19.5 ± 0.3	16.6 ± 0.4
	r	0.997	0.997	0.989
	P<	0.001	0.001	0.001
	t2	5.6 ± 0.2	14.2 ± 0.2	24.1 ± 0.2
First-order (Equation 1.3)	K_3	0.0554 ± 0.0023	0.0299 ± 0.0009	0.0205 ± 0.0004
	r	0.993	0.995	0.986
	P<	0.01	0.001	0.001
	t3	6.4 ± 0.3	15.6 ± 0.9	27.2 ± 0.4
Hixon-Crowell (Equation 1.4)	K_4	0.0696 ± 0.0030	0.0379 ± 0.0009	0.0260 ± 0.0007
	r	0.997	0.997	0.990
	P<	0.001	0.001	0.001
	t4	5.5 ± 0.3	14.3 ± 0.1	25.4 ± 0.2

* Key: See table 6.1.

time decreased from about 80 min to about 30 min after the inclusion of 5% HPMC into the Surelease coat for pellets with a 20% coating load.

6.3.3 RELEASE KINETICS FOR METOCLOPRAMIDE HYDROCHLORIDE

Correlation coefficients (r) of the fits of metoclopramide hydrochloride release data to different kinetic models are shown in Tables 6.1-6.3. The correlation coefficients for the best statistical fits revealed that, similar to pellets coated with Surelease solely, the first-order kinetic model is probably the most applicable model to all the release data. The coating load and also the HPMC content in the film did not appear to change the kinetic model which provided the best fit for the data.

Tables 6.7-6.9 summarize the values of K, n and l obtained from equation 1.6 and 1.7. The lower sums of squares and Schwartz information criterion indicate a better fit of the data to equation 1.7. Coating load had no apparent effect on the value of n for each HPMC content in the film. Generally the values of n for pellets coated with mixtures of Surelease and 5% HPMC were slightly higher than those observed for pellets coated with mixtures of Surelease and 7.5% or 10% HPMC. To gain an insight into the release mechanism the values of n (equation 1.7) were averaged. The mean value of n was 0.57 ± 0.09 which resembled those obtained for pellets coated solely with Surelease (0.60 ± 0.03; Table 5.3). The value of release exponent (n) indicates that similar to pellets coated with Surelease solely, diffusion is the predominant mechanism controlling the release of metoclopramide hydrochloride from pellets coated with Surelease/HPMC E15.

Table 6.7. The values of K_1, n, based on equation 1.6, K_2, l, n, based on equation 1.7 calculated in the range of 15-60% metoclopramide hydrochloride release from Surelease/5% HPMC E15 coated pellets. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	l*	n	ss	Schwartz
8%	0.80	1.040	99.20	40.93	5.00	13.40	0.628	18.40	29.54
12%	0.17	1.140	123.0	52.70	2.18	36.90	0.677	18.90	36.23
16%	0.11	1.100	132.0	58.47	1.84	72.50	0.639	21.50	40.93
20%	0.03	1.280	125.0	67.85	0.80	104.0	0.751	27.80	50.92

Table 6.8. The values of K_1, n, based on equation 1.6, K_2, l, n, based on equation 1.7 calculated in the range of 15-60% metoclopramide hydrochloride release from Surelease/7.5% HPMC E15 coated pellets. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	l*	n	ss	Schwartz
8%	1.37	1.040	136.0	33.06	9.36	9.46	0.552	16.60	22.21
12%	0.23	1.270	97.0	35.91	5.04	23.20	0.609	5.64	17.94
16%	0.21	1.150	82.2	34.75	6.03	46.00	0.500	2.60	12.51
20%	0.13	1.160	113.0	41.94	4.59	64.80	0.522	4.12	17.55

Table 6.9. The values of K_1, n, based on equation 1.6, K_2, l, n, based on equation 1.7 calculated in the range of 15-60% metoclopramide hydrochloride release from Surelease/10% HPMC E15 coated pellets. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	l*	n	ss	Schwartz
8%	3.36	0.869	67.9	24.31	20.50	9.18	0.364	0.69	-3.00
12%	0.48	1.250	149.0	33.59	7.26	14.40	0.593	17.60	22.59
16%	0.32	1.160	160.0	39.40	5.91	28.60	0.553	15.00	24.80
20%	0.29	1.130	164.0	39.59	7.39	38.50	0.483	7.10	19.55

* Key: The units of K_1 and K_2 are $\%min^{-n}$ and the unit of l is min.

6.3.4 RELEASE KINETICS FOR DICLOFENAC SODIUM

Correlation coefficients (r) of the fits of diclofenac sodium release data to different kinetic models are shown in Tables 6.4-6.6. The correlation coefficients for the best statistical fits revealed that the zero-order kinetic model is probably the most applicable to all the release data. Coating load and HPMC content of the coat did not change the best kinetic model.

Tables 6.10-6.12 summarize the values of K, n and l obtained from equations 1.6 and 1.7. The lower sums of squares and Schwartz information criterion indicate a better fit of release data to equation 1.7 except for those coated with the mixture of Surelease and 7.5% HPMC which showed no improvement in the fit when using equation 1.7. The coating load and HPMC content in the film had no apparent effect on the mechanism of drug release. The mean value of n (equation 1.7) is 1.28 ± 0.25. A comparison of release exponent n with those obtained for pellets coated with Surelease solely (Table 5.4) showed that different mechanisms control drug release from pellets coated with Surelease/HPMC blends and those coated with solely Surelease. The values of n indicate erosion controlled release mechanism. Therefore it may be concluded that in systems with numerous pores present in the coat diffusion of drug is a rapid process and is not the rate limiting step. In this case it is probable that the rate of pore formation control drug release.

6.3.5 LEACHING OF HPMC E15 FROM SURELEASE FILM

In order to understand the mechanisms of the enhancement of release rate of the drugs through Surelease coat following the addition of HPMC E15, studies were

Table 6.10. The values of K_1, n, based on equation 1.6, K_2, l, n, based on equation 1.7 calculated in the range of 15-60% diclofenac sodium release from Surelease/5% HPMC E15 coated pellets. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	l*	n	ss	Schwartz
8%	1.770	1.280	4.88	6.95	6.270	2.81	0.875	0.000	-146.4
12%	0.036	1.910	19.80	18.14	0.974	13.50	1.150	6.630	14.28
16%	0.008	2.050	10.80	17.86	0.138	16.20	1.460	4.920	14.93
20%	0.004	2.030	3.88	11.72	0.045	20.20	1.550	1.840	9.02

Table 6.11. The values of K_1, n, based on equation 1.6, K_2, l, n, based on equation 1.7 calculated in the range of 15-60% diclofenac sodium release from Surelease/7.5% HPMC E15 coated pellets. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	l*	n	ss	Schwartz
8%	Not enough data points								
12%	0.12	1.720	24.30	19.16	1.69	10.10	1.080	7.53	14.92
16%	0.02	1.890	14.00	22.39	0.05	6.59	1.660	12.60	23.59
20%	0.01	1.860	8.63	18.98	0.04	11.60	1.590	7.21	19.66

Table 6.12. The values of K_1, n, based on equation 1.6, K_2, l, n, based on equation 1.7 calculated in the range of 15-60% diclofenac sodium release from Surelease/10% HPMC E15 coated pellets. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	l*	n	ss	Schwartz
8%	Not enough data points								
12%	0.68	1.450	7.10	10.61	2.65	3.21	1.060	0.07	-6.54
16%	0.18	1.510	18.90	21.20	1.150	8.666	1.090	8.30	18.07
20%	0.04	1.690	21.70	28.78	0.22	9.90	1.350	14.00	27.37

* Key: The units of K_1 and K_2 are $\%min^{-n}$ and the unit of l is min.

performed on free films containing 7.5% HPMC E15 representative of Surelease/HPMC films. The amount of HPMC leached out is presented in Table 6.13. Aqueous extracts of the membranes yielded 45.5% of the total HPMC in the film after just 30 min, while for Surelease films without any HPMC, no soluble material was recovered.

This suggests that as pellets undergo dissolution, HPMC in the coat would dissolve and leach out, leaving pores through which the drug may be released. These results are in accord with those published by Donbrow and Samuelov (1980) and Lindholm et al (1986) for the effects of polyethylene glycol or polysorbate 20 in ethylcellulose films, respectively. However these results contradict those published by Donbrow and Samuelov (1980) for the effect of hydroxypropylcellulose (HPC) as an additive in ethylcellulose films. These authors stated that the increase in permeation through the ethylcellulose/HPC film was due to retention of the HPC in the film and the formation of swollen hydrated channels. The difference between the results of this study and those performed by Donbrow and Samuelov may be due to the differences in the type of cellulose ether used. The reduced interaction of HPMC with ethylcellulose due to its increased substitution (Sakellariou et al, 1986) may be responsible for the leaching out of HPMC from these films.

Table 6.13. The results of leaching studies for Surelease and Surelease/7.5% HPMC films.

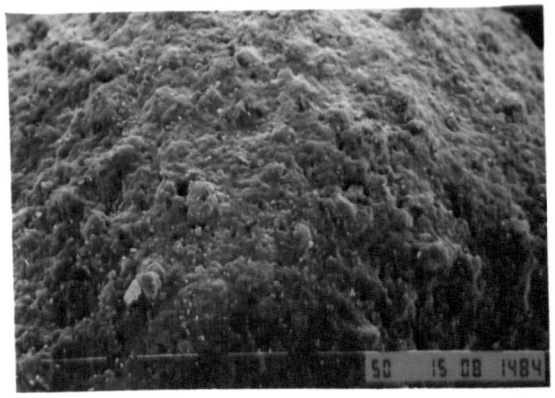
Type of film	Percent of HPMC leached out of the film
Surelease/7.5% HPMC E15	45.5 ± 2.1
Surelease	0

6.3.6 SURFACE MORPHOLOGY OF THE PELLETS

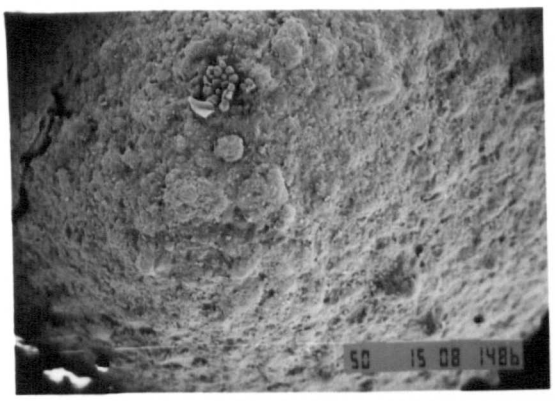
The surfaces of the coated pellets were also examined by scanning electron microscopy before and after dissolution. The surface characteristics of either the metoclopramide hydrochloride or diclofenac sodium pellets coated with Surelease/HPMC (in all HPMC content) films at high coating load, such as 20%, were similar before and after dissolution. Due to the porous nature of the coat it was not possible to distinguish between pores resulting from dissolution of HPMC and pores which already existed in the coat.

However at the lower coating load (8%) there were few cracks on the surface of the some of the pellets after dissolution which has been shown as an example for pellets coated with Surelease containing 7.5% HPMC in Figure 6.7. Such these cracks were not observed for pellets coated with Surelease solely.

The development of these cracks at low coating loads may be explained as follows: As the retention of the HPMC in the ethylcellulose/HPMC blend depends on the coating thickness (Shah and Sheth, 1972), it is more likely that at a low coating load (8%) the dissolution and leaching out of HPMC occurs through the full thickness of the coat. However at the higher coating load (20%), with increased coating thickness, the possibility of retention of HPMC in the inner layers is more than at the lower coating load. Leaching out of HPMC provides some weak points in the membrane which cause it to be ruptured under the internal stresses as water penetrate the core. However at a high coating load, the support provided by the inner layers of the coat prevents development of these cracks.



(a)



(b)

Figure 6.7. Micrographs of diclofenac sodium pellets coated with Surelease containing 7.5% HPMC E15 at the 8% coating load. a) before dissolution b) after 5 h dissolution (Magnification × 150).

6.4. GENERAL DISCUSSION

The results of this study indicate that the addition of the hydrophilic HPMC increased the release rate of both drugs from pellets coated with Surelease. Hydrophilic additives can increase the permeability of hydrophobic films by several mechanisms. Some additives make the film more porous such as polyethylene glycol (Donbrow and Friedman, 1975) or form a hydrated network inside the film such as hydroxypropylcellulose (Donbrow and Samuelov, 1980). Others may act as carriers for drugs such as Span 20 for salicylic acid through ethylcellulose films (Lindholm and Juslin, 1982) or form complexes, which increase the solubility of the drug in the membrane or increase the diffusion coefficient, such as the complex of tetrabutylammonium bromide with salicylic acid (Lindholm et al, 1982).

The ability of HPMC to modify the release of drugs from systems coated with water insoluble polymers has been demonstrated previously for ethylcellulose films (Kannikoski et al, 1984; Ghebre-Sellassie et al, 1988; Gilligan and Po, 1991) and Eudragit films (Govender et al, 1995). Studies on free films revealed that the HPMC dissolved and consequently the formation of pores in the film was probable. These pores, which might facilitate the ingress of water into the pellets and release of the drug from the pellets were responsible for the faster release rates of drugs. According to Sakellariou et al (1986) the formation of pores is expected in films prepared from mixtures of HPMC and ethylcellulose as these blends show phase separation. They suggested that in pharmaceutical formulations coated with these blends, the soluble component would leach out leaving pores available for drug release.

It was observed that diclofenac sodium was released more quickly than metoclopramide hydrochloride from pellets coated with solely Surelease (chapter 5). One explanation which may describe this faster release is that the mechanism involved in the release of these drugs from Surelease coated pellets is diffusion through the intact polymeric film. In this case, drugs of low water solubility may be released more rapidly than expected (Porter and Ghebre-Sellassie, 1994). However when the drug is released via diffusion through water filled pores or channels within the coat, the solubility of the drug in water will be a significant factor in determining the release rate (Porter and Ghebre-Sellassie, 1994).

The change in the release mechanism from diffusion through intact coat to diffusion through pores upon addition of HPMC to an ethylcellulose coat has been discussed by Gilligan and Po (1991). The faster release of diclofenac sodium compared to metoclopramide hydrochloride was also observed for pellets coated with Surelease containing HPMC. It may be concluded that differences in the release rates of the two drugs are not due to differences in their rates of diffusion through the polymer as this behaviour was also observed for those pellets coated with Surelease/HPMC E15 blends. Therefore other possible causes must be explored to explain the differences between release behaviour of these drugs from Surelease coated pellets.

Addition of HPMC increased the release of diclofenac sodium to a larger extent than metoclopramide hydrochloride (Tables 6.1-6.3 and 6.4-6.6). The values of n were higher for diclofenac sodium than metoclopramide hydrochloride indicating different mechanisms for the release of these drugs. Release of metoclopramide hydrochloride

was controlled mainly vai diffusion. However the contribution of diffusion as a rate limiting step in the release of diclofenac sodium was reduced. The different release behaviour of these two drugs may stem from their interaction with either polymer in the coat. It has been reported that diclofenac sodium dehydrates the HPMC and reduces its cloud point (Rajabi-Siahboomi et al, 1994a) while hydrochloride salts of organic compounds salt in HPMC and increase its solubility (Mitchell et al, 1993c). If this interaction occurred in pellets coated with Surelease/HPMC blends, for metoclopramide hydrochloride pellets, faster hydration of HPMC and consequently faster dissolution of this polymer would result in the rapid formation of pores and dissolution of the drug. Therefore diffusion of metoclopramide hydrochloride should be a rapid process and faster than diclofenac sodium. However slower release of metoclopamide hydrochloride than diclofenacs sodium from pellets coated with Surelease/HPMC ruled out the occurrence of these interactions and therefore other possible interactions must be investigated.

6.5 CONCLUSIONS

The release rates of both drugs increased with increasing the amount of hydrophillic polymer in the film. The ratio of Surelease to the HPMC had a major effect on drug release rate. High proportions of HPMC component in Surelease membrane caused a rapid release of drugs even at high coating loads. This effect was probably related to the leaching out of the HPMC from the Surelease film, which led to the formation of pores. These pores may act as points for entry of dissolution medium through the film into the core and consequent dissolution and release of drug from the pellets. Diclofenac sodium released faster than metoclopramide hydrochloride. The

mechanism of release of these two drugs were also different.

The possible explanations for different release behaviour of these drugs are discussed in more details in chapter 8.

CHAPTER 7. EFFECT OF APPLICATION OF HPMC SEAL-COAT OR UNDERCOAT ON THE DRUG RELEASE FROM COATED PELLETS

7.1 INTRODUCTION

Metoclopramide hydrochloride was released more slowly than diclofenac sodium from Surelease-coated pellets despite the higher water solubility of the former (chapter 5). The differences between the release behaviour of these two drugs were also observed for pellets coated with mixtures of Surelease/HPMC E15 (chapter 6). Any interaction between a drug and the coating formulation during the application of the film might influence the release. These interactions may be prevented by application of a seal-coat (Porter, 1989a). In an attempt to elucidate if migration of the drugs to the coat had occurred and to evaluate the existence of any interaction between the drugs and the Surelease during application, drug-loaded pellets were initially seal-coated with 2% w/w HPMC E5 prior to the application of the Surelease coat.

On the other hand the release of both drugs was very rapid from pellets coated with as much as 20% HPMC E15 (chapter 4). As the performances of HPMC E5 and E15 were similar (section 4.3.1), in order to evaluate the effect of seal-coat load on drug release from Surelease-coated pellets and also to investigate the effect of a Surelease coat in preventing the rapid erosion and disintegration of HPMC E15 coated pellets, pellets coated with 20% HPMC E15 were overcoated with Surelease.

7.1.1 AIMS AND OBJECTIVES

The objectives were to evaluate if and how a 2% w/w seal-coat of the water soluble polymer (HPMC E5) affected the release of metoclopramide hydrochloride or diclofenac sodium from Surelease coated pellets.

The study was also performed to examine how the application of Surelease overcoat on the pellets which have been coated with 20% w/w HPMC E15 affected drug release from these pellets. Therefore as these pellets already contained a 20% w/w HPMC E15 coat, Surelease was applied only up to 12% w/w. The results were compared to those obtained for pellets containing 2% seal-coat in order to ascertain the effect of seal-coat load on drug release.

7.2 MATERIALS AND METHODS

7.2.1 MATERIALS

Metoclopramide hydrochloride, diclofenac sodium, HPMC E5, HPMC E15, Surelease, talc, triacetin, non-pareils (0.710-0.850 mm), as described in section 2.1, and drug-loaded pellets which had already been coated with 20% w/w HPMC E15, prepared as described in section 4.2.2.3, were used in this study.

7.2.2 METHODS

7.2.2.1 Coating of non-pareils with drug

Batches of 4500 g non-pareils were coated with metoclopramide hydrochloride or diclofenac sodium as described in section 4.2.2.1. The drug layering process

produced pellets with a metoclopramide hydrochloride load of 3.95 ± 0.1% w/w and a diclofenac sodium load of 3.98 ± 0.05% w/w.

7.2.2.2 Seal-coating of drug loaded pellets with HPMC E5

Batches of 4500 g drug-layered pellets from section 7.2.2.1 were seal-coated with a 2% w/w HPMC E5 to 2% weight increase using the formulation shown in Table 2.2 and under the conditions outlined in Table 3.4 (section 3.6).

7.2.2.3 Coating of seal-coated or undercoated drug layered pellets with Surelease

Batches of 4500 g seal-coated, drug-layered pellets from section 7.2.2.2 were coated with Surelease under the conditions outlined in Table 3.4. By taking into consideration the coating efficiency, samples of 50 g of coated pellets were removed from the coating pan when the coating loads had reached 4%, 8%, 12%, 16% and 20% w/w.

Batches of 4500 g metoclopramide hydrochloride or diclofenac sodium loaded pellets which had been already coated with 20% w/w HPMC E15 (section 4.2.2.3) were overcoated with Surelease under the same conditions as above. By taking into consideration the coating efficiency, samples of 50 g coated pellets were removed from the coating pan when the coating load had reached 4%, 8% and 12% w/w.

7.2.2.4 Dissolution testing

Dissolution studies on coated pellets were performed as explained in section 2.2.6.

7.2.2.5 Release kinetics for coated pellets

The release data between 15-60% were fitted to the different kinetic models described in section 2.2.7.

7.2.2.6 Scanning electron microscopy

Scanning electron microscopy on pellets before and after dissolution was performed as described in section 2.2.4.3.

7.3 RESULTS AND DISCUSSION

7.3.1 EFFECT OF SURELEASE COATING LOAD ON THE RELEASE OF METOCLOPRAMIDE HYDROCHLORIDE FROM SEAL-COATED OR UNDERCOATED PELLETS

7.3.1.1 Pellets seal-coated with 2% HPMC E5

The coating load of Surelease had a major effect on metoclopramide hydrochloride release from seal-coated pellets (Figure 7.1). Table 7.1 lists the release rates and lag times calculated based on equations 1.1-1.4. As the coating load increased the release rates progressively decreased. Similar to pellets coated with only Surelease, a lag time was developed and became longer as the coating load increased. A comparison of release rates of seal-coated pellets coated with Surelease with those obtained for pellets coated with Surelease without a seal-coat (Table 5.1) indicated that application of a seal-coat resulted in a decrease in the release rates of metoclopramide hydrochloride.

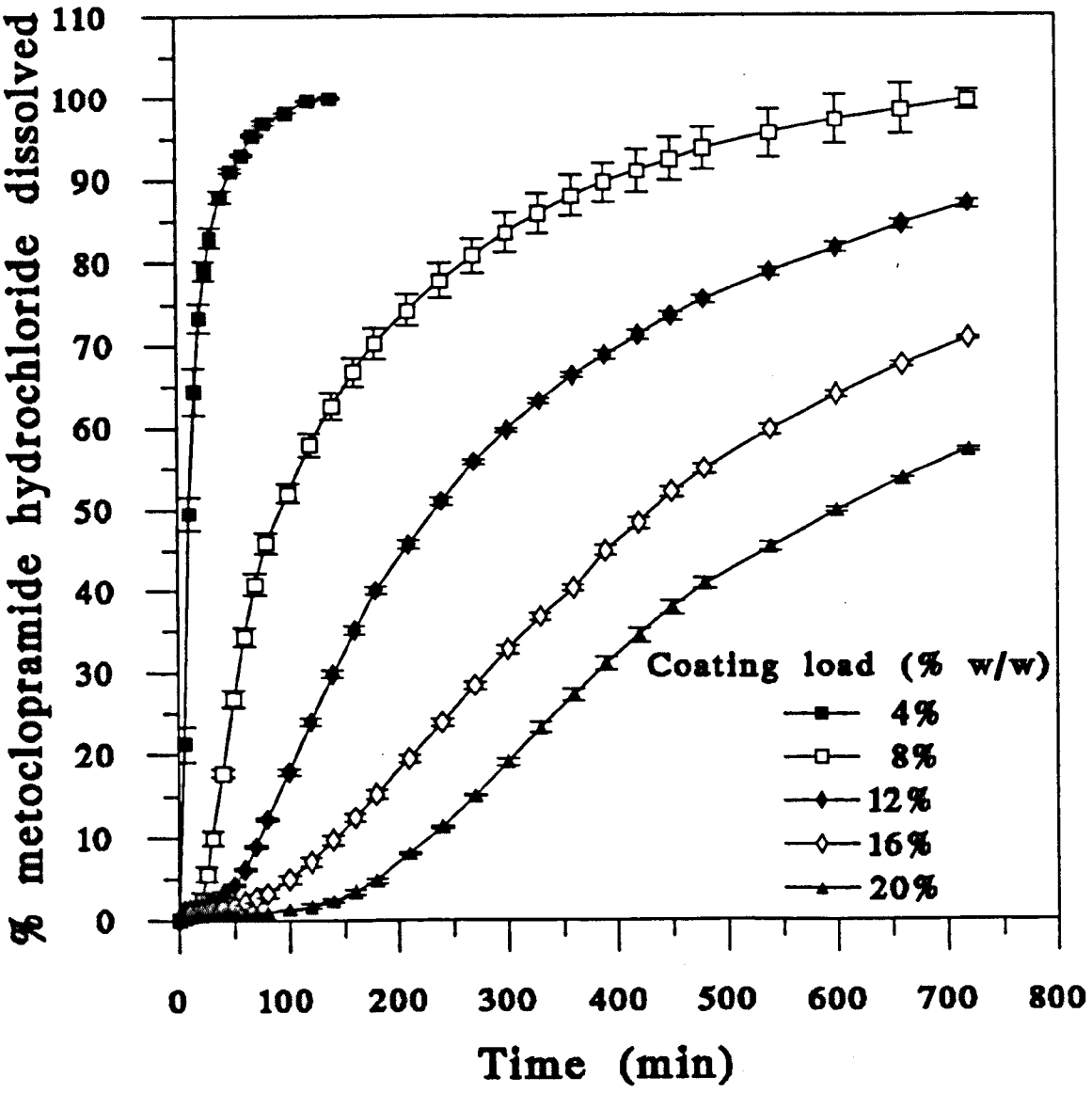


Figure 7.1. Effect of Surelease coating load on the release of metoclopramide hydrochloride from pellets which had been seal-coated with 2% w/w HPMC E5.

Table 7.1. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from pellets which had been seal-coated with 2% HPMC E5 and overcoated with Surelease, using equations 1.1-1.4.

Model	*	Percent of coating				
		4%	8%	12%	16%	20%
Zero-order (Equation 1.1)	K_1	4.32 ± 0.36	0.55 ± <0.01	0.22 ± <0.01	0.12 ± <0.01	0.10 ± <0.01
	r	0.984	0.971	0.989	0.993	0.987
	P<	0.1	0.001	0.001	0.001	0.001
	t1	-0.6 ± 1.6	1.9 ± 0.9	15.8 ± 1.3	41.9 ± 3.4	91.5 ± 13.9
Square-root (Equation 1.2)	K_2	26.6 ± 2.2	9.3 ± 0.1	5.8 ± <0.1	4.6 ± <0.1	4.2 ± <0.1
	r	0.995	0.989	0.998	0.998	0.996
	P<	0.1	0.001	0.001	0.001	0.001
	t2	1.9 ± 0.7	17.1 ± 0.4	45.9 ± 0.6	101.7 ± 2.5	151.7 ± 7.8
First-order (Equation 1.3)	K_3	0.0796 ± 0.0029	0.0089 ± 0.0002	0.0037 ± 0.0001	0.0021 ± 0.0001	0.0016 ± <0.0001
	r	0.997	0.992	0.999	0.999	0.998
	P<	0.1	0.001	0.001	0.001	0.001
	t3	1.7 ± 0.9	15.1 ± 0.5	42.7 ± 3.2	99.7 ± 5.4	149.6 ± 11.1
Hixon-Crowell (Equation 1.4)	K_4	0.0998 ± 0.0050	0.0119 ± 0.0003	0.0047 ± <0.0001	0.0026 ± <0.0001	0.0021 ± <0.0001
	r	0.994	0.986	0.997	0.998	0.995
	P<	0.1	0.001	0.001	0.001	0.001
	t4	1.1 ± 1.0	10.9 ± 0.3	35.3 ± 1.2	85.8 ± 3.5	134.8 ± 9.4

* Key: The units of release constants are: K_1 ($\%min^{-1}$), K_2 ($\%min^{-1/2}$), K_3 (min^{-1}), K_4 ($\%^{1/3}min^{-1}$) and the units of the lag times corresponding to different equations (1.1-1.4) t1, t2, t3 and t4 are (min). P is the degree of significance.

7.3.1.2 Pellets undercoated with 20% w/w HPMC E15

Figure 7.2 indicates that increasing the coating load of Surelease decreased the metoclopramide hydrochloride release from pellets already coated with 20% HPMC E15. However pellets coated with a 4% Surelease overcoat, disintegrated after 5 minutes and therefore rapidly released all their contents.

The calculated release rates and lag times based on equations 1.1-1.4, are shown in Table 7.2. No release data were obtained for the 4% w/w coating load as these pellets rapidly disintegrated. Increasing the Surelease coating load from 8% to 12% w/w decreased the zero-order release rate by about 56%. Pellets with a Surelease overcoat on 20% HPMC E15 undercoat released their drug at a faster rate than pellets with 2% HPMC E5 seal-coat (Table 7.1). The scanning electron micrographs of these pellets before and after dissolution tests revealed that there were big pores and cracks in the pellets undercoated with 20% HPMC E15 and overcoated with 12% Surelease following dissolution (Figure 7.3). Similar pores and cracks were not observed in the pellets with an overcoat of 12% Surelease onto 2% HPMC E5 after dissolution. These cracks may be a consequence of the hydration and swelling of the HPMC undercoat which lead to the rupture of the Surelease overcoat. These cracks and pores accounted for the faster release rate from pellets with the 20% HPMC E15 undercoat than from 2% HPMC E5 seal-coat.

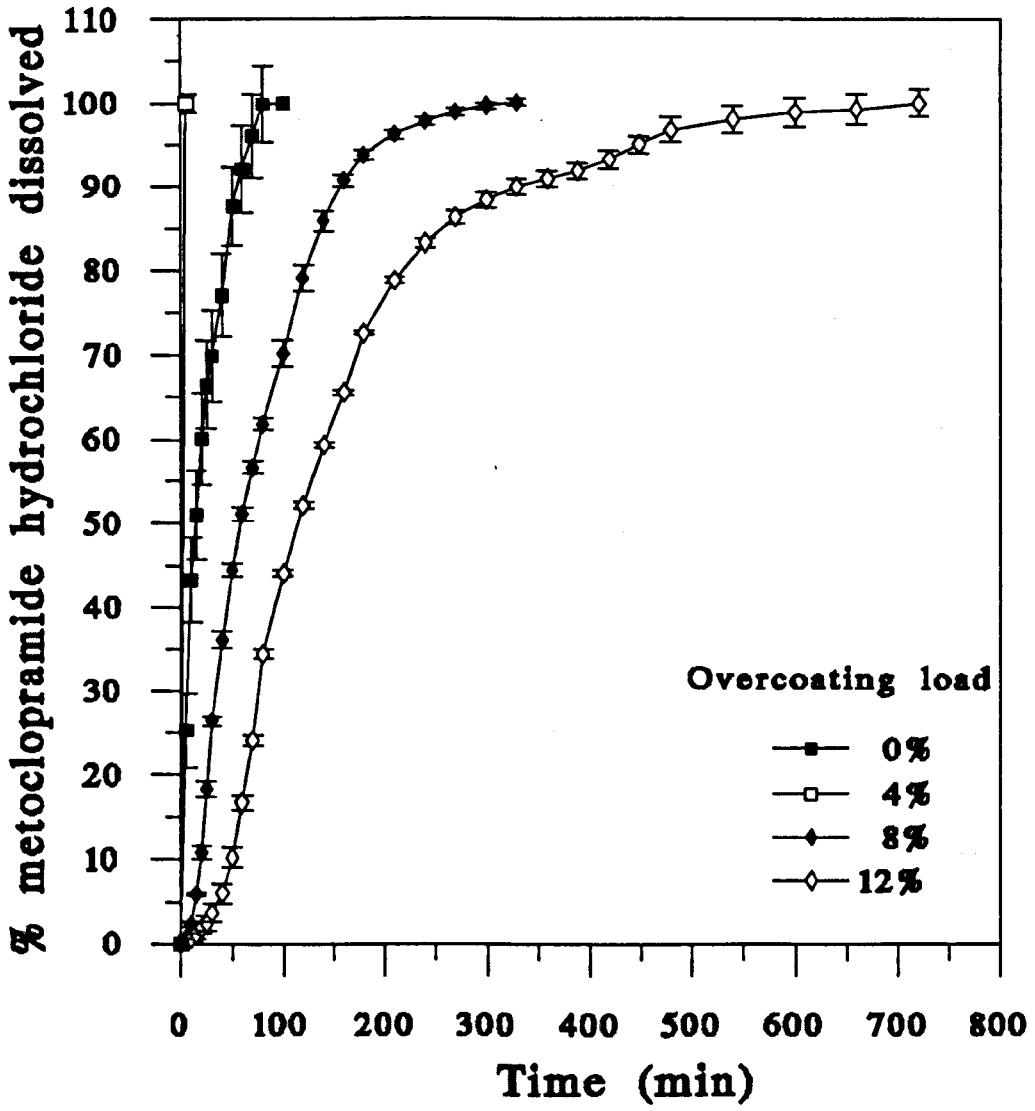


Figure 7.2. Effect of Surelease coating load on the release of metoclopramide hydrochloride from pellets already coated with 20% w/w HPMC E15.

Table 7.2. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from pellets already coated with 20% HPMC E15 and overcoated with Surelease, using equations 1.1-1.4.

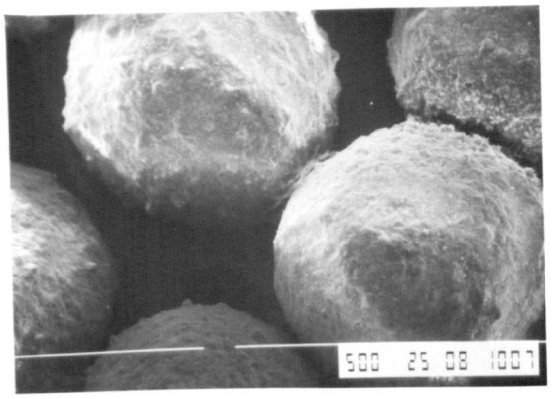
Model	*	Percent of coating	
		8%	12%
Zero-order (Equation 1.1)	K_1	0.83 ± <0.01	0.46 ± <0.01
	r	0.983	0.992
	P<	0.001	0.001
	t1	0.9 ± 0.8	30.5 ± 2.3
Square-root (Equation 1.2)	K_2	11.3 ± 0.1	9.8 ± 0.1
	r	0.995	0.998
	P<	0.001	0.001
	t2	10.9 ± 0.5	43.2 ± 1.4
First-order (Equation 1.3)	K_3	0.0140 ±<0.0001	0.0078 ± <0.0001
	r	0.997	1
	P<	0.001	0.001
	t3	9.9 ± 0.2	45.5 ± 1.2
Hixon-Crowell (Equation 1.4)	K_4	0.0181 ± 0.0002	0.0101 ± <0.0001
	r	0.994	0.999
	P<	0.001	0.001
	t4	6.8 ± 0.7	42.1 ± 1.5

* Key: See table 7.1.

7.3.2 EFFECT OF SURELEASE COATING LOAD ON THE RELEASE OF DICLOFENAC SODIUM FROM SEAL-COATED OR UNDERCOATED PELLETS

7.3.2.1 Pellets seal-coated with 2% HPMC E5

Similar to metoclopramide hydrochloride seal-coated pellets, release of diclofenac sodium markedly decreased as the coating load of Surelease increased (Figure 7.4). A comparison of release profile between seal-coated pellets and pellets without seal-



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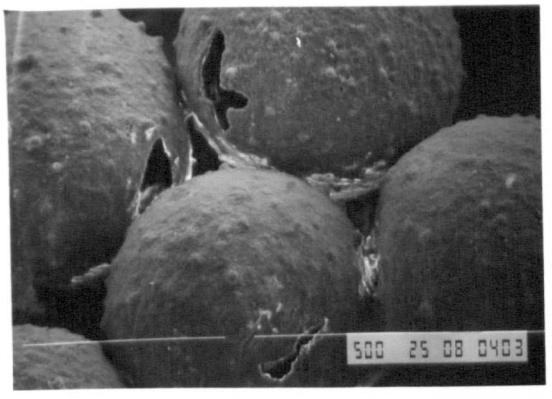


(b)

Figure 7.3. Micrographs of metoclopramide hydrochloride pellets already coated with 20% HPMC E15 and overcoated with 12% Surelease a) Surface structure of the pellet before the dissolution b) Surface structure of the pellets after 12 h dissolution testing (Magnification × 50).

coat (Figure 5.2) showed that the application of a seal-coat had a profound effect on the release of diclofenac sodium from 4% Surelease coated pellets. While more than 70% of the drug was released in 5 min from 4% Surelease-coated pellets without seal-coat, those pellets with seal-coat released 20% of the drug in 5 min.

Table 7.3 lists the release rates and lag times calculated using equations 1.1-1.4. A lag time before establishing the controlled release profile was also observed for diclofenac sodium seal-coated pellets which became larger with increasing coating load. A comparison of release rates of seal-coated pellets coated with Surelease with those obtained for pellets coated with Surelease without a seal-coat (Table 5.2) indicated that application of a seal-coat decreased the release rates of diclofenac sodium at equivalent coating loads.

7.3.2.2 Pellets undercoated with 20% HPMC E15

Figure 7.5 shows that again the coating load of Surelease had a great influence on the release of diclofenac sodium from pellets already coated with 20% HPMC E15.

Release rates decreased as the Surelease coating load increased (Table 7.4). There were not enough data points to allow regression analysis for pellets coated with 4% Surelease. Increasing the Surelease coating load from 8% to 12% decreased the release rate by about 52%. Pellets with a Surelease overcoat on 20% HPMC E15 undercoat released their drug at a faster rate than pellets with 2% HPMC E5 seal-coat (Table 7.3). Similar to metoclopramide hydrochloride pellets, a comparison of

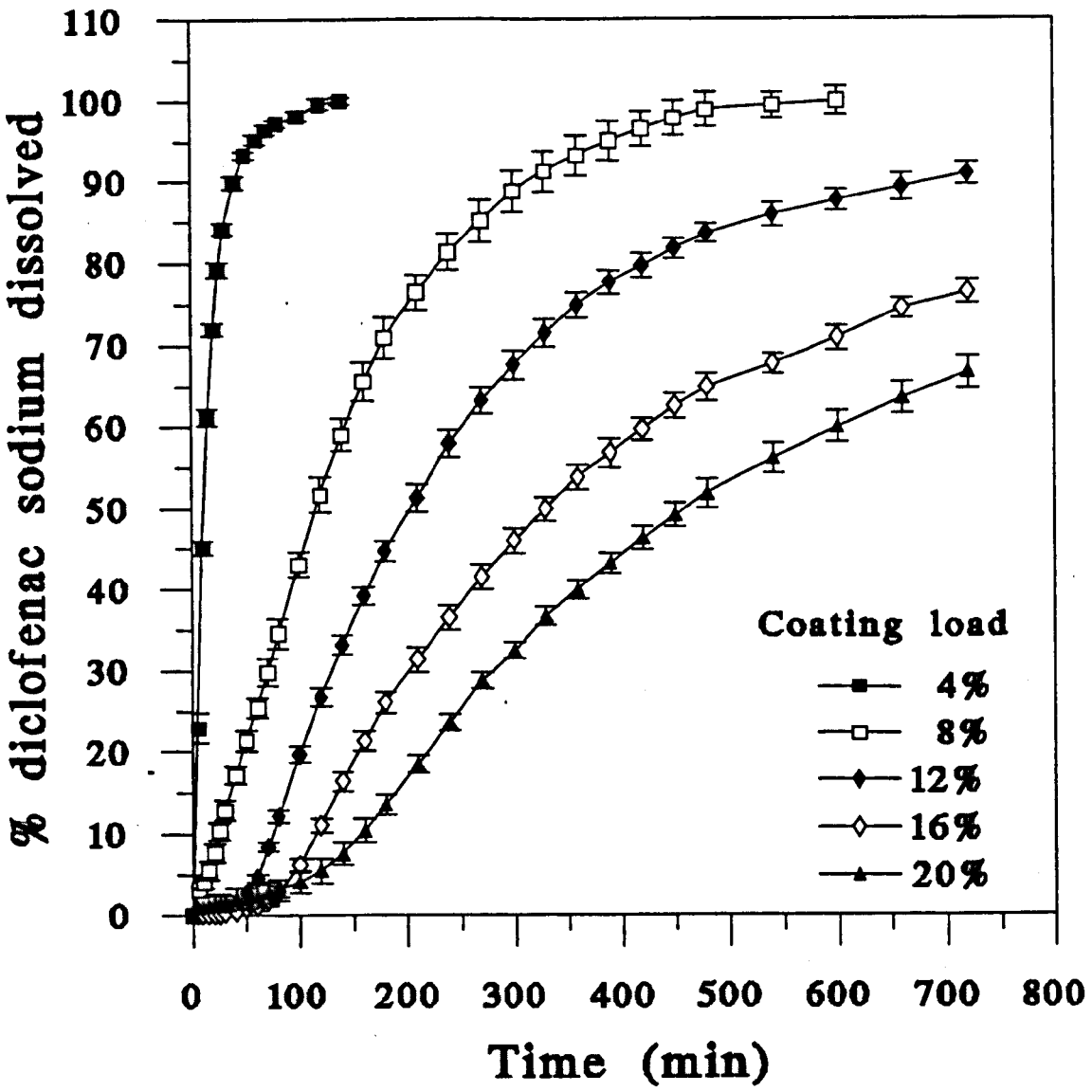


Figure 7.4. Effect of Surelease coating load on the release of diclofenac sodium from pellets which had been seal-coated with 2% w/w HPMC E5.

Table 7.3. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of diclofenac sodium from pellets which had been seal-coated with 2% HPMC E5 and overcoated with Surelease, using equations 1.1-1.4.

Model	*	Percent of coating				
		4%	8%	12%	16%	20%
Zero-order (Equation 1.1)	K_1	3.82 ± 0.26	0.41 ± <0.01	0.27 ± <0.01	0.15 ± <0.01	0.11 ± <0.01
	r	0.995	0.998	0.992	0.989	0.986
	P<	0.1	0.001	0.001	0.001	0.001
	t1	1.3 ± 0.8	1.6 ± 1.8	22.4 ± 2.8	18.3 ± 7.4	22.7 ± 12.4
Square-root (Equation 1.2)	K_2	23.4 ± 1.6	7.3 ± 0.2	6.8 ± 0.1	5.0 ± 0.1	4.3 ± 0.2
	r	0.999	0.994	0.998	0.998	0.996
	P<	0.01	0.001	0.001	0.001	0.001
	t2	1.5 ± 0.3	15.9 ± 0.8	50.1 ± 1.5	70.6 ± 3.9	97.8 ± 6.3
First-order (Equation 1.3)	K_3	0.0683 ± 0.0044	0.0069 ± 0.0002	0.0044 ± <0.0001	0.0025 ± <0.0001	0.0018 ± <0.0001
	r	1	0.999	0.999	0.999	0.998
	P<	0.05	0.001	0.001	0.001	0.001
	t3	1.1 ± 0.6	15.2 ± 1.4	52.7 ± 1.5	64.8 ± 3.7	94.6 ± 9.5
Hixon-Crowell (Equation 1.4)	K_4	0.0868 ± 0.0056	0.0091 ± 0.0004	0.0059 ± 0.0002	0.0034 ± <0.0001	0.0024 ± 0.0001
	r	0.999	0.998	0.998	0.997	0.995
	P<	0.05	0.001	0.001	0.001	0.001
	t4	0.7 ± 0.3	10.3 ± 0.8	42.9 ± 2.1	52.6 ± 4.2	70.4 ± 9.8

* Key: See table 7.1.

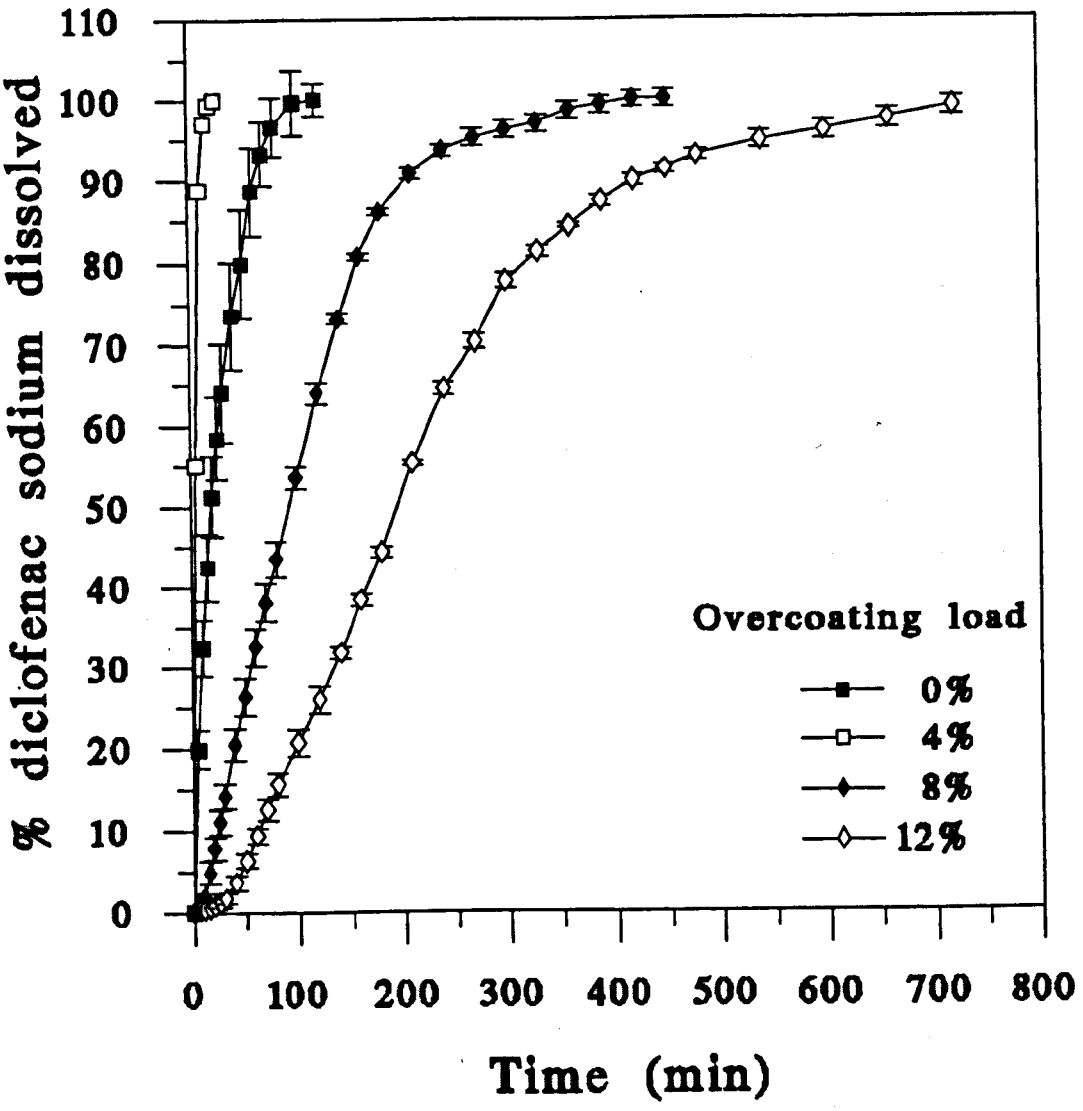


Figure 7.5. Effect of Surelease coating load on the release of diclofenac sodium from pellets already coated with 20% w/w HPMC E15.

Table 7.4. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of diclofenac sodium from pellets already coated with 20% HPMC E15 and overcoated with Surelease using, equations 1.1-1.4.

Model	*	Percent of coating	
		8%	12%
Zero-order (Equation 1.1)	K_1	0.56 ± <0.01	0.29 ± <0.01
	r	0.999	0.997
	P<	0.001	0.001
	t1	3.3 ± 0.9	44.1 ± 5.0
Square-root (Equation 1.2)	K_2	8.8 ± 0.1	7.3 ± 0.1
	r	0.997	0.987
	P<	0.001	0.001
	t2	15.6 ± 1.8	61.5 ± 3.0
First-order (Equation 1.3)	K_3	0.0092 ± 0.0001	0.0051 ± <0.0001
	r	0.995	0.979
	P<	0.001	0.001
	t3	15.7 ± 1.5	70.3 ± 4.1
Hixon-Crowell (Equation 1.4)	K_4	0.0121 ± 0.0002	0.0064 ± <0.0001
	r	0.998	0.987
	P<	0.001	0.001
	t4	11.9 ± 2.9	62.8 ± 3.5

* Key: See table 7.1.

the scanning electron micrographs of the pellets overcoated with 12% Surelease before and after the dissolution test showed development of big pores and cracks following dissolution (Figure 7.6). These pores and cracks were not observed in pellets with overcoat of Surelease on 2% HPMC E5 coated pellets.

7.3.3 RELEASE KINETICS FOR METOCLOPRAMIDE HYDROCHLORIDE RELEASE FROM SEAL-COATED OR UNDERCOATED PELLETS OVERCOATED WITH SURELEASE

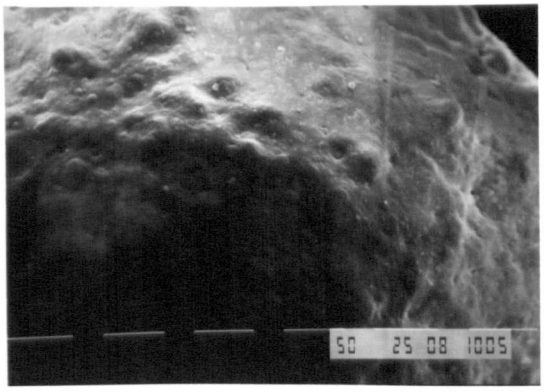
7.3.3.1 Pellets seal-coated with 2% HPMC E5

Correlation coefficients (r) of the fits of release data to the different kinetic models (Table 7.1) showed that the first-order kinetic model was probably the most applicable to all coating loads. Neither the coating load of Surelease nor the presence of a 2% seal-coat changed the kinetic model which produced the best fit compared to those without a seal-coat (Table 5.1). Table 7.5 shows the values of K, n and l obtained from equations 1.6 and 1.7. Again the application of equation 1.7 gave the lower sums of squares and Schwartz information criterion indicating the better fit of data to this model.

To understand the mechanism of drug release the values of n (equation 1.7) were averaged. The mean value of n is 0.60 ± 0.06 and is similar to those pellets coated with Surelease without any seal-coat (Table 5.3). Therefore the application of a 2% seal-coat did not change the mechanism of drug release and diffusion mainly controlled drug release.

7.3.3.2 Pellets undercoated with 20% HPMC E15

Correlation coefficients (r) of the fits of release data to different kinetic model (Table 7.2) showed that, similar to pellets with a 2% seal-coat of HPMC E5 the first-order kinetic model is probably the most applicable model to all the release data.



(a)

(b)

Figure 7.6. Micrographs of diclofenac sodium pellets already coated with 20% HPMC E15 and overcoated with 12% Surelease a) Surface structure of the pellet before the dissolution b) Surface structure of the pellets after 12 h dissolution testing (Magnification × 150).

Table 7.5 The values of K_1, n, based on equation 1.6, K_2, l, n, based on equation 1.7 calculated in the range of 15-60% metoclopramide hydrochloride release from Surelease coated pellets which had been seal-coated with 2% HPMC E5. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	l*	n	ss	Schwartz
8%	0.87	0.88	148.00	49.38	5.74	27.60	0.51	24.70	35.43
12%	0.18	1.00	50.90	43.91	2.07	64.00	0.61	5.12	23.23
16%	0.06	1.10	68.30	64.40	0.89	121.00	0.69	12.00	42.74
20%	0.02	1.20	97.30	64.63	1.33	212.00	0.61	8.53	35.56

* Key: The units of K_1 and K_2 are $\%min^{-n}$ and the unit of l is min.

Table 7.6 shows the values of K, n and l obtained from equations 1.6 and 1.7. Comparison of the values of n (equation 1.7) for these pellets with the corresponding values in Table 7.5 shows that the values of n is slightly higher than those obtained for pellets with a 2% seal-coat of HPMC E5 at equivalent coating loads of Surelease. This suggests that the contribution of diffusion as a rate limiting step was reduced in these pellets. This may be attributed to the ease of diffusion due to the presence of the cracks in the coat. However comparison of the values of n with that obtained for 20% HPMC E15 coated pellets (Table 4.8) shows that release mechanism has changed to erosion. This may be attributed to the presence of Surelease overcoat on top of the HPMC E15 which reduced the rate of erosion of the HPMC undercoat and made the erosion as a rate limiting process.

Table 7.6 The values of K_1, n, based on equation 1.6, K_2, l, n, based on equation 1.7 calculated in the range of 15-60% metoclopramide hydrochloride release from pellets already coated with 20% HPMC E15 and overcoated with Surelease. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	l*	n	ss	Schwartz
8%	0.71	1.03	119.0	47.42	4.24	13.90	0.64	21.00	34.00
12%	0.10	1.29	173.0	50.77	2.01	37.30	0.73	45.40	40.93

* Key: See table 7.5.

7.3.4 RELEASE KINETICS FOR DICLOFENAC SODIUM RELEASE FROM SEAL-COATED OR UNDERCOATED PELLETS OVERCOATED WITH SURELEASE

7.3.4.1 Pellets seal-coated with 2% HPMC E5

Table 7.3 showed that, similar to metoclopramide hydrochloride pellets, the first-order kinetic model was probably the most applicable model to all the release data. Again neither Surelease coating load nor presence of a 2% seal-coat changed the kinetic model which produced the best fit compared to pellets coated with Surelease without seal-coat (Table 5.2).

Table 7.7 shows the values of K, n and l obtained from equations 1.6 and 1.7. Again equation 1.7 gave better fit than equation 1.6 (except for the 8% coating load). The value of n was higher for the 8% coating load, probably because at this coating load more pores exist in the coat (Figure 5.4) which facilitated diffusion of the drug and hence the contribution of diffusion as a rate limiting step was reduced. While lower value of n for coating loads of ≥12 indicates that release mechanism is

predominantly diffusion controlled. The mean value of n (equation 1.7) is 0.69 ± 0.15 which is similar to that obtained for pellets coated with Surelease without a seal-coat (Table 5.4).

Table 7.7 The values of K_1, n, based on equation 1.6, K_2, l, n, based on equation 1.7 calculated in the range of 15-60% diclofenac sodium release from Surelease coated pellets which had been seal-coated with 2% HPMC E5. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1*	n	ss	Schwartz	K_2*	l*	n	ss	Schwartz
8%	0.44	0.99	1.02	4.55	0.54	2.92	0.95	0.86	5.28
12%	0.08	1.20	33.90	32.34	1.76	63.20	0.68	1.19	7.63
16%	0.12	1.03	37.00	43.71	2.29	109.00	0.57	1.11	8.31
20%	0.08	1.03	76.00	61.42	1.92	152.00	0.56	5.39	29.59

* Key: See table 7.5.

7.3.4.2 Pellets undercoated with 20% HPMC E15

Table 7.4 shows that zero-order kinetic model is probably the most applicable model to the release data for diclofenac sodium. While for pellets with 2% HPMC E5 seal-coat, the first-order kinetic model gave the best fit.

Table 7.8 shows that application of equation 1.7 gave the lower sums of squares and Schwartz information criterion. Comparison of the values of n (equation 1.7) with the corresponding values in Table 7.7 shows that the value of n is higher than those obtained for pellets with a 2% HPMC E5 seal-coat at equivalent coating loads of Surelease. The higher value of n for these pellets may be due to development of

pores or cracks which facilitate diffusion of the drug through the coat and eliminate the diffusion as a rate limiting step. However comparison of the values of n with that obtained for 20% HPMC E15 coated pellets (Table 4.9) shows that release mechanism has changed to erosion. This maybe ascribed to the slower erosion of HPMC undercoat in the presence of Surelease.

Table 7.8 The values of K_1, n, based on equation 1.6, K_2, l, n, based on equation 1.7 calculated in the range of 15-60% diclofenac sodium release from pellets already coated with 20% HPMC E15 and overcoated with Surelease. The values of ss and Schwartz information criterion are also given.

Coating load	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	l*	n	ss	Schwartz
8%	0.41	1.06	12.80	30.06	1.18	11.10	0.85	0.39	-2.39
12%	0.04	1.34	5.47	23.49	0.11	15.90	1.18	2.75	18.32

* Key: See table 7.5.

7.4 GENERAL DISCUSSION

The application of a 2% seal-coat of HPMC to drug-layered pellets, decreased the release rate of both drugs from Surelease coated pellets compared to pellets without the seal-coat at an equivalent coating load of Surelease. The retardation of drug release after application of a seal-coat has been reported and ascribed to the reduced drug migration during the application of the sustaining coat (Ghebre-Sellassie et al, 1987; Porter, 1989b; Yang and Ghebre-Sellassie, 1990).

The presence of a 2% HPMC E5 seal-coat did not change the drug release

mechanism for either drug and diffusion appeared to be the most important mechanism controlling drug release from the Surelease coated pellets.

Although diclofenac sodium was released more slowly than metoclopramide hydrochloride from a 2% seal-coated pellets at Surelease coating loads of 4% and 8% (Tables 7.1 and 7.3), at coating loads of ≥12% again diclofenac sodium showed faster release rate than metoclopramide hydrochloride. This indicates that interactions between drugs and coating formulation (such as migration) during film application is not the only factor responsible for the observed differences between these two drugs as again at coating loads of ≥12% Surelease diclofenac sodium was released slightly faster than metoclopramide hydrochloride. These interactions will be discussed in details in chapter 8.

When Surelease was applied on pellets which have already been coated with 20% w/w HPMC E15 both drugs were released faster than those when Surelease applied on pellets with a 2% seal-coat of HPMC E5. The values of n were also higher than those for pellets containing a 2% HPMC E5 seal-coat indicating a change in the release mechanism. The faster release of both drugs was attributed to the development of cracks in the barrier coat due to the swelling of HPMC undercoat. This was resulted in a loss of protective properties of the membrane. The application of a water insoluble polymer on top of a coat of a swelling agent has been used by Ueda et al (1994) to develop a novel controlled drug release system, called the time-controlled explosion system (TES). In this system, expansion of the swelling agent

following water penetration through the insoluble outer membrane caused destruction of the membrane by stress due to swelling. Therefore rapid drug release occurred after a lag time. In these systems lag times can be controlled by the thickness of the outer membrane.

The comparison between metoclopramide hydrochloride and diclofenac sodium release rates from pellets already coated with 20% HPMC and overcoated with Surelease (Table 7.2 and 7.4) showed that metoclopramide hydrochloride released faster than diclofenac sodium. Opposite results were obtained for the pellets with a 2% seal-coat overcoated with 12% Surelease (Tables 7.1 and 7.3). Several factors may contribute to the faster release of metoclopramide hydrochloride from these pellets. The solubility of metoclopramide hydrochloride in water is much higher than diclofenac sodium. As the cracks and pores penetrate the whole thickness of the Surelease coat (Figures 7.3 and 7.6) therefore water solubility could play an important role in drug release.

The faster release of metoclopramide hydrochloride may also be ascribed to the build-up of a higher osmotic pressure in the core due to the higher solubility of this drug. According to Van't Hoff and More equation the osmotic pressure of a solution (π) can be calculated by equation 7.1:

$$\pi = cRT \qquad \textit{Equation 7.1}$$

where c is the concentration of the solute in moles per litter, R is the gas constant

and T is the absolute temperature. Therefore in the saturated solutions of these drugs (as it may be obtained in microenvironment of the pellets), the concentration of the metoclopramide hydrochloride solutions would be higher than diclofenac sodium solutions due to the higher solubility of the former. This results in production of a higher osmotic pressure inside metoclopramide hydrochloride loaded pellets. The higher osmotic pressure generated by highly water soluble metoclopramide hydrochloride might amplify the stresses due to the swelling of HPMC and cause the development of more cracks and pores in a shorter period of time.

The other reason may be due to the effect of drugs on swelling properties of HPMC. Diclofenac sodium reduces the cloud point of HPMC and dehydrate this polymer (Rajabi-Siahboomi et al, 1994a) while hydrochloride salts of organic compound increase the cloud point of HPMC and facilitate hydration of this polymer (Mitchell et al, 1993c). Therefore it may be expected that HPMC can swell to a greater extent in the presence of metoclopramide hydrochloride than in the presence of diclofenac sodium. The higher extent of swelling may create more cracks and therefore increase the release rate of metoclopramide hydrochloride to a higher degree than diclofenac sodium.

7.5 CONCLUSIONS

The application of a 2% w/w seal-coat of water-soluble HPMC E5 decreased release rates of either drug from Surelease coated pellets compared to those pellets coated with Surelease without any seal-coat. However the application of a seal-coat did not

have any effect on the mechanism of drug release. Release of diclofenac sodium was faster than metoclopramide hydrochloride at coating loads of ≥12 of Surelease over a 2% HPMC E5 seal-coated pellets.

When Surelease was applied on pellets with 20% w/w coat of HPMC E15, the release of both drugs was faster compared to those pellets containing a 2% seal-coat of HPMC E5. The faster release of drugs was due to the rupture of the barrier coat. Surelease even at 12% coating load was unable to withstand the stresses caused by the swelling of the HPMC undercoat. Metoclopramide hydrochloride was released faster than diclofenac sodium which may be because of the higher water solubility of thisg drug.

CHAPTER 8. FACTORS AFFECTING THE RELEASE OF DICLOFENAC SODIUM OR METOCLOPRAMIDE HYDROCHLORIDE FROM PELLETS COATED WITH SURELEASE

8.1 INTRODUCTION

The physicochemical property of a drug is one of the factors which has a profound impact on its release from coated pellets. The water solubility is of outmost importance to the formulation of coated pellets when the mechanism of release is mainly by transport of the dissolved drug through water-filled pores or channels within the coating. Water solubility is also a major factor affecting the osmotic pressure inside the coated pellets when the pellets are in contact with dissolution medium. As the difference between the osmotic pressure inside the pellets and the dissolution medium plays an important role in the release of drug from coated pellets (Ghebre-Sellassie et al, 1987; Rekhi et al, 1995), it may be expected that a highly water soluble drug which could generate more osmotic pressure will be released faster than a drug with a lower solubility (Nesbitt et al, 1985).

The results in chapters 5 and 6 revealed that water solubility may not be an important factor in the release of metoclopramide hydrochloride and diclofenac sodium from pellets coated with Surelease. Diclofenac sodium was released faster than metoclopramide hydrochloride from pellets coated with Surelease or Surelease/HPMC despite its lower solubility.

The differences between the rates of diffusion of these two drugs through the membrane could not also account for the observed differences in the release rates of two drugs from pellets coated with Surelease as the difference in the release rates was also observed for pellets coated with Surelease/HPMC (chapter 6). As the molecular weights of drugs are similar (353.3 and 318.13 for metoclopramide hydrochloride and diclofenac sodium, respectively), the molecular size was also not responsible for the slower release of metoclopramide hydrochloride from pellets coated with Surelease.

8.1.1 AIMS AND OBJECTIVES

The intent of the studies in this chapter was to examine the possible factors which may explain the unexpected slower release of metoclopramide hydrochloride compared to diclofenac sodium from pellets coated with Surelease. These factors include:

1- The physico-mechanical properties of the drug-loaded non-pareils such as its size and morphology which could influence the release rate of a drug considerably.

2- The interaction between core ingredients and Surelease.

8.2 MATERIALS AND METHODS

8.2.1 MATERIALS

Non-pareils coated with metoclopramide hydrochloride or diclofenac sodium obtained in section 7.2.2.1, drug-loaded 2% HPMC E5 seal-coated pellets overcoated with 12% Surelease obtained in (section 7.2.2.3), metoclopramide hydrochloride

(section 2.1), diclofenac sodium (section 2.1), ammonia solution (General Purpose Reagent with specific gravity 0.88 g/ml and about 35% NH_3) and oleic acid obtained from British Drug Houses (Poole, Dorset, UK) were used in this study.

8.2.2 METHODS

8.2.2.1 Sieve analysis

The average particle sizes and size distributions of the pellets before and after drug layering were evaluated by mechanical sieving using a series of sieves (Endcotts Ltd., London, U.K.) with aperture size 1 mm, 0.850 mm, 0.710 mm and 0.600 mm as indicated in section 2.2.4.2. The load of the sample was 100 g. The weight of the portion of the sample retained on each sieve after sieving was determined. The method of Parrot (1986) was used to determine the average particle size of the pellets. The size of pellets retained on each sieve was taken as the arithmetic mean of the two sieves (the larger sieve which pellets passed through and the smaller sieve which pellets were retained on). The percentage weight of sample retained on each sieve was multiplied by the arithmetic mean of two sieves and added to the values obtained for the other sieves. Then the value of sums was divided by 100 and used as the average pellet size. Duplicate samples were run for each batch of pellets.

8.2.2.2 Scanning electron microscopy and energy dispersive X-ray microanalysis

The surfaces of drug-layered pellets were examined by scanning electron microscopy (section 2.2.4.3).

The distribution of metoclopramide hydrochloride across a section of coated pellets was examined using a scanning electron microscope (JSM 840, Tokyo, Japan) coupled with an X-ray spectrometer (model Link 860 II, London, U.K.). X-ray microanalysis is a non-destructive technique that allows the detection of elements in situ. In this technique, bombarding the sample with an electron beam results in emission of X-rays which are specific to each element. The emitted X-rays were detected by the X-ray spectrometer. The coated pellets were sliced using razor blade, mounted on stubs and coated with gold prior to scanning as described in section 2.2.4.3. Since metoclopramide hydrochloride has chlorine atoms in its structure, the X-ray characteristics of chlorine were used to trace the distribution of the drug.

8.2.2.3 Preparation of metoclopramide hydrochloride base

Ammoniated water containing 0.5% w/w ammonia (which corresponds to the concentration of ammonia in the diluted Surelease) was prepared by appropriate dilution of 35% w/w ammonia solution. Metoclopramide hydrochloride (2 g) was added to 100 ml water containing 0.5% w/w ammonia and stirred. The precipitate formed following addition of metoclopramide hydrochloride was collected on filter paper (Whatman No.1) and washed with 20 ml water. The precipitate was dried at 50°C for 24 h.

8.2.2.4 Differential scanning calorimetry

DSC was performed as described on section 2.2.8.2.

8.2.2.5 Curing of the pellets

Quantities of 2% seal-coated pellets overcoated with 12% Surelease equivalent to 15 mg of either drug were spread on paper trays and stored at 60°C for 1, 3 or 6 days. Drug release from the cured pellets was studied.

8.2.2.6 Dissolution testing

Dissolution studies were performed as described in section 2.2.6.

8.2.2.7 Release kinetics for coated pellets

The release data between 15-60% were fitted to the different kinetic models (equations 1.1-1.4) as described in section 2.2.7.

8.2.2.8 Dialysis studies

In order to investigate the interaction between the drugs and the surfactant present in Surelease, it was necessary to prepare ammonium oleate. This was accomplished by adding 690 mg of 35% w/w ammonia solution to 4 g of oleic acid precisely weighed using an Oertling analytical balance (West Midland, UK). The blend was mixed thoroughly and left at room temperature for 24 h to nearly dry.

Lengths of 20 cm visking dialysis tubes (size 5, diameter 14/32", cut off 12000-14000 Dalton; Medicell International Ltd., London, U.K.) were boiled in distilled water for 20 minutes. A double knot was tied at one end of each tube.

500 mg of the prepared ammonium oleate was dissolved in 50 ml water. Samples (1 ml) equivalent to 10 mg ammonium oleate, were transferred to 5 ml beakers. Then 15 mg of either metoclopramide hydrochloride or diclofenac sodium accurately weighed was added to the beakers and mixed. Each solution was poured into a dialysis tubes. The respective beakers were washed with the aid of an additional 4 ml of water in two steps (2 × 2 ml) and added to the tubes. A double knot was tied at the top of each dialysis tubes so that the length between the two ties was 6 cm. A reference dialysis tube was prepared containing 15 mg of either metoclopramide hydrochloride or diclofenac sodium in 1 ml of water instead of 1 ml ammonium oleate solution and prepared exactly as above (5 ml total volume). The tubes were immersed into the dissolution vessels of the Pharmatest dissolution tester (section 2.2.6) containing 900 ml distilled water at 37°C and stirred with a paddle (USP apparatus II) at 50 rpm. The media were automatically sampled at 30 min intervals using an Ismatic peristaltic pump (section 2.2.6). Drug passage from the tubes was determined spectrophotometrically using a Hewlett Packard spectrophotometer (section 2.2.6) at 309 nm and 275 nm for metoclopramide hydrochloride and diclofenac sodium respectively. The mean of three determinations is reported for each system.

In another series of experiments, the above procedure was repeated using Surelease instead of the ammonium oleate solution. Quantities of Surelease (about 460 mg) equivalent to 10 mg ammonium oleate were added to the beakers and the procedure was carried out as above.

8.3 RESULTS AND DISCUSSION

8.3.1 PHYSICO-MECHANICAL PROPERTIES OF DRUG-LOADED NON-PAREIL SEEDS

8.3.1.1 Size and size distribution of the drug-loaded non-pareil seeds

The surface areas of the pellets, which are a function of the pellet size, size distribution and shape (Bertelsen et al, 1994) considerably influence the release rate of a drug. The average sizes of the pellets before and after drug layering are shown in Table 8.1. Although the results indicated that the drug layering process may have increased the average pellet particle size, the Student's t test showed no significant differences ($P< 0.05$) between the size of the pellets before and after drug layering (for both drugs). Student's t test also showed that there was no significant differences between the size of pellets coated with metoclopramide hydrochloride or those coated with diclofenac sodium ($P< 0.05$). Therefore, the differences between release rates of two drugs can not attributed to differences in the sizes of the pellets.

Table 8.1. The average particle size of non-pariels before layering and after layering with metoclopramide hydrochloride or diclofenac sodium.

Sample	Average particle size (μm)
Non-pareil seeds	783 ± 4
Metoclopramide hydrochloride-layered pellets	806 ± 15
Diclofenac sodium-layered pellets	800 ± 10

The effects of particle size on drug release have been previously demonstrated. Porter (1989a) showed that chlorpheniramine maleate release from pellets coated with 10% Surelease was faster from beads of smaller size (30-35 mesh) than from

those of larger size (14-18 mesh). This effect was attributed to the higher surface area of the smaller pellets. Similar results were reported by Li et al (1989a) for the release of indomethacin from non-pareil seeds.

The size distribution of pellets should also be as narrow as possible in order to limit variation in the coating thickness due to variation in the surface area of pellets which must be covered during coating (Mehta, 1989). The size distributions of the drug-layered pellets are shown in Figure 8.1. This indicates that although the percent of larger particles was higher for metoclopramide hydrochloride-layered pellets, overall the pellets remained approximately in the same size range as before layering.

8.3.1.2 Morphology of surfaces of the drug-loaded non-pareil seeds

Scanning electron micrographs of pellets layered with metoclopramide hydrochloride or diclofenac sodium are shown in Figure 8.2. There were only small differences in terms of roughness between the surface characteristics of pellets.

As the surface characteristics of pellets affect the surface area that must be covered by coating fluids, the surface morphology of pellets can therefore dramatically influence the release of a drug (Zhang et al, 1991b). When an equivalent amount of coating was applied to drug-layered non-pareils, smoother pellets produced lower release rates than those pellets with rough surfaces (Mehta, 1989; Porter, 1989a). This effect was due to the fact that pellets with rougher surfaces had a greater surface area for covering by the coating formulation.

The small differences observed between the surface characteristics of the drug-layered pellets do not explain the differences in release rates of the two drugs from Surelease-coated pellets.

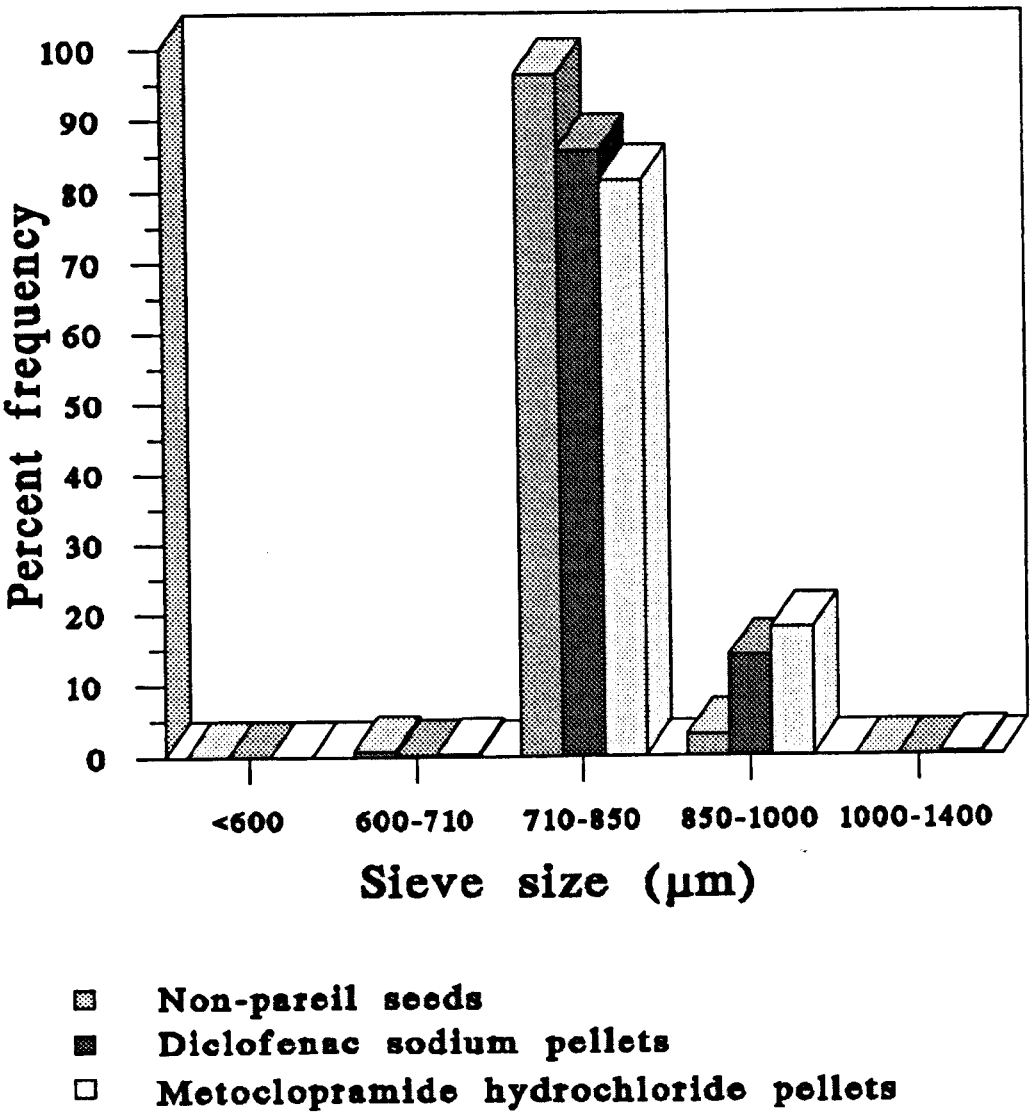
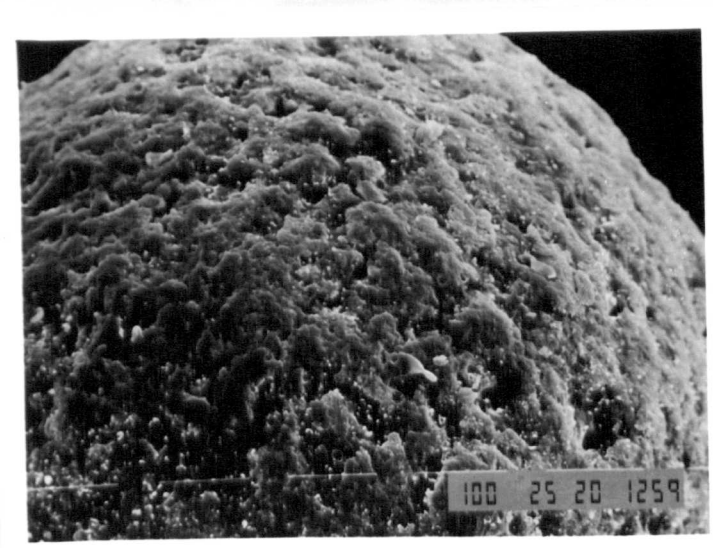
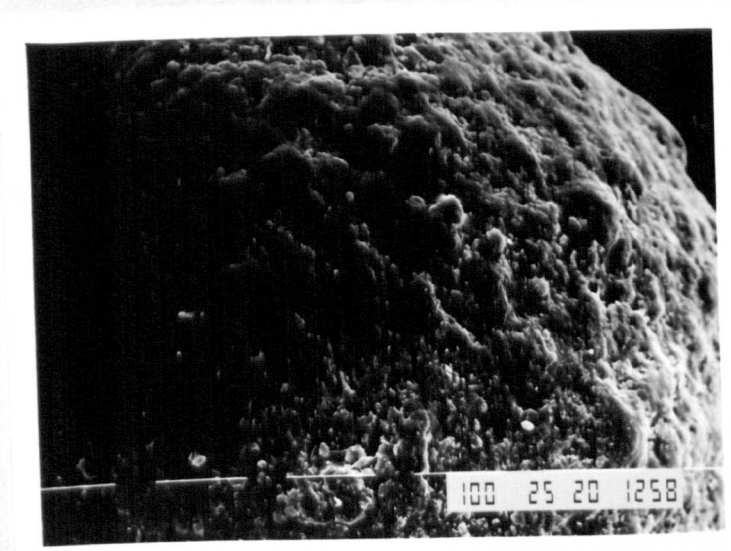


Figure 8.1. The size distribution of the pellets before layering and after layering with metoclopramide hydrochloride or diclofenac sodium.



(a)



(b)

Figure 8.2. Micrographs of pellets layered with (a) Metoclopramide hydrochloride and (b) Diclofenac sodium (Magnification × 150).

8.3.2 INTERACTION BETWEEN CORE INGREDIENTS AND SURELEASE

8.3.2.1 Interaction between core ingredients and Surelease during film application

The existence of an interaction between either drug and the Surelease during film application was assessed by applying a 2% w/w seal-coat of HPMC E5 onto drug-layered pellets before the application of Surelease (chapter 7). The application of a 2% seal-coat of HPMC E5 before Surelease decreased the release of both drugs from Surelease-coated pellets (Tables 7.1 and 7.3) compared to those coated with Surelease without a seal-coat (Tables 5.1 and 5.2). This decrease was more pronounced for diclofenac sodium than metoclopramide hydrochloride at low coating loads. For example application of a 2% HPMC E5 seal-coat prior to Surelease coat reduced the amount of diclofenac sodium released after 5 min from 75% (for those pellets coated with 4% Surelease without seal-coat) to 20% at 4% Surelease coat. The corresponding values for metoclopramide hydrochloride were 33% and 21%.

As mentioned in section 7.1, any interaction between a core and a coating formulation during the application of the film might substantially affect the release rates. It is well known that aqueous polymeric dispersions coagulate upon addition of ionic solutions (Lippold et al, 1990; Porter and Ghebre-Sellassie, 1994). Bodmeier and Paeratakul (1989) reported that the addition of salts of basic drugs to ethylcellulose pseudolatexes resulted in latex flocculation or coagulation due to interaction of the cationic drug with anionic surfactants contained in the pseudolatex. The type and concentration of the ions determine the extent of coagulation. Nesbitt

et al (1994) reported the interaction between cores containing different drugs during application of Aquacoat. This accounted for the formation of a discontinuous membrane around the core.

Interactions between the active substrate and the aqueous polymeric dispersion during the application of the coat may cause deposition of a non-uniform film in the early stages of the film coating process and therefore more layers of coating should be applied to obtain the desired release profiles (Porter and Ghebre-Sellassie, 1994). Sodium salts of active substance are reported to be more likely to interact with aqueous polymeric dispersions than chloride ions (Porter and Ghebre-Sellassie, 1994).

The problem of interaction may be prevented by the application of a seal-coat prior to application of the retarding membrane. On the other hand, the active substance may be soluble in the coating fluid and migrate into the coat layers during application of the film. The degree of migration of the active substance during the application of the sustaining coat has a significant role in the performance of the coating materials (Ghebre-Sellassie et al, 1987). A porous structure may, as a consequence, be formed during dissolution. The use of a seal-coat is also effective in preventing the migration of drugs during the application of the sustaining coat for those drugs which are soluble in the coating fluid (Ghebre-Sellassie et al, 1987; Porter, 1989a).

Since metoclopramide hydrochloride is a highly water soluble drug, its migration through the film during the coating process might be anticipated. However when a small amount of metoclopramide hydrochloride was added to ammoniated water containing about 0.5% w/w ammonia a white precipitate was formed. Figure 8.3 shows a typical DSC scan of this precipitate. Two peaks were observed at 127°C and 148°C. These peaks correspond to those observed for metoclopramide base (Mitchell, 1985). The first peak corresponds to a solid-solid transition while the second peak corresponds to the melting point of metoclopramide base (Mitchell, 1985). Therefore, it may be concluded that migration of metoclopramide hydrochloride into the Surelease coat during film application is negligible due to the low solubility of this drug at high pH. Therefore the decrease in release rate of the drug after seal-coat application may be attributed mostly to the covering the irregularities and smoothing the surface of the drug-layered pellets after application of a seal-coat.

Diclofenac sodium is the sodium salt of an acidic substance with a pK_a of 4 (Adeyeye and Li, 1990). According to the Henderson-Hasselbalch relationship for a weak acid (equation 8.1) at pH 9.5-11.5, which corresponds to the pH of the Surelease dispersion (Moore, 1989), 99.99% of the drug would be in its ionized form. Therefore this drug may potentially interact with the Surelease during deposition of the film.

$$\% \ Ionized = \frac{100}{1 + antilog\ (pK_a - pH)} \qquad Equation\ 8.1$$

As diclofenac sodium is freely soluble at pH > 6 (Navarro and Ballesteros, 1994),

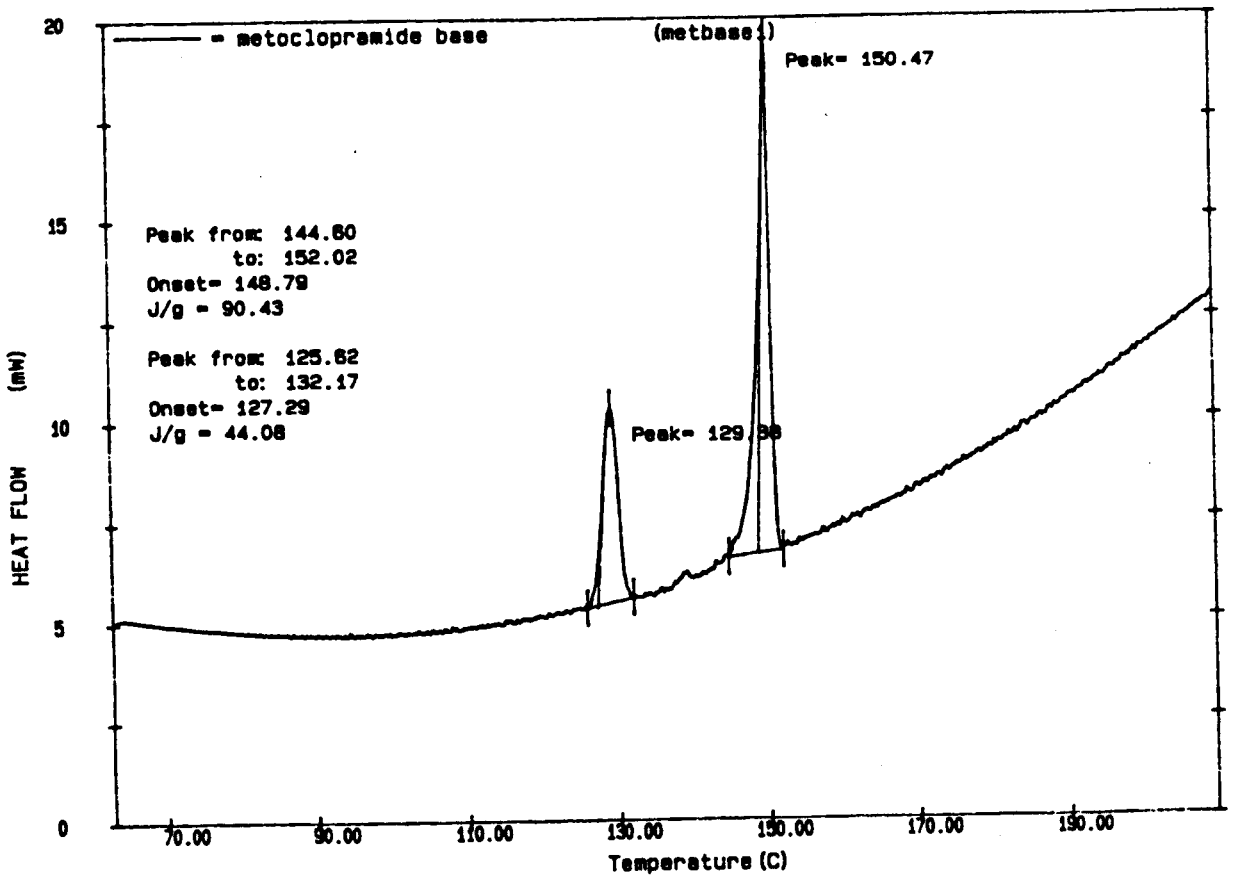


Figure 8.3. DSC scan of precipitate formed upon addition of metoclopramide hydrochloride to 0.5% w/w ammonia solution.

it is also more likely to migrate to the applied coat than metoclopramide hydrochloride. These facts suggests that the extent of interaction between diclofenac sodium and Surelease or migration of this drug into the Surelease during application of film may be more than metoclopramide hydrochloride. Here a seal-coat not only imparts smoothness to the surface of the drug-layered pellets but also prevents migration of diclofenac sodium into the Surelease film. This should decrease the drug release to a greater extent than metoclopramide hydrochloride.

Although diclofenac sodium release was slower from pellets coated with 4% or 8% Surelease on 2% HPMC E5 seal-coated pellets, at a coating load of ≥12% again diclofenac sodium showed faster release than metoclopramide hydrochloride. These findings indicate that migration of diclofenac sodium into Surelease during the application of the coat has been an effective factor causing faster release of diclofenac sodium specially at low coating loads. However the difference between the release rates of these two drugs was also observed for 2% seal-coated pellets at coating loads of ≥12.

8.3.2.1.1 The effect of curing on the release of drug

The effect of curing on the release of metoclopramide hydrochloride from 2% seal-coated pellets overcoated with 12% Surelease (as an intermediate coating load) is shown in Figure 8.4. Table 8.2 lists the release rates for these pellets using different kinetic models. The release rates increased as the curing time increased. Release rates were also faster for the cured pellets than for the uncured pellets (Table 7.1).

Similar to uncured pellets, the best statistical fit was obtained when using the first-order kinetic model.

The release of diclofenac sodium from 2% HPMC E5 seal-coated pellets overcoated with 12% Surelease were almost the same before and after curing (Figure 8.5) suggesting that complete film coalescence had taken place during film application (Porter, 1989a; Dyer et al, 1995). Table 8.3 lists the release rates for these pellets using different kinetic models. No special trend was observed between release rates and curing times. The release rates of diclofenac sodium from cured pellets resembled those observed for uncured pellets (Table 7.3). The best statistical fit was with the Hixon-Crowell model.

It has been reported that pseudolatexes undergo a process of further gradual coalescence after initial film formation, to form a homogeneous continuous film (Miller and Vadas, 1984; Onion, 1986b). Further gradual coalescence is both temperature and time dependent (Murthy and Ghebre-Sellassie, 1993).

Coated dosage forms are generally subjected to elevated temperatures for a specified period of time to accelerate the curing process. As stated above, the release of metoclopramide hydrochloride increased after curing while that of diclofenac sodium was nearly unchanged. These results contradict those published by Ghebre-Sellassie et al (1988). They showed that storage of pellets at 60°C led to a significant reduction in release rates of drugs (diphenhydramine hydrochloride and

pseudoephedrine hydrochloride) from pellets coated with mixtures of Surelease and HPMC. Similar reduction in the release rates after curing had been reported by Goodhart et al (1984) for release of phenylpropanolamine hydrochloride from Aquacoat coated pellets. Their results suggested that a curing step after coating is necessary to prevent changes in the release characteristics of the final products on storage.

However Porter (1989a) showed that this step may not always be necessary. Complete coalescence of a latex or pseudolatex coating is dependent on heat and capillary forces created as a result of water evaporation during film deposition. These are affected by the process conditions. Therefore use of optimized process conditions eliminates the post-coating curing step (Porter, 1989a). Similar results were reported by Chang and Hsiao (1989) for the release of theophylline from pellets coated with Eudragit RS and by Dyer et al (1995) for the release of ibuprofen from Surelease-coated pellets indicating that gradual coalescence was completed within the coating time.

On the other hand the increase in the release of metoclopramide hydrochloride after curing was in agreement with results of Porter and Ghebre-Sellassie (1994). An increase in release of chlorpheniramine maleate from pellets coated with Aquacoat was reported by these authors and attributed to the migration of the water soluble drug through the coat during drying.

Table 8.2. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from 2% seal-coated pellets overcoated with 12% Surelease and cured at 60°C for 1, 3 and 6 days, using equations 1.1-1.4.

Model	*	1 day	3 days	6 days
Zero-order (Equation 1.1)	K_1	0.38 ± 0.01	0.48 ± 0.01	0.66 ± 0.01
	r	0.965	0.956	0.943
	P<	0.001	0.001	0.001
	t1	-3.3 ± 2.5	-3.3 ± 1.7	-14.5 ± 6.4
Square-root (Equation 1.2)	K_2	7.9 ± 0.2	8.8 ± 0.2	9.5 ± 0.3
	r	0.982	0.981	0.973
	P<	0.001	0.001	0.001
	t2	23.6 ± 1.2	16.5 ± 0.8	6.5 ± 2.1
First-order (Equation 1.3)	K_3	0.0067 ± 0.0002	0.0083 ± 0.0002	0.0113 ± 0.0002
	r	0.990	0.986	0.975
	P<	0.001	0.001	0.001
	t3	19.8 ± 1.8	11.9 ± 1.0	0.1 ± 3.3
Hixon-Crowell (Equation 1.4)	K_4	0.0086 ± 0.0003	0.0107 ± 0.0003	0.0146 ± 0.0001
	r	0.983	0.978	0.966
	P<	0.001	0.001	0.001
	t4	12.9 ± 1.9	7.1 ± 1.4	-2.5 ± 5.6

* Key: The units of release constants are: K_1 ($\%min^{-1}$), K_2 ($\%min^{-1/2}$), K_3 (min^{-1}), K_4 ($\%^{1/3}min^{-1}$) and the units of the lag times corresponding to different equations (1.1-1.4) t1, t2, t3 and t4 are min. P is the degree of significance.

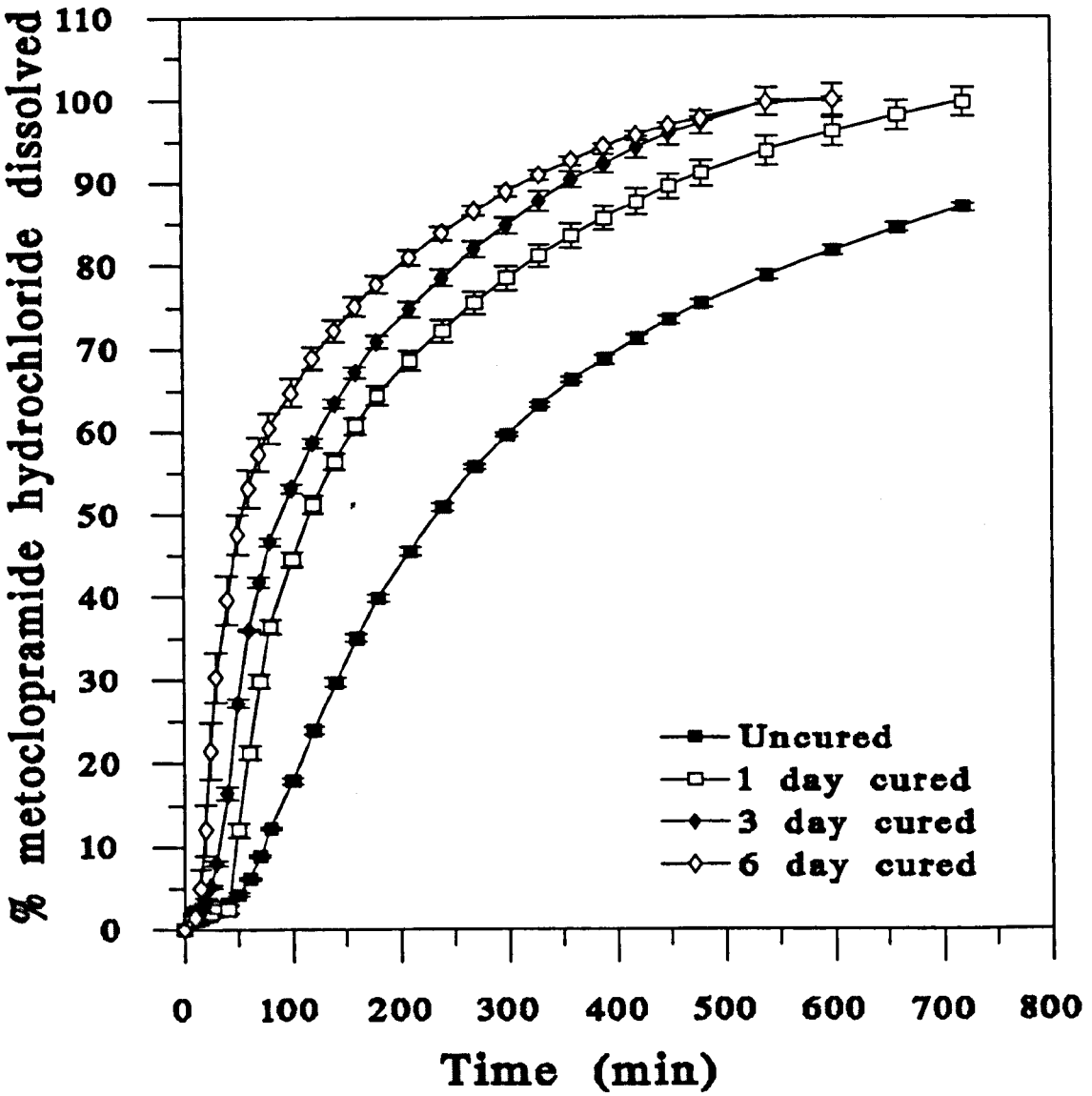


Figure 8.4. The effect of curing time on the release of metoclopramide hydrochloride from pellets coated with 12% Surelease over a seal-coat of 2% HPMC E5.

Table 8.3. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of diclofenac sodium from 2% seal-coated pellets overcoated with 12% Surelease and cured at 60°C for 1, 3 and 6 days, using equations 1.1-1.4.

Model	*	1 day	3 days	6 days
Zero-order (Equation 1.1)	K_1	0.25 ± 0.01	0.26 ± <0.01	0.23 ± <0.01
	r	0.997	0.998	0.997
	P<	0.001	0.001	0.001
	t1	8.7 ± 4.0	10.4 ± 2.5	10.4 ± 3.9
Square-root (Equation 1.2)	K_2	5.9 ± 0.1	6.1 ± <0.1	5.6 ± 0.1
	r	0.997	0.995	0.995
	P<	0.001	0.001	0.001
	t2	43.2 ± 2.1	34.9 ± 1.4	36.6 ± 1.9
First-order (Equation 1.3)	K_3	0.0041 ± 0.0002	0.0044 ± 0.0001	0.0039 ± 0.0001
	r	0.997	0.996	0.996
	P<	0.001	0.001	0.001
	t3	33.1 ± 3.3	35.3 ± 2.4	34.8 ± 3.2
Hixon-Crowell (Equation 1.4)	K_4	0.0054 ± 0.0002	0.0056 ± <0.0001	0.0049 ± 0.0001
	r	0.999	0.998	0.998
	P<	0.001	0.001	0.001
	t4	26.4 ± 2.7	27.8 ± 2.2	27.9 ± 2.4

* Key: See table 8.2.

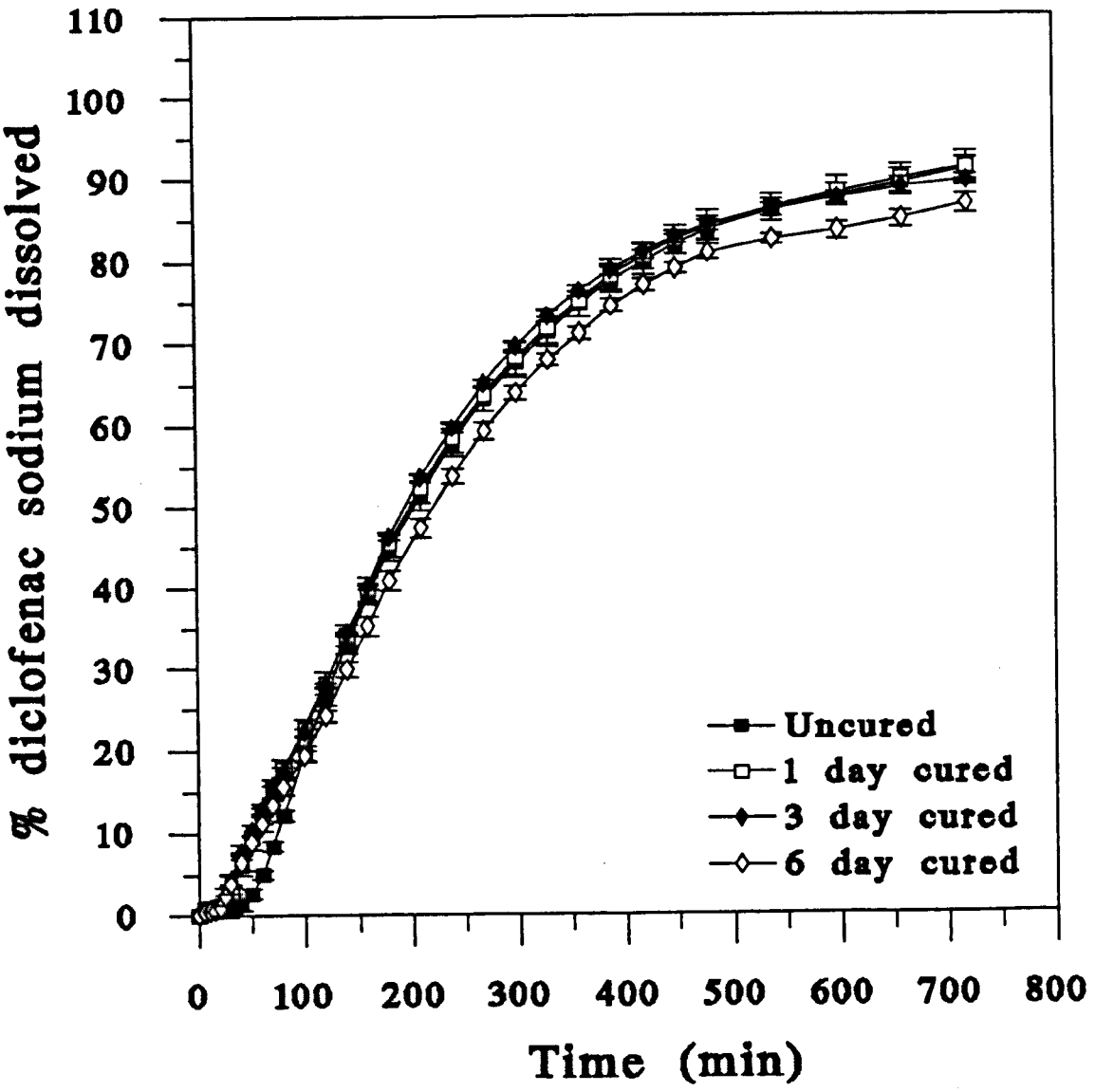


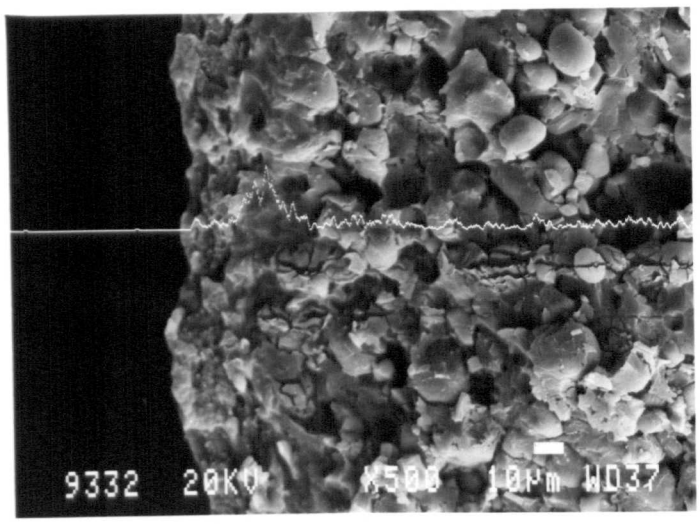
Figure 8.5. The effect of curing time on the release of diclofenac sodium from pellets coated with 12% Surelease over a seal-coat of 2% HPMC E5.

The migration of metoclopramide hydrochloride during storage at elevated temperature was investigated using X-ray microanalysis for 2% seal-coated pellets overcoated with 12% Surelease. The white line which is the scan of chlorine (Figure 8.6) across the sample shows a maximum just beneath the coat. No chlorine was traced in the thickness of the coat (Figure 8.6). Indeed the distinct boundary between the coat and drug layer confirmed that no migration had occurred during storage at elevated temperature. Therefore the increase in release rate of metoclopramide hydrochloride from Surelease coated pellets after curing was not related to the migration of the drug into the coat.

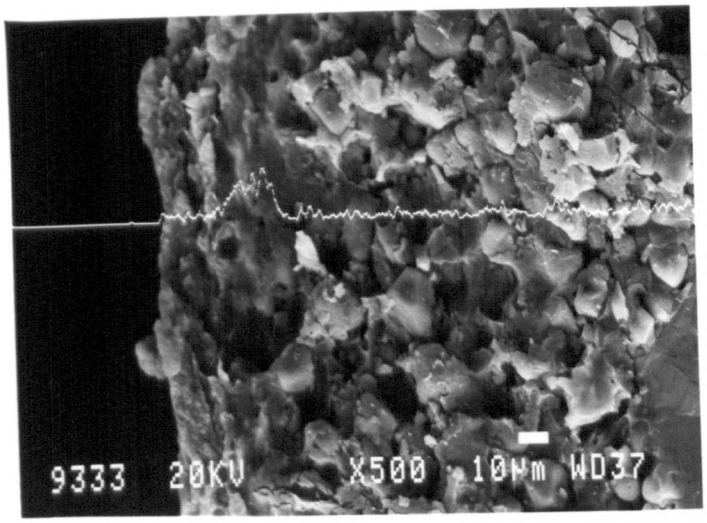
8.3.2.2 Interaction between core ingredients and surelease during dissolution

8.3.2.2.1 Dialysis studies

Another possible interaction which may describe the slower release of metoclopramide hydrochloride is related to the interaction between the cationic metoclopramide hydrochloride and the anionic ammonium oleate, present in the Surelease. The potential for interaction between either drug and anionic surfactant (ammonium oleate) was investigated by dialysis studies (section 8.2.2.8). When metoclopramide hydrochloride was added to the ammonium oleate solution, a precipitate was formed while the solution containing diclofenac sodium was clear. Figure 8.7 shows that, the passage of metoclopramide hydrochloride from a solution containing ammonium oleate through the dialysis bag was much slower than that of metoclopramide hydrochloride from water. This retardation was due to the formation of the precipitate. However, the passage of diclofenac sodium from the solution



(a)



(b)

Figure 8.6. Metoclopramide hydrochloride distribution across Surelease coated pellets a) before and b) after curing (Magnification × 500).

containing ammonium oleate was very little different to that from water.

When metoclopramide hydrochloride was added to the beakers containing Surelease, a precipitate could not be seen because Surelease is a milky liquid. Figure 8.8 shows the dramatic reduction which was observed for the passage of metoclopramide hydrochloride from tubes containing Surelease compared to tubes containing water. This retardation may be ascribed, not only to the interaction between metoclopramide hydrochloride and ammonium oleate, but also to the precipitation of metoclopramide hydrochloride as a base at high pH of Surelease (section 8.3.2.1). Again passage of diclofenac sodium from tubes containing Surelease was similar to those containing water.

In general, surfactants are added to the aqueous dispersions of polymers in order to decrease the interfacial tension between the organic polymer solution and the aqueous phase during preparation of the pseudolatex. They prevent agglomeration and coalescence of the dispersed polymer particles during storage (Bodmeier and Paeratakul, 1991). Surelease contains oleic acid as stabiliser in ammoniated water. Therefore the formation of ammonium oleate acting as an anionic surfactant is predicted. Surfactants will also remain in the coating after formation of the film.

The retardation effect of ionic surfactants (such as sodium dodecyl sulphate) on the release of drugs (chlorpheniramine maleate and propranolol hydrochloride) from matrices has been documented (Feely and Davis, 1988a; Ford et al, 1991b).

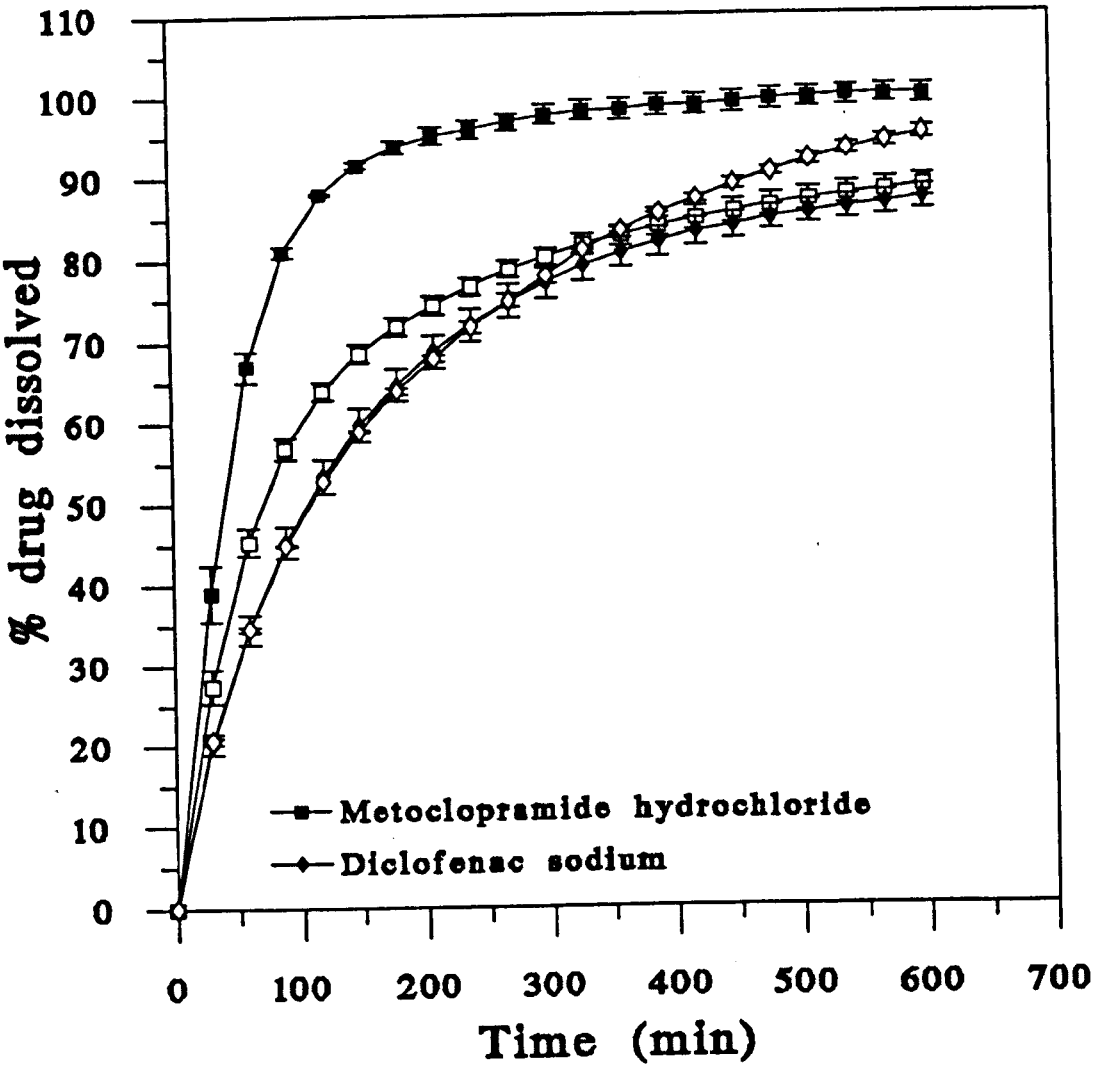


Figure 8.7. Passage of metoclopramide hydrochloride or diclofenac sodium from dialysis tubes. Closed symbols in the presence of water. Open symbols in the presence of ammonium oleate solution.

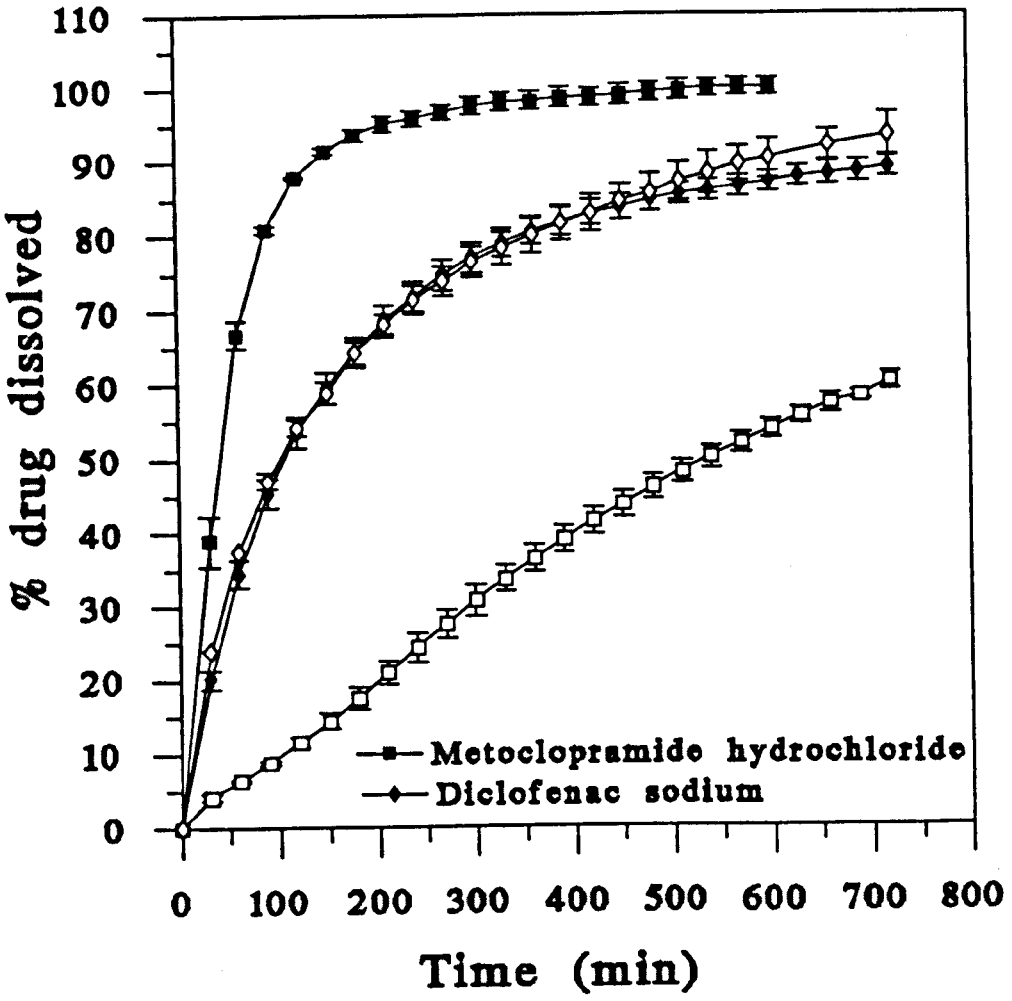


Figure 8.8. Passage of metoclopramide hydrochloride or diclofenac sodium from dialysis tube. Closed symbols in the presence of water. Open symbols in the presence of Surelease.

It has been claimed that ammonia is evaporated during the coating process (Bodmeier and Paeratakul, 1991) leaving ammonium oleate as oleic acid. However it is possible that some of anionic surfactant remains in the coat after formation of the film and interacts with the drug.

Therefore, the slower release of metoclopramide hydrochloride from Surelease coated pellets may be due to the in situ formation of a poorly soluble complex of the drug and surfactant. This complex, because of its lower solubility than metoclopramide hydrochloride or its large molecular size, may diffuse more slowly through the film and hence cause a reduction in the release rate of metoclopramide hydrochloride from Surelease coated pellets.

8.4 GENERAL DISCUSSION

In order to understand the mechanism of slower release of metoclopramide hydrochloride than diclofenac sodium from pellets coated with Surelease (chapter 5) several factors were investigated. Application of either drug on the non-pareil seeds produced drug-layered pellets with similar size and surface morphology which could not account for the observed differences in the release of these drugs from Surelease-coated pellets.

It was thought that due to the higher solubility and also complete ionization of diclofenac sodium at high pH of Surelease, the extent of interaction between diclofenac sodium and Surelease and/or migration of this drug into the coat was

greater than those might happen with metoclopramide hydrochloride. Interaction between either drug with Surelease during its application was studied by applying a 2% seal-coat of HPMC E5 before Surelease. As coat of water soluble polymer prevents direct contact of the drug with Surelease therefore it reduces the extent of migration of drug and/or flocculation of the Surelease if these interactions are responsible for different release behaviour of these drugs. However after 2% seal-coat application the release of diclofenac sodium was slower than metoclopramide hydrochloride only at 4% and 8% Surelease coating load but at higher coating loads metoclopramide hydrochloride was released more slowly than diclofenac sodium.

Changes in the release rates after curing was more pronounced for metoclopramide hydrochloride than diclofenac sodium. In addition the release of diclofenac sodium was slower than metoclopramide hydrochloride after curing. These results suggested that other interactions might exist between drugs and Surelease. In vitro experiments showed that metoclopramide hydrochloride precipitated in the presence of surfactant (ammonium oleate).

Therefore interaction between the cationic metoclopramide hydrochloride and anionic ammonium oleate is the most probable reason for the observed differences in the release of metoclopramide hydrochloride and diclofenac sodium. The amount of surfactant at low coating loads of Surelease (4% and 8%) over a 2% seal-coat of HPMC E5 might not be enough to slow down the release of metoclopramide hydrochloride. However at higher coating loads which corresponded to the higher

concentration of surfactant in the coat the extent of interaction between metoclopramide hydrochloride and ammonium oleate might increase. This interaction could also describe the release characteristics of the drugs after the curing process. During curing, ammonia was evaporated from the pellets. The release of ammonia may be due to dissociation of the ammonium oleate to oleic acid and ammonia when heated. This could explain the marked increase in the release rate of metoclopramide following curing. The interaction between cationic drug and anionic surfactant was minimized by reduced concentration of anionic surfactant after curing and hence increase in release rate would be expected.

As indicated by Ford et al (1991b) presence of HPMC facilitated the precipitation of the complex formed between drug and surfactant. A similar explanation may also be used to explain the differences observed between release of diclofenac sodium and metoclopramide hydrochloride from pellets coated with mixtures of Surelease and HPMC (chapter 6). Addition of 5% HPMC in Surelease (section 6.3.1 and 6.3.2) markedly increased release rate of diclofenac sodium while this amount of HPMC had lower effect on the release of metoclopramide hydrochloride from Surelease coated pellets.

8.5 CONCLUSIONS

From the results of particle size analysis it can be concluded that the mean particle size and distribution could be eliminated as factors contributing to the observed differences in the release behaviour of metoclopramide hydrochloride and diclofenac

sodium from Surelease coated pellets. The drug polymer interaction during film application was found to have a little effect in this regard. However the interaction between cationic drug and surfactant (ammonium oleate) in the coat in situ is the most possible cause of difference in release rate of the drug.

CHAPTER 9. DRUG RELEASE FROM HYDROXYPROPYLMETHYLCELLULOSE MATRICES

9.1 INTRODUCTION

Hydroxypropylmethylcellulose is the water soluble polymer most commonly used in the formulation of sustained release hydrophilic matrices. Rapid formation of the gel layer around the matrix is the basis for the performance of these matrices (Alderman, 1984). The drug is released by a combination of diffusion through and erosion of the gel layer. The release kinetics are dependent upon the relative magnitude of the rate of polymer swelling at the moving rubbery/glassy front and the rate of polymer erosion at the swollen polymer/dissolution medium front (Kim, 1995). Synchronization of these phenomena is necessary in order to obtain zero-order release kinetics (Colombo et al, 1996). With HPMC matrices, synchronization of front movement is difficult to achieve, therefore the kinetics of drug release depend on the relative movement of the erosion and swelling fronts. Drug release patterns from HPMC matrices generally fit a square-root of time kinetic model (Ford et al, 1985a; 1985b; 1987).

Factors influencing the in vitro drug release from HPMC matrices have been the focus of a many studies. The effect of polymer:drug ratio (Ford et al, 1985a; 1985 b), presence of lubricant (Ford et al, 1985a), presence of surfactants (Daly et al, 1984; Ford et al, 1991b), effect of drug particle size (Ford et al, 1985c; Bodea et al, 1995), effect of drug molecular weight (Baveja et al, 1988), effect of tablet shape

(Ford et al, 1987), compaction force (Ford et al, 1987; Bodea et al, 1995), polymer particle size (Alderman, 1984; Mitchell et al, 1993d), particle shape (Bonferoni et al, 1995), polymer moisture content (Mosquera et al, 1996) and polymer viscosity grade (Salomon et al, 1979; Daly et al, 1984; Ford et al, 1985a) have been studied extensively. However there are conflicting reports about the effect of polymer viscosity on the release rate of the drug.

9.1.1 AIMS AND OBJECTIVES

The performance of HPMC of low viscosity grade as a rate retarding membrane on pellets was evaluated in earlier chapters. It was observed that the application of HPMC of low viscosity to coated pellets was not successful in retarding the release rates of metoclopramide hydrochloride or diclofenac sodium. On the other hand it is impossible to easily use a high viscosity grade of HPMC for coating due to the long processing time required (Gazzaniga et al, 1995).

The main objectives of this chapter were to examine how the HPMC of low and high viscosity grade affected the dissolution rates and release mechanisms of metoclopramide hydrochloride and diclofenac sodium from matrices. In addition, the effect of substitution type of HPMC on the release of these two drugs was also investigated.

9.2 MATERIALS AND METHODS

9.2.1 MATERIALS

Metoclopramide hydrochloride, diclofenac sodium, HPMC K4M, HPMC K100, HPMC E4M, HPMC E15 and magnesium stearate, as described in section 2.1, were used.

9.2.2 METHODS

9.2.2.1 Preparation of tablets

Tablets containing 15 mg metoclopramide hydrochloride or diclofenac sodium, and 45, 60, 75 or 150 mg of HPMC K4M, HPMC K100, HPMC E4M or HPMC E15 were prepared as described in section 2.2.5. The tablet weights were 60, 75, 90 or 165 mg based on the polymer content.

9.2.2.2 Dissolution testing

Dissolution studies were performed as described in section 2.2.6.

9.2.2.3 Release kinetics for matrices

Release data between 15-60% of drug release were fitted to different kinetic models as described in section 2.2.7.

9.3 RESULTS AND DISCUSSION

9.3.1 Release of metoclopramide hydrochloride from HPMC matrices

The release profiles of metoclopramide hydrochloride from tablets containing

different amounts of HPMC E15, HPMC E4M, HPMC K100 and HPMC K4M are shown in Figures 9.1-9.4 respectively. All the dissolution data were plotted as a percentage of drug released against square-root of time. An increase in HPMC content resulted in a decrease in the percent of drug release at each time interval for all grades of HPMC used. These results are in agreement with those published by Ford et al (1985b) and Mitchell et al (1993b) who stated that the major factor controlling the release of drug from matrices is the drug/polymer ratio. A higher amount of HPMC in the matrix absorbed more water and caused a greater of swelling (Wan et al, 1993). This in turn increased the diffusional path length and decreased the rate at which drug was released. Skoug et al (1993) considered that an increase in polymer concentration caused an increase in the viscosity of the gel layer. This caused a decrease in the effective diffusion coefficient of drug. However Mitchell et al (1993b) claimed that decrease in the apparent diffusion coefficient of drug through the gel was due to the formation of a more concentrated gel and increased gel tortuosity at higher amounts of HPMC.

Tables 9.1-9.4 represent the release rates which were calculated from regression analysis of release data using different kinetic models. As the polymer content in the matrix increased the release rates decreased for each type of matrix. The lag times predicted by the models generally showed negative values, except for those predicted from square-root kinetics. The release rates were faster for matrices containing HPMC E15 than HPMC E4M at equivalent polymer content. Similar results were obtained by Daly et al (1984) for the release of the water soluble, chlorpheniramine

maleate from HPMC E15 and HPMC E4M matrices. Metoclopramide hydrochloride was also released faster from matrices containing HPMC K100 than from matrices containing HPMC K4M. These results are in agreement with those published by Ford et al (1985a) who showed that promethazine hydrochloride was released faster from HPMC K100 matrices than from HPMC K4M matrices. The release rates were similar for HPMC K4M and HPMC E4M at equivalent polymer contents suggesting that the substitution type of HPMC may have little effect on the release of drug from HPMC matrices. However, matrices containing HPMC E15 showed faster release rates than HPMC K100 matrices which may ascribed to its lower viscosity.

9.3.2 RELEASE OF DICLOFENAC SODIUM FROM HPMC MATRICES

Similar to metoclopramide hydrochloride, the drug:polymer ratio had a great influence on the release of diclofenac sodium from HPMC E15, HPMC E4M, HPMC K100 and HPMC K4M matrices (Figures 9.5-9.8).

The release rates decreased as the polymer content increased (Tables 9.5-9.8). The release rates of diclofenac sodium from HPMC E15 matrices were faster than those observed for HPMC E4M at equivalent polymer content. Comparison of release rates for HPMC K100 and HPMC K4M matrices at the same polymer content indicated a faster release of diclofenac sodium from HPMC K100 matrices. These results indicate that increasing the polymer viscosity decreases the release rate of the drug. Such dependency of release rate of diclofenac sodium on the viscosity of HPMC matrices has been reported by Sheu et al (1992) when using HPMC K100 and HPMC

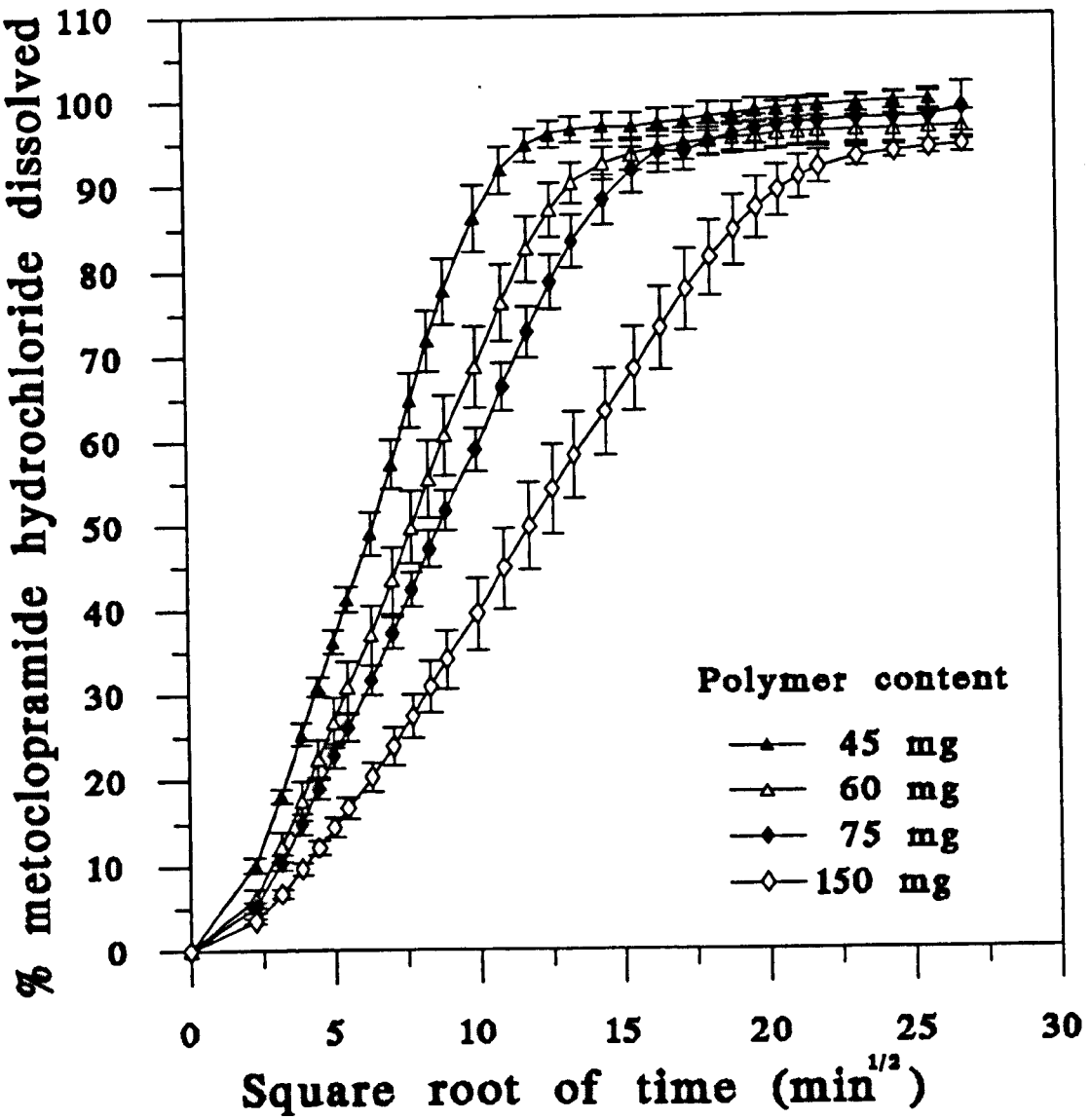


Figure 9.1. The effect of HPMC content on the release of metoclopramide hydrochloride from matrices containing 45, 60, 75 and 150 mg HPMC E15.

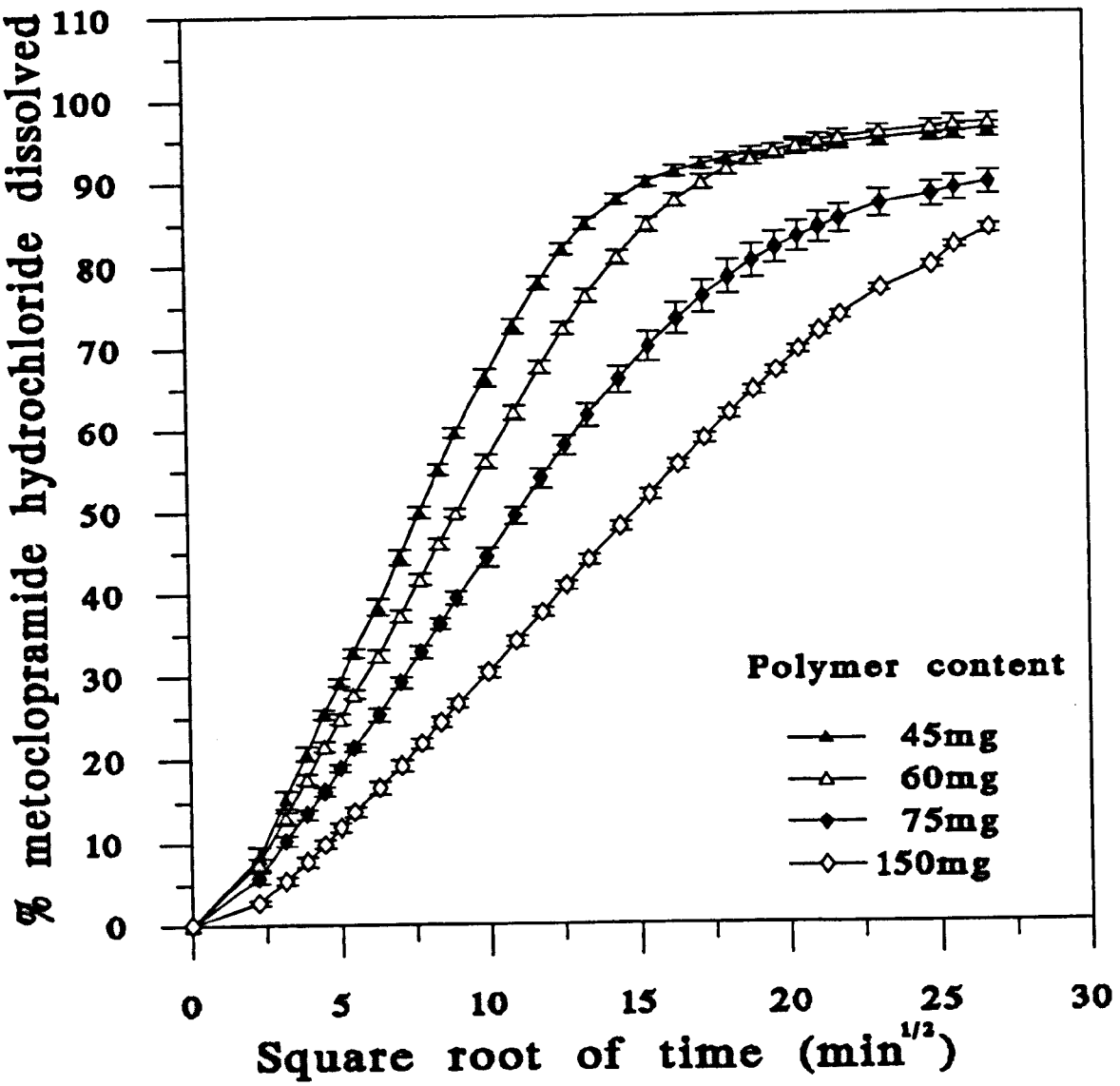


Figure 9.2. The effect of HPMC content on the release of metoclopramide hydrochloride from matrices containing 45, 60, 75 and 150 mg HPMC E4M.

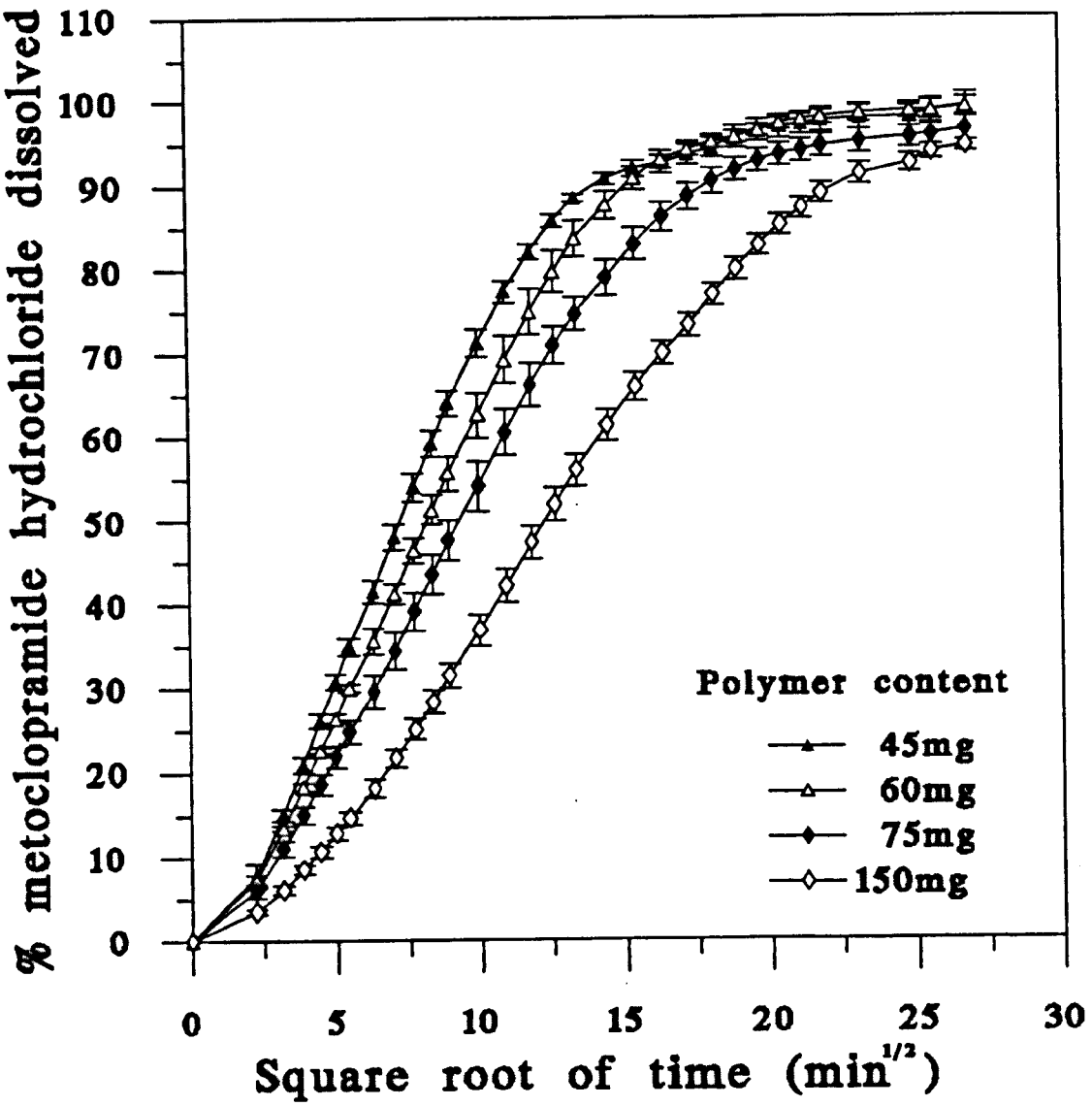


Figure 9.3. The effect of HPMC content on the release of metoclopramide hydrochloride from matrices containing 45, 60, 75 and 150 mg HPMC K100.

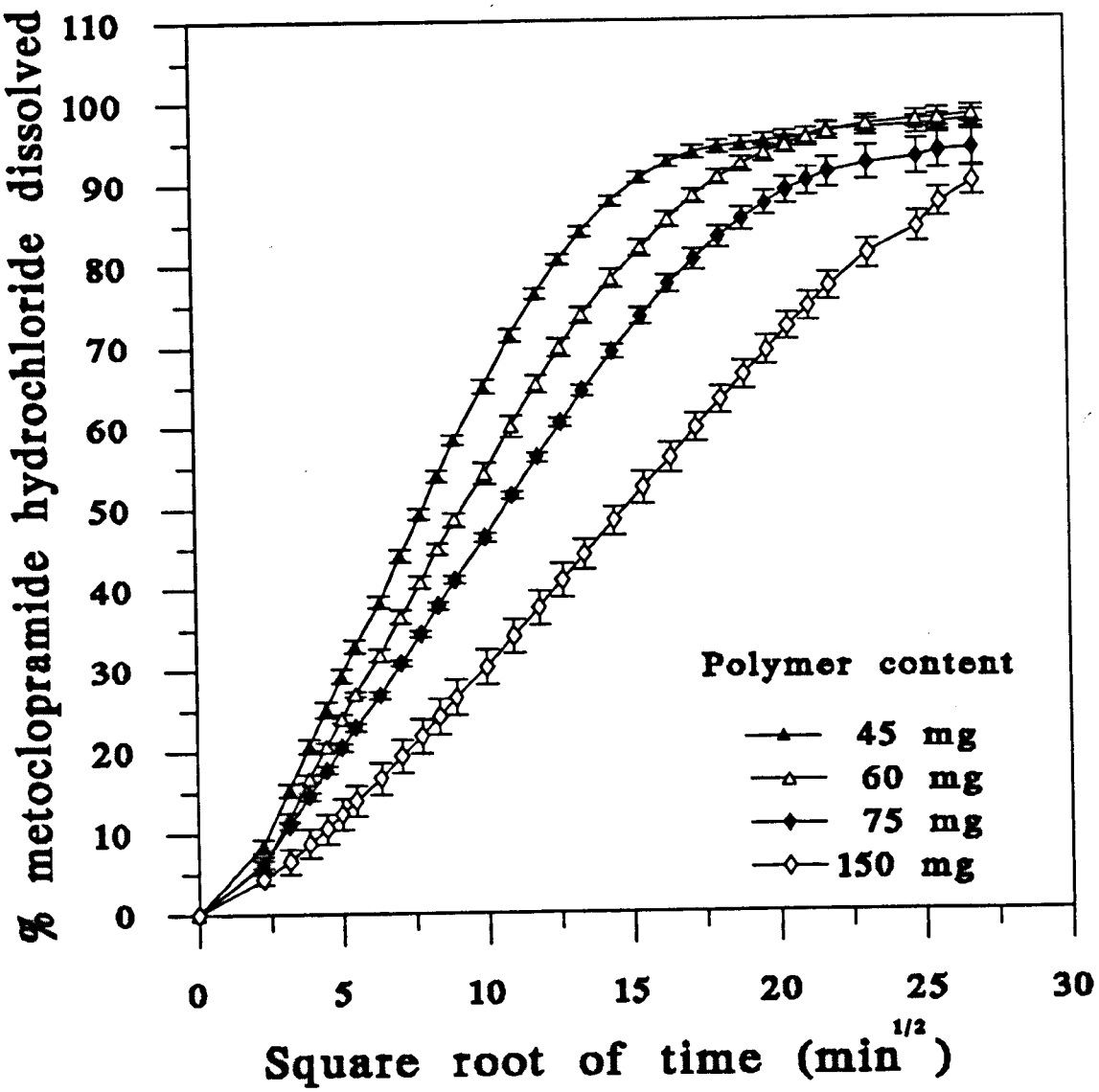


Figure 9.4. The effect of HPMC content on the release of metoclopramide hydrochloride from matrices containing 45, 60, 75 and 150 mg HPMC K4M.

Table 9.1. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from HPMC E15 matrices, using equations 1.1-1.4.

Model	*	HPMC E15 content (mg)			
		45	60	75	150
Zero-order (Equation 1.1)	K_1	0.96 ± 0.06	0.63 ± 0.04	0.48 ± 0.02	0.27 ± 0.02
	r	0.991	0.992	0.992	0.992
	P<	0.001	0.001	0.001	0.001
	t1	-10.1 ± 1.3	-16.1 ± 2.3	-22.6 ± 2.5	-36.3 ± 2.7
Square-root (Equation 1.2)	K_2	9.9 ± 0.6	8.3 ± 0.5	7.3 ± 0.3	5.2 ± 0.5
	r	0.998	0.998	0.998	0.998
	P<	0.001	0.001	0.001	0.001
	t2	1.8 ± 0.4	3.2 ± 0.6	3.5 ± 0.6	5.4 ± 0.6
First-order (Equation 1.3)	K_3	0.0165 ± 0.0016	0.0113 ± 0.0014	0.0087 ± 0.0007	0.0046 ± 0.0007
	r	0.999	0.999	0.999	0.999
	P<	0.001	0.001	0.001	0.001
	t3	-1.9 ± 1.4	-1.8 ± 1.5	-4.3 ± 1.4	-10.4 ± 3.9
Hixon-Crowell (Equation 1.4)	K_4	0.0211 ± 0.0017	0.0144 ± 0.0014	0.0110 ± 0.0007	0.0059 ± 0.0007
	r	0.998	0.998	0.998	0.998
	P<	0.001	0.001	0.001	0.001
	t4	-4.4 ± 1.1	-5.9 ± 1.5	-9.7 ± 1.7	-17.5 ± 2.8

* Key: The units of release constants are: K_1 (%min^{-1}), K_2 (%$min^{-1/2}$), K_3 (min^{-1}), K_4 (%$^{1/3}min^{-1}$) and the units of the lag times corresponding to different equations (1.1-1.4) t1, t2, t3 and t4 are min. P is the degree of significance.

Table 9.2. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from HPMC E4M matrices, using equations 1.1-1.4.

Model	*	HPMC E4M content (mg)			
		45	60	75	150
Zero-order (Equation 1.1)	K_1	0.56 ± <0.01	0.44 ± <0.01	0.29 ± <0.01	0.16 ± <0.01
	r	0.988	0.987	0.988	0.987
	P<	0.001	0.001	0.001	0.001
	t1	-24.9 ± 1.1	-30.3 ± 1.2	-45.7 ± 2.2	-85.9 ± 6.5
Square-root (Equation 1.2)	K_2	7.5 ± <0.01	6.3 ± <0.1	5.1 ± 0.1	3.8 ± <0.1
	r	0.999	0.999	0.999	1
	P<	0.001	0.001	0.001	0.001
	t2	1.3 ± 0.2	1.1 ± 0.2	1.4 ± 0.3	3.7 ± 0.6
First-order (Equation 1.3)	K_3	0.0101 ± 0.0002	0.0074 ± 0.0002	0.0048 ± 0.0001	0.0028 ± 0.0002
	r	0.999	0.998	0.998	0.999
	P<	0.001	0.001	0.001	0.001
	t3	-8.1 ± 1.1	-12.5 ± 0.2	-19.8 ± 2.4	-30.9 ± 4.1
Hixon-Crowell (Equation 1.4)	K_4	0.0128 ± 0.0001	0.0095 ± 0.0001	0.0063 ± 0.0002	0.0034 ± <0.0001
	r	0.997	0.996	0.996	0.996
	P<	0.001	0.001	0.001	0.001
	t4	-13.1 ± 0.8	-17.8 ± 0.7	-27.6 ± 2.2	-47.1 ± 2.8

* Key: See table 9.1.

Table 9.3. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from HPMC K100 matrices, using equations 1.1-1.4.

Model	*	HPMC K100 content (mg)			
		45	60	75	150
Zero-order (Equation 1.1)	K_1	0.66 ± 0.03	0.54 ± 0.03	0.45 ± 0.02	0.25 ± <0.01
	r	0.991	0.990	0.991	0.992
	P<	0.001	0.001	0.001	0.001
	t1	-17.7 ± 0.9	-21.9 ± 2.5	-22.7 ± 1.9	-37.5 ± 2.9
Square-root (Equation 1.2)	K_2	8.3 ± 0.4	7.3 ± 0.4	6.4 ± 0.3	5.2 ± 0.1
	r	1	0.999	0.998	0.999
	P<	0.001	0.001	0.001	0.001
	t2	1.9 ± 0.2	1.8 ± 0.5	2.4 ± 0.4	7.8 ± 0.7
First-order (Equation 1.3)	K_3	0.0115 ± 0.0009	0.0092 ± 0.0007	0.0074 ± 0.0005	0.0044 ± 0.0002
	r	0.999	0.998	0.999	1
	P<	0.001	0.001	0.001	0.001
	t3	-5.0 ± 1.2	-7.6 ± 2.1	-7.1 ± 1.6	-5.3 ± 0.2
Hixon-Crowell (Equation 1.4)	K_4	0.0149 ± 0.0010	0.0119 ± 0.0009	0.0095 ± 0.0006	0.0056 ± 0.0002
	r	0.998	0.997	0.998	0.998
	P<	0.001	0.001	0.001	0.001
	t4	-8.6 ± 1.1	-11.7 ± 2.6	-12.4 ± 1.5	-15.2 ± 1.6

* Key: See table 9.1.

Table 9.4. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from HPMC K4M matrices, using equations 1.1-1.4.

Model	*	HPMC K4M content (mg)			
		45	60	75	150
Zero-order (Equation 1.1)	K_1	0.55 ± 0.01	0.39 ± <0.01	0.31 ± <0.01	0.16 ± <0.01
	r	0.987	0.983	0.987	0.991
	P<	0.001	0.001	0.001	0.001
	t1	-26.3 ± 1.9	-34.6 ± 0.9	-43.4 ± 1.7	-72.6 ± 14.1
Square-root (Equation 1.2)	K_2	7.3 ± 0.1	6.1 ± 0.1	5.2 ± <0.1	3.9 ± <0.1
	r	0.999	0.999	0.999	0.999
	P<	0.001	0.001	0.001	0.001
	t2	1.1 ± 0.3	1.2 ± 0.1	1.2 ± 0.2	4.4 ± 2.6
First-order (Equation 1.3)	K_3	0.0097 ± 0.0001	0.0069 ± 0.0002	0.0053 ± 0.0002	0.0028 ± 0.0001
	r	0.998	0.998	0.998	0.998
	P<	0.001	0.001	0.001	0.001
	t3	-9.5 ± 1.4	-13.3 ± 0.4	-17.6 ± 0.3	-27.5 ± 7.5
Hixon-Crowell (Equation 1.4)	K_4	0.0123 ± 0.0002	0.0089 ± 0.0002	0.0067 ± <0.0001	0.0036 ± 0.0001
	r	0.997	0.995	0.996	0.998
	P<	0.001	0.001	0.001	0.001
	t4	-14.7 ± 1.5	-19.5 ± 0.5	-25.8 ± 1.3	-41.7 ± 9.7

* Key: See table 9.1.

K4M and by Liu et al (1995) when using HPMC 60-SH, 50 mPa.s and HPMC 60-SH, 4000 mPa.s.

The release rates of diclofenac sodium from HPMC K4M matrices were similar to those observed for HPMC E4M matrices at equivalent polymer content. However the release of drug was faster when HPMC E15 was used than when HPMC K100 was used which may be attributed to the lower viscosity of the HPMC E15 matrices.

9.3.3 RELEASE KINETICS FOR METOCLOPRAMIDE HYDROCHLORIDE

Correlation coefficients for the best statistical fit for the release of metoclopramide hydrochloride from HPMC matrices are shown in Tables 9.1-9.4. The close values of correlation coefficients for the square-root, first-order and Hixon-Crowell models made it difficult to judge about the best applicable model to the release data. This might indicate that mixtures of these models can be used to describe the release profiles.

The mechanism of drug release was investigated by fitting the data to equations 1.6 and 1.7. Statistical analyses showed that at each polymer content, the best fit with the lowest sums of squares of errors and the lowest information criteria were found when equation 1.7 was used (Tables 9.9-9.12). As there was no special trend between the polymer content and the value of n for the different grades of HPMC, the values of n (equation 1.7) were averaged in order to characterise the mechanism of drug release.

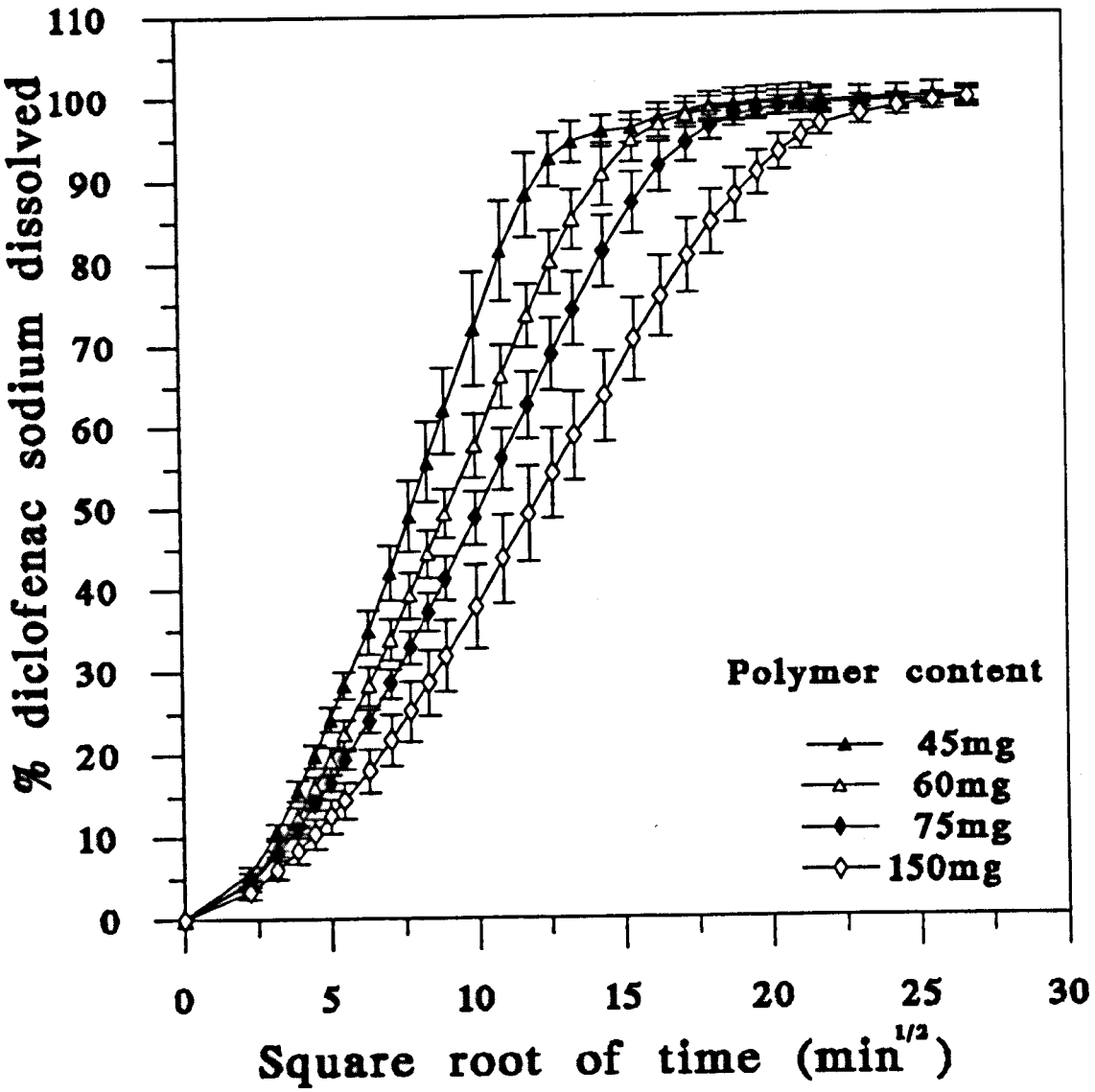


Figure 9.5. The effect of HPMC content on the release of diclofenac sodium from matrices containing 45, 60, 75 and 150 mg HPMC E15.

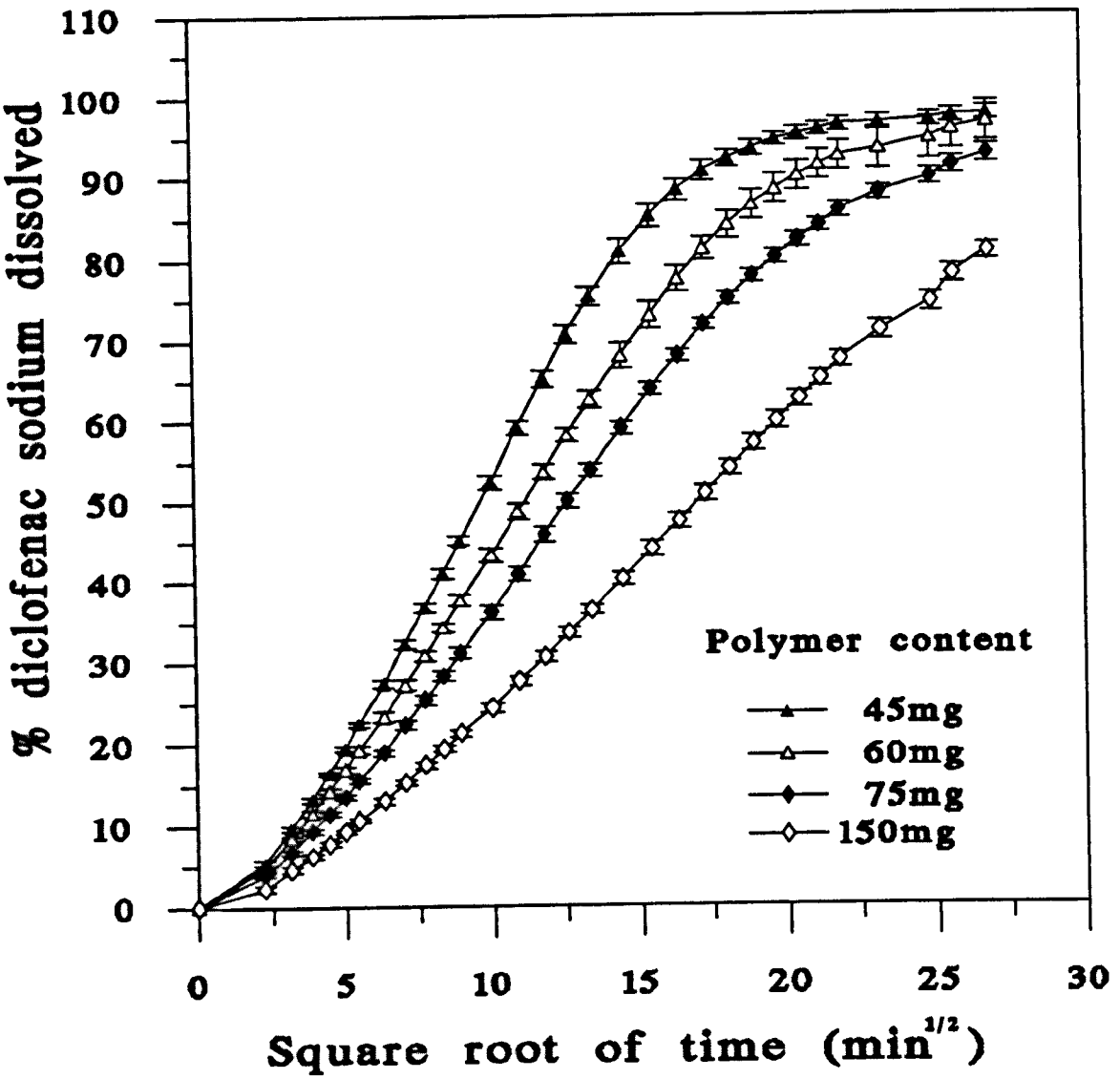


Figure 9.6. The effect of HPMC content on the release of diclofenac sodium from matrices containing 45, 60, 75 and 150 mg HPMC E4M.

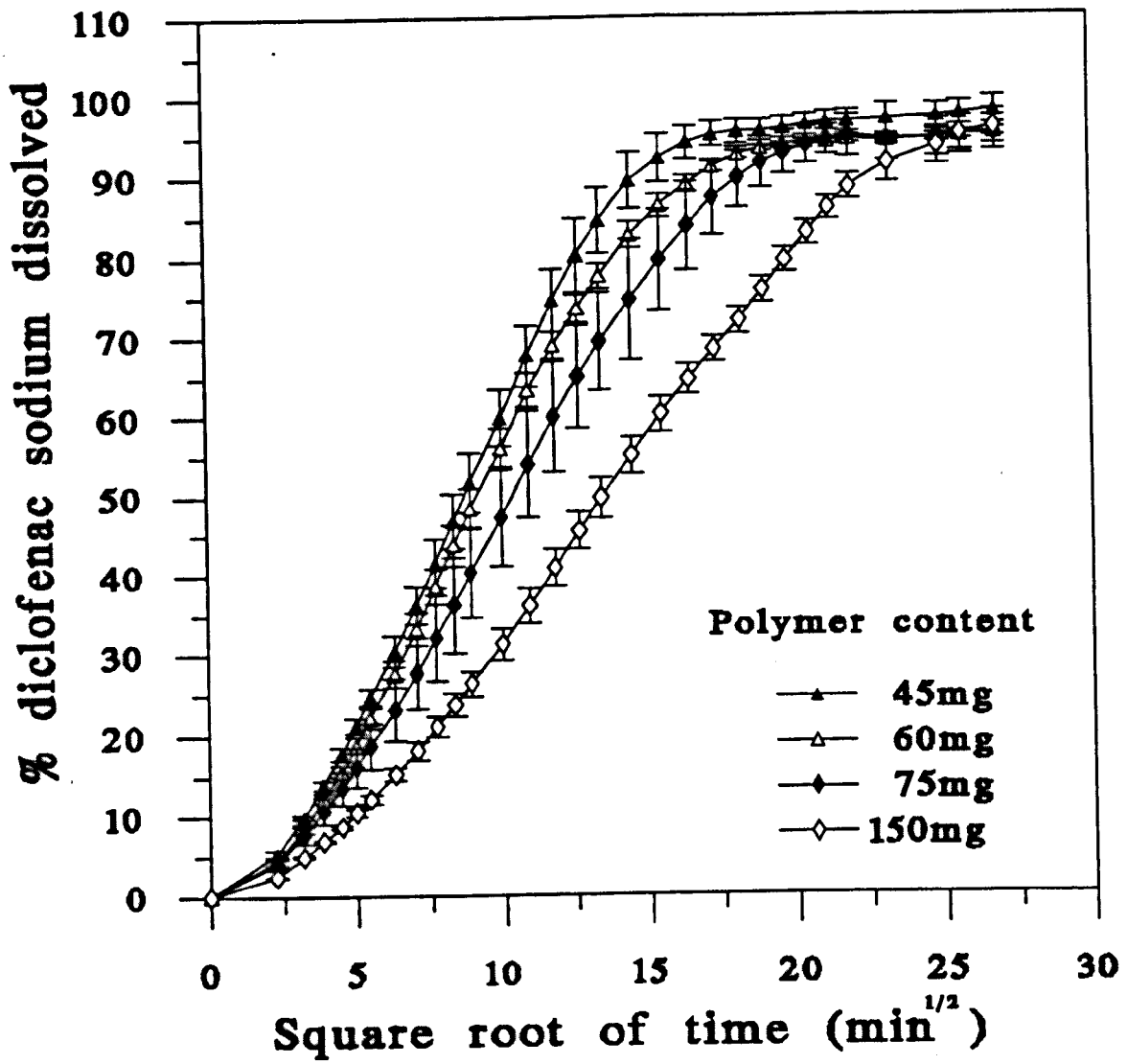


Figure 9.7. The effect of HPMC content on the release of diclofenac sodium from matrices containing 45, 60, 75 and 150 mg HPMC K100.

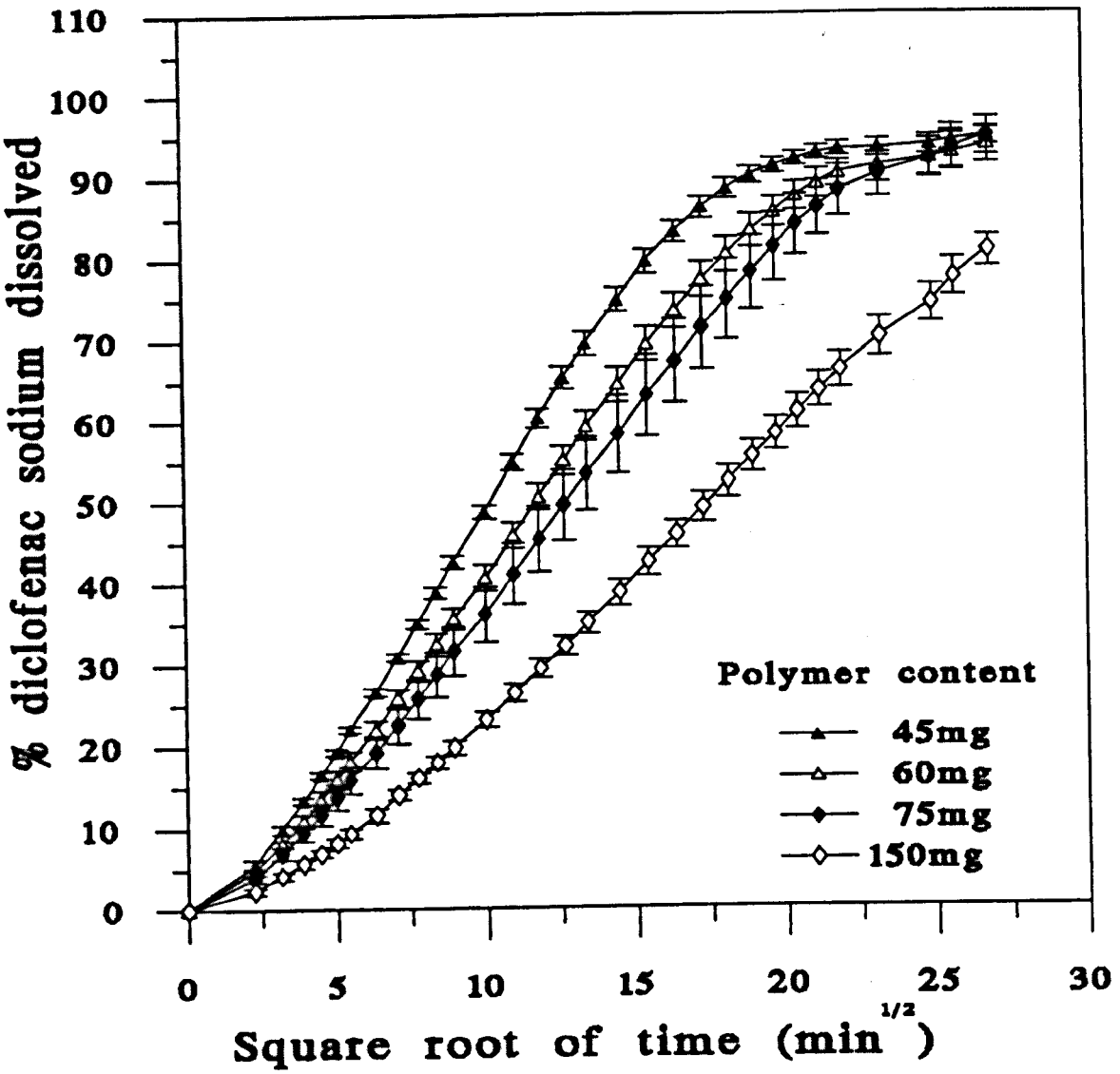


Figure 9.8. The effect of HPMC content on the release of diclofenac sodium from matrices containing 45, 60, 75 and 150 mg HPMC K4M.

Table 9.5. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of diclofenac sodium from HPMC E15 matrices, using equations 1.1-1.4.

Model	*	HPMC E15 content (mg)			
		45	60	75	150
Zero-order (Equation 1.1)	K_1	0.73 ± 0.06	0.51 ± 0.03	0.41 ± 0.02	0.28 ± 0.02
	r	0.997	0.996	0.997	0.995
	P<	0.001	0.001	0.001	0.001
	t1	-7.5 ± 0.9	-13.7 ± 1.6	-18.6 ± 1.3	-25.7 ± 7.7
Square-root (Equation 1.2)	K_2	8.9 ± 0.7	7.6 ± 0.4	6.6 ± 0.5	5.6 ± 0.5
	r	0.996	0.998	0.997	0.997
	P<	0.001	0.001	0.001	0.001
	t2	4.7 ± 0.3	6.0 ± 0.5	6.7 ± 0.4	9.7 ± 2.5
First-order (Equation 1.3)	K_3	0.0119 ± 0.0018	0.0087 ± 0.0009	0.0067 ± 0.0007	0.0048 ± 0.0007
	r	0.996	0.998	0.998	0.998
	P<	0.001	0.001	0.001	0.001
	t3	1.7 ± 1.5	1.7 ± 1.2	1.1 ± 2.1	0.1 ± 3.5
Hixon-Crowell (Equation 1.4)	K_4	0.0156 ± 0.0020	0.0113 ± 0.0009	0.0088 ± 0.0009	0.0063 ± 0.0007
	r	0.998	0.999	0.999	0.999
	P<	0.001	0.001	0.001	0.001
	t4	-0.8 ± 1.2	-2.7 ± 1.3	-5.8 ± 2.1	-7.1 ± 5.1

* Key: See table 9.1.

Table 9.6. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of diclofenac sodium from HPMC E4M matrices, using equations 1.1-1.4.

Model	*	HPMC E4M content (mg)			
		45	60	75	150
Zero-order (Equation 1.1)	K_1	0.41 ± <0.01	0.31 ± <0.01	0.23 ± <0.01	0.13 ± <0.01
	r	0.994	0.993	0.992	0.994
	P<	0.001	0.001	0.001	0.001
	t1	-23.9 ± 0.7	-37.9 ± 1.5	-46.6 ± 1.8	-85.1 ± 2.9
Square-root (Equation 1.2)	K_2	6.5 ± 0.1	5.4 ± 0.1	4.7 ± 0.1	3.5 ± <0.1
	r	0.998	0.998	0.999	0.999
	P<	0.001	0.001	0.001	0.001
	t2	4.1 ± 0.2	3.8 ± 0.3	5.5 ± 0.4	8.4 ± 0.6
First-order (Equation 1.3)	K_3	0.0071 ± 0.0002	0.0051 ± 0.0001	0.0039 ± 0.0001	0.0021 ± 0.0001
	r	0.999	0.999	1	1
	P<	0.001	0.001	0.001	0.001
	t3	-3.8 ± 1.3	-11.3 ± 2.4	-12.9 ± 2.9	-27.6 ± 5.4
Hixon-Crowell (Equation 1.4)	K_4	0.0092 ± 0.0002	0.0066 ± 0.0001	0.0051 ± 0.0001	0.0028 ± <0.0001
	r	0.998	0.998	0.999	0.999
	P<	0.001	0.001	0.001	0.001
	t4	-10.2 ± 0.6	-13.3 ± 0.7	-22.7 ± 1.6	-44.6 ± 3.0

* Key: See table 9.1.

Table 9.7. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of diclofenac sodium from HPMC K100 matrices, using equations 1.1-1.4.

Model	*	HPMC K100 content (mg)			
		45	60	75	150
Zero-order (Equation 1.1)	K_1	0.51 ± 0.05	0.49 ± 0.02	0.36 ± 0.05	0.22 ± <0.01
	r	0.994	0.994	0.995	0.995
	P<	0.001	0.001	0.001	0.001
	t1	-17.8 ± 2.4	-14.6 ± 0.9	-22.8 ± 3.3	-36.1 ± 3.7
Square-root (Equation 1.2)	K_2	7.6 ± 0.7	7.3 ± 0.3	6.4 ± 0.9	4.9 ± 0.2
	r	0.998	0.998	0.998	0.998
	P<	0.001	0.001	0.001	0.001
	t2	4.7 ± 0.8	5.7 ± 0.2	6.7 ± 0.9	11.4 ± 1.0
First-order (Equation 1.3)	K_3	0.0092 ± 0.0014	0.0081 ± 0.0005	0.0067 ± 0.0014	0.0037 ± 0.0002
	r	0.998	0.998	0.998	0.998
	P<	0.001	0.001	0.001	0.001
	t3	-0.7 ± 4.0	0	-0.6 ± 3.4	-1.2 ± 2.4
Hixon-Crowell (Equation 1.4)	K_4	0.0117 ± 0.0016	0.0111 ± 0.0005	0.0079 ± 0.0015	0.0049 ± 0.0002
	r	0.999	0.999	0.999	0.999
	P<	0.001	0.001	0.001	0.001
	t4	-5.7 ± 3.2	-4.3 ± 0.6	-5.9 ± 5.2	-11.9 ± 2.1

* Key: See table 9.1.

Table 9.8. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of diclofenac sodium from HPMC K4M matrices, using equations 1.1-1.4.

Model	*	HPMC K4M content (mg)			
		45	60	75	150
Zero-order (Equation 1.1)	K_1	0.36 ± 0.01	0.27 ± <0.01	0.22 ± 0.01	0.12 ± <0.01
	r	0.992	0.992	0.990	0.993
	P<	0.001	0.001	0.001	0.001
	t1	-32.5 ± 1.9	-43.2 ± 4.1	-50.9 ± 4.1	-81.8 ± 4.3
Square-root (Equation 1.2)	K_2	5.9 ± 0.2	5.1 ± 0.2	4.7 ± 0.3	3.5 ± 0.1
	r	0.998	0.998	0.998	0.999
	P<	0.001	0.001	0.001	0.001
	t2	3.1 ± 0.4	3.9 ± 0.9	4.7 ± 0.8	10.6 ± 0.9
First-order (Equation 1.3)	K_3	0.0062 ± 0.0002	0.0046 ± 0.0002	0.0041 ± 0.0005	0.0021 ± 0.0002
	r	0.999	0.999	0.999	1
	P<	0.001	0.001	0.001	0.001
	t3	-9.7 ± 2.1	-13.3 ± 2.5	-13.9 ± 3.8	-24.1 ± 4.9
Hixon-Crowell (Equation 1.4)	K_4	0.0079 ± 0.0002	0.0059 ± 0.0002	0.0050 ± 0.0005	0.0027 ± 0.0001
	r	0.999	0.998	0.998	0.999
	P<	0.001	0.001	0.001	0.001
	t4	-16.2 ± 1.9	-22.5 ± 3.2	-25.0 ± 2.8	-40.3 ± 2.8

* Key: See table 9.1.

The mean values of n are 0.63 ± 0.01, 0.54 ± 0.01, 0.60 ± 0.03 and 0.56 ± 0.04 for HPMC E15, HPMC E4M, HPMC K100 and HPMC K4M matrices. These values indicate that the mechanism of drug release from all grades of HPMC is anomalous transport or non-Fickian diffusion (Ritger and Peppas, 1987). In other words a combination of diffusion through the gel and erosion of the polymer controlled drug release.

Generally the values of n for matrices containing lower viscosity HPMCs (HPMC E15 and HPMC K100) were higher than those for HPMC of higher viscosity grades (HPMC E4M and HPMC K4M). This higher value of n indicate that the role of erosion in controlling drug release was greater for lower viscosity grade HPMCs than for higher viscosity grades.

9.3.4 RELEASE KINETICS FOR DICLOFENAC SODIUM

Tables 9.5-9.8 show the correlation coefficients for the release of diclofenac sodium from HPMC matrices. Again due to the close values of (r) for square-root, first order and Hixon-Crowell model it is not possible to consider one model as a best fit. Therefore it may be concluded that mixtures of these models may apply to the release data.

The values of the release exponents are listed in Tables 9.13-9.16. Statistical analyses showed that at each polymer content, the best fit was found when equation 1.7 was used. The mean value of n (equation 1.7) is 0.74 ± 0.04, 0.63 ± 0.01, 0.68 ± <0.01

Table 9.9. The values of K_1, n, based on equation 1.6, K_2, n, l, based on equation 1.7 calculated in the range of 15-60% metoclopramide hydrochloride release, from matrices containing HPMC E15. The values of the sums of squares of errors (ss) and Schwartz criteria are also given.

HPMC E15 content (mg)	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	n	l*	ss	Schwartz
45	3.83	0.69	4.71	18.35	5.01	0.63	2.00	0.60	2.07
60	2.54	0.73	2.95	15.41	3.54	0.65	3.24	0.59	1.61
75	2.44	0.69	7.49	29.12	3.50	0.62	4.38	0.89	6.00
150	1.68	0.68	5.20	28.35	2.27	0.63	6.02	2.02	17.75

* Key: The units of K_1 and K_2 are $\%min^{-n}$ and the unit of l is min.

Table 9.10. The values of K_1, n, based on equation 1.6, K_2, n, l, based on equation 1.7 calculated in the range of 15-60% metoclopramide hydrochloride release, from matrices containing HPMC E4M. The values of the sums of squares of errors (ss) and Schwartz criteria are also given.

HPMC E4M content (mg)	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	n	l*	ss	Schwartz
45	4.06	0.61	5.29	23.11	5.36	0.55	3.37	1.88	14.13
60	3.70	0.59	4.49	24.65	4.66	0.54	3.38	0.77	4.35
75	3.00	0.58	7.76	36.15	3.96	0.53	5.58	2.20	19.92
150	1.89	0.60	6.02	36.17	2.58	0.55	10.50	1.25	12.29

* Key: See table 9.9.

Table 9.11. The values of K_1, n, based on equation 1.6, K_2, n, l, based on equation 1.7 calculated in the range of 15-60% metoclopramide hydrochloride release, from matrices containing HPMC K100. The values of the sums of squares of errors (ss) and Schwartz criteria are also given.

HPMC K100 content (mg)	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	n	l*	ss	Schwartz
45	3.64	0.65	4.92	20.53	5.33	0.57	3.99	0.31	-4.89
60	3.33	0.64	3.89	19.72	4.44	0.58	3.38	0.82	5.06
75	2.70	0.65	4.43	24.47	3.40	0.60	3.22	1.25	10.39
150	1.39	0.71	9.52	36.83	2.07	0.64	8.89	4.12	27.74

* Key: See table 9.9.

Table 9.12. The values of K_1, n, based on equation 1.6, K_2, n, l, based on equation 1.7 calculated in the range of 15-60% metoclopramide hydrochloride release, from matrices containing HPMC K4M. The values of the sums of squares of errors (ss) and Schwartz criteria are also given.

HPMC K4M content (mg)	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	n	l*	ss	Schwartz
45	4.21	0.60	5.12	22.77	5.68	0.53	3.69	1.03	7.53
60	3.57	0.59	9.10	33.83	4.96	0.52	4.78	0.68	2.74
75	3.13	0.58	2.64	19.97	3.68	0.55	2.79	0.47	-3.11
150	1.68	0.68	5.20	28.35	2.27	0.63	6.01	2.02	17.75

* Key: See table 9.9.

and 0.61 ± 0.01 for HPMC E15, HPMC E4M, HPMC K100 and HPMC K4M matrices. The mean values of n indicate that although both diffusion and erosion control the mechanism of diclofenac sodium release, the role of erosion is greater than that was a case for metoclopramide hydrochloride. These values of n are in the range reported by Liu et al (1993) for the release of diclofenac sodium from HPMC of different viscosity (0.64-0.87). However Liu et al (1995) obtained values of 0.56 and 0.61 for the release of diclofenac sodium from matrices containing HPMC 4000 mPa.s and HPMC 50 mPa.s respectively. Values of n reported by other workers include 0.78 (Sheu et al, 1992) for release of diclofenac sodium from HPMC K4M matrices, 0.77 (Liu et al, 1993) and 0.82 (Sheu et al, 1992) for release of diclofenac sodium from HPMC K100 matrices and 0.83 (Bain et al, 1991) for the release of this drug from HPMC E15 matrices.

Again the values of n for matrices containing the lower viscosity HPMCs (HPMC E15 and HPMC K100) were higher than those of HPMC of higher viscosity grades (HPMC E4M and HPMC K4M) indicating that erosion has a higher contribution to the release of diclofenac sodium from matrices containing the low viscosity grade HPMC.

9.4 GENERAL DISCUSSION

The release rates of metoclopramide hydrochloride or diclofenac sodium from HPMC E15 matrices were higher than for HPMC E4M matrices. Similar results were obtained for the release rates of these two drugs from matrices containing HPMC

Table 9.13. The values of K_1, n, based on equation 1.6, K_2, n, l, based on equation 1.7 calculated in the range of 15-60% diclofenac sodium release, from matrices containing HPMC E15. The values of the sums of squares of errors (ss) and Schwartz criteria are also given.

HPMC E15 content (mg)	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	n	l*	ss	Schwartz
45	1.71	0.82	0.71	1.18	1.89	0.80	0.91	0.57	1.22
60	1.58	0.78	2.28	13.88	2.11	0.72	3.62	0.58	1.14
75	1.43	0.77	0.51	-3.18	1.60	0.74	1.58	0.25	-9.28
150	1.15	0.76	7.82	31.86	1.67	0.69	7.40	4.67	27.73

* Key: See table 9.9.

Table 9.14. The values of K_1, n, based on equation 1.6, K_2, n, l, based on equation 1.7 calculated in the range of 15-60% diclofenac sodium release, from matrices containing HPMC E4M. The values of the sums of squares of errors (ss) and Schwartz criteria are also given.

HPMC E4M content (mg)	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	n	l*	ss	Schwartz
45	2.09	0.69	1.68	11.23	2.60	0.66	3.20	0.36	-4.69
60	2.07	0.66	2.11	15.73	2.56	0.62	3.72	0.32	-8.06
75	1.62	0.67	3.08	21.04	2.10	.0.63	6.01	1.18	10.21
150	1.21	0.65	1.71	16.12	1.45	0.63	6.88	0.65	0.61

* Key: See table 9.9.

9.15. The values of K_1, n, based on equation 1.6, K_2, n, l, based on equation 1.7 calculated in the range of 15-60% diclofenac sodium release, from matrices containing HPMC K100. The values of the sums of squares of errors (ss) and Schwartz criteria are also given.

HPMC K100 content (mg)	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	n	l^*	ss	Schwartz
45	2.01	0.74	3.52	18.64	2.81	0.67	4.33	0.80	4.79
60	1.65	0.77	5.99	24.48	2.48	0.68	5.20	2.12	15.48
75	1.54	0.74	3.77	20.89	2.12	0.68	5.27	1.45	11.90
150	1.00	0.75	5.43	28.97	1.42	0.69	8.54	2.72	21.90

* Key: See table 9.9.

9.16. The values of K_1, n, based on equation 1.6, K_2, n, l, based on equation 1.7 calculated in the range of 15-60% diclofenac sodium release, from matrices containing HPMC K4M. The values of the sums of squares of errors (ss) and Schwartz criteria are also given.

HPMC K4M content (mg)	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	n	l^*	ss	Schwartz
45	2.40	0.65	1.86	13.16	2.91	0.61	3.23	0.45	-2.78
60	2.05	0.64	2.79	19.65	2.62	0.60	5.03	0.69	2.77
75	1.84	0.64	5.19	30.12	2.48	0.59	7.52	21.2	1.48
150	1.01	0.68	0.49	-7.38	1.35	0.63	10.00	0.25	-17.29

* Key: See table 9.9.

K100 and matrices containing HPMC K4M. Therefore, the release of either drug was affected by the viscosity of the HPMC. However there are conflicting reports about the effect of viscosity of the HPMC on the release of drugs, some of them stating that viscosity does not have any effect and some have introduced viscosity as an important factor in the control of drug release from matrices.

Salomon et al (1979) showed that only the lag time for the release of potassium chloride was affected by the viscosity of HPMC in matrices while the release rates were the same for each viscosity grade of HPMC examined. Alderman (1984) stated that the release of a drug would be slower if a higher viscosity grade of HPMC was used in the matrix and this was attributed to an increase in gel layer viscosity. Similar results were found by Daly et al (1984) for the release of chlorpheniramine maleate from HPMC E5, HPMC E15, HPMC E50 or HPMC E4M matrices.

Ford et al (1985a; 1985b) reported that matrices composed of HPMC K4M, HPMC K15M or HPMC K100M showed similar release profiles for promethazine hydrochloride, propranolol hydrochloride and aminophylline while the lowest viscosity grade (HPMC K100) behaved differently and gave faster release rates. Ford et al (1985b) showed that both the lag times and release rates were generally unaffected by the viscosity grade of HPMC for propranolol hydrochloride and aminophylline. Ford et al (1985c) claimed that for a poorly water soluble drug, such as indomethacin, the viscosity grade plays a major role in controlling the rate of drug release. In the present study the viscosity grade of the HPMC affected the release of

both drugs.

Baveja et al (1988) reported the that release rates of a series of bronchodilators did not vary significantly for matrices containing HPMC K4M, HPMC K15M and HPMC K100M which was in agreement with earlier studies (Salomon et al, 1979: Ford et al 1985a; 1985b).

Cheong et al (1992) showed that the viscosity grade had no major effect on the release of propranolol hydrochloride from matrices containing 50-75% w/w polymer (HPMC K4M, HPMC K15M, HPMC K30M and HPMC K100M) in the formulation while it had a tremendous effect on the release rate of drug when the amount of polymer was in the range of 5-25% w/w of formulation. However, in this study using lower viscosity grades of HPMC, the effect of viscosity was observed in matrices containing 75-90% polymer in the formulation.

What we may conclude from the results of this study and other reports is that there is a treshhold for viscosity of the HPMC above which there is no effect on drug release rate but below it, the drug release is greatly affected by the viscosity. These results are confirmed by Gao et al (1996) who showed that gel layer thickness and consquently dissolution of drug have been affected by the viscosity of HPMC below a critical molecular weight. For matrices containing high viscosity HPMCs (>4000 mPa.s) the gel composition and thickness is identical. However for low viscositiy HPMCs (<100 mPa.s) the swelling is not homogeneous maybe due to rapid

dissolution of polymer (Gao et al, 1996).

The mathematical modelling of release data proved that drug release mechanism was controlled by both diffusion through and erosion of the polymer for both drugs. However depending on the type of drug used one mechanism may have more significant role than the other. The values of n were between, 0.53-0.64 for metoclopramide hydrochloride release from HPMC matrices with different viscosity grades. Previously Ford et al (1987) reported values of n between 0.65-0.71 for the release of soluble drugs from HPMC K15M matrices. Other values of n were 0.63 (Ranga Rao et al, 1990) or 0.60 (Dabbagh, 1995) for propranolol hydrochloride release from HPMC K4M matrices. The value of n obtained for metoclopramide hydrochloride is approximately in the range obtained by other workers.

The values of n for diclofenac sodium release from HPMC matrices with different viscosity were in the range of 0.59-0.80. However the values of n reported by Ford et al (1987) for insoluble drugs were 0.82-0.90. Hence the value of n for diclofenac sodium was lower than those obtained for insoluble drugs. This may be attributed to the higher water solubility of diclofenac sodium compared to those drugs (indomethacin and diazepam) used by Ford et al (1987).

A comparison of the release exponents for metoclopramide hydrochloride and diclofenac sodium (Table 9.17) shows that the value of n is higher for the latter drug. This indicates different mechanisms control the release of these drugs. The release

of the more water soluble drug is predominantly controlled by diffusion through HPMC matrices while the higher value of n for diclofenac sodium shows that there is a larger contribution by erosion to the release of this drug. This is in agreement with findings of Skoug et al (1993), Pham and Lee (1994) and Tahara et al (1996). Skoug et al (1993) showed that the release of flurbiprofen from HPMC matrices was mainly an erosion-controlled mechanism while adinazolam mesylate exhibited an entirely diffusion-controlled mechanism. Alprazolam release was controlled by both diffusion and erosion. Pham and Lee (1994) also reported that the release of a water soluble compound occurred mostly by swelling-controlled diffusion process while for relatively water insoluble drugs and/or lower viscosity grades of HPMC, polymer dissolution plays a more significant part in control of drug release rate.

Table 9.17. The value of n for the release of metoclopramide hydrochloride or diclofenac sodium from matrices containing different grade and viscosity of HPMC.

Drug	HPMC E15	HPMC E4M	HPMC K100	HPMC K4M
Metoclopramide hydrochloride	0.63 ± 0.01	0.54 ± 0.01	0.60 ± 0.03	0.56 ± 0.04
Diclofenac sodium	0.74 ± 0.04	0.63 ± 0.01	0.68 ± 0.01	0.61 ± 0.01

It has been claimed that, due to faster hydration, HPMC K type produced slower release rates than HPMC E type (Alderman, 1984). Recent studies have shown that the extent and rate of gel formation is similar for different types of HPMC (Mitchell et al, 1993a; Rajabi-Siahboomi, 1994b). Rajabi-Siahboomi (1996) suggested that HPMC K4M gel offered a greater diffusional resistance to water within the inner gel

region. However the results of this study indicated that the performance of HPMC K4M and HPMC E4M were similar for the release of metoclopramide hydrochloride or diclofenac sodium. These results are in agreement with those published by Mitchell et al (1993a) who reported that substitution type had a little effect on the dissolution of propranolol hydrochloride. Indeed, no differences observed for the release rate of propranolol hydrochloride from matrices containing HPMC K4M, HPMC E4M or HPMC F4M (Mitchell et al, 1993a).

9.5 CONCLUSIONS

The results of this study indicated that the polymer/drug ratio has a great effect on the release of drug from HPMC matrices. The release rates of both drugs decreased as the polymer content increased. The rate of metoclopramide hydrochloride or diclofenac sodium release was greatly affected by the viscosity of the HPMC polymer. The lower viscosity grade polymers produced faster release rates for both drugs.

The results also showed that drug solubility affected not only the release rate but also the release mechanism. The drug with the lower solubility was released more slowly than the more water soluble drug. Erosion had a greater contribution in the release mechanism of diclofenac sodium than metoclopramide hydrochlordie from HPMC matrices.

CHAPTER 10. DRUG RELEASE FROM MATRICES PREPARED BY WET GRANULATION PROCEDURE USING SURELEASE

10.1 INTRODUCTION

The release of metoclopramide hydrochloride and diclofenac sodium from HPMC matrices was characterised in chapter 9. Changes in polymer content, viscosity or type produced zero-order release for neither drug. It has been reported that sustained release dosage forms based on mixtures of HPMC and ionic cellulose ethers such as sodium carboxymethylcellulose may produce zero-order release (Baveja et al, 1987; 1988; Ranga Rao et al, 1988; Dabbagh, 1995). However few studies investigated mixtures of HPMC with the non-ionic ethylcellulose. Feely and Davis (1988b) found that the addition of ethylcellulose as a powder to HPMC matrices did not have any profound effect on the release of chlorpheniramine maleate. Indeed, a slight increase in the release rate was observed after the addition of ethylcellulose. Similarly Dabbagh et al (1996) stated that as the proportion of ethylcellulose (as powder) in HPMC matrices increased, the release rates of propranolol hydrochloride increased.

Aqueous dispersions of ethylcellulose have been used as a granulating agent to produce tablets, containing drug and excipients such as dicalcium phosphate, with sustained release properties (Klinger et al, 1990). However there are no reports on the application of these dispersions in the granulation of HPMC. In order to obtain the desired release profiles from hydrophilic matrices, it is essential to use either high molecular weight polymers or a high concentration of the polymer. The use of

a high molecular weight polymer, or a high concentration of it, caused unacceptable flow characteristics which could be troublesome, especially when high-speed tableting machines are used (Sheskey et al, 1994). Therefore, to ensure good content uniformity and to avoid flow-related problems, granulation may be the preferred procedure to manufacture commercial hydrophilic sustained release matrix tablets (Timmins et al, 1991).

10.1.1 AIMS AND OBJECTIVES OF THE STUDY

The aims of the work presented in this chapter were to examine the potential for sustained release of HPMC matrices granulated with Surelease.

10.2 MATERIALS AND METHODS

10.2.1 MATERIALS

HPMC K4M, metoclopramide hydrochloride (<90 μm particle size), diclofenac sodium (<90 μm particle size), Surelease and magnesium stearate, as described in section 2.1, were used.

10.2.2 METHODS

10.2.2.1 Preparation of granules

The granules were prepared on a small scale. Mixtures (12 g) of 1:5 drug:HPMC K4M blends were prepared using a tumbler mixer as described in section 2.2.5. The mixed powders were transferred to a blender (Moulinex Blender 531, Spain). As Surelease contains 25% w/w solid, the amount of dispersion that can be used at each

step of the granulation was low because otherwise the granulation become too damp to process with larger volumes of dispersion. Quantities (4 g) of undiluted Surelease were weighed using an Oertling analytical balance (West Midland, UK) and were added to the mixture of the drug and polymer in stages and mixed thoroughly for 1 min. The wet mass was passed manually through a 600 μm sieve and dried at 50°C for 45 min, before further granulating agent was added as required. This procedure was repeated until the desired amount of Surelease was added, to produce granules containing 14.28%, 25% or 33.33% w/w (based on the dried weight) Surelease. This resulted in granules which contained 1:5:1, 1:5:2 or 1:5:3 drug:HPMC K4M:Surelease ratios. The final granules were dried overnight at 50°C. Control granules were prepared by the addition of 4 g water to the drug and polymer mixtures instead of Surelease and processed as described above.

10.2.2.2 Preparation of tablets

The granules prepared in section 10.2.2.1 were mixed with 0.5% w/w magnesium stearate for 5 min using a tumbler mixer. Flat-faced tablets, 7.14 mm in diameter, containing amounts of granules equivalent to 15mg of drug, were compressed on a Manesty F3 single punch tableting machine at 20 kN compaction force as described in section 2.2.5. The tablet weights were 105, 120 or 135 mg based on the Surelease content in the granules.

10.2.2.3 Evaluation of matrices

The crushing strengths of the tablets were measured using a motorised tablet

hardness tester (Scleuniger, model 2E, Switzerland) 24 h after compaction. An Air Comparison Pycnometer (Model 930, Beckman Instruments Ltd. UK) was used to determine the true densities of the physical mixtures of drug and HPMC K4M and their granules. The mean of three determinations was used for each sample. The thicknesses and diameters of the tablets were measured using a screw-gauge micrometer (Mitutoyo, Japan) in order to calculate the volume of the tablets. The porosities of the tablets were determined consequently using equation 10.1.

$$\epsilon = (1 - \rho_a / \rho_t) \times 100 \qquad \textit{Equation 10.1}$$

In equation 10.1, ε is the porosity of the tablet, ρ_a is the apparent density of the tablet ($g.cm^{-3}$) and ρ_t is the true density of the powder or granule ($g.cm^{-3}$). The means of four determinations were used to calculate the porosity of the tablets prepared from physical mixtures and those prepared from granules. The mean values of 4 tablets for each formulation are reported.

Dissolution was carried out as described in section 2.2.6. The release data between 15-60% were fitted to different kinetic models as described in section 2.2.7.

10.3 RESULTS AND DISCUSSION

10.3.1 CRUSHING STRENGTHS AND POROSITIES

Table 10.1 shows the crushing strengths of tablets made from physical mixtures and of those prepared by wet granulation using either water or Surelease. The crushing strengths of the tablets decreased after granulation suggesting the formation of hard

granules which resist deformation during compaction. The crushing strengths of the tablets were generally independent of the amount of Surelease applied (Table 10.1).

These results are in agreement with those published by Liu et al (1993) who showed that increasing the amount of water used in the preparation of HPMC granules lowered the hardness of the resultant tablets. Similar findings have been reported for other cellulose derivatives. Microcrystalline cellulose (MCC) pellets, granulated with water, resisted rupture on compaction due to the high bond strength (Millili and Schwartz, 1990). This resulted in low surface to surface contacts for bonding, thus producing weaker tablets. Similarly Schwartz et al (1994) claimed that MCC beads prepared by extrusion/spheronisation using water were hard and did not easily deform.

Table 10.1. Crushing strengths of tablets (kP) prepared from physical mixtures and granules containing different amount of Surelease.

Tablets prepared from:	Metoclopramide hydrochloride	Diclofenac sodium
Physical mixture	7.60 ± 0.17	6.43 ± 0.26
Water granulated	2.13 ± 0.09	3.03 ± 0.05
Granules containing 14.28% Surelease	2.50 ± 0.21	3.10 ± 0.04
Granules containing 25% Surelease	3.36 ± 0.12	3.50 ± 0.22
Granules containing 33.33% Surelease	2.73 ± 0.12	3.67 ± 0.19

Table 10.2 illustrates the porosities of the tablet. The porosities of the tablets increased, for both drugs, after granulation. Therefore the low crushing strenghts of tablets prepared from granules may be ascribed to the higher pororsities of these

tablets. The porosities were generally independent of the amount of Surelease used.

Table 10.2. Porosities of tablets (%) prepared from physical mixtures and granules containing different amounts of Surelease.

Tablets prepared from:	Porosity (%)	
	Metoclopramide hydrochloride	Diclofenac sodium
Physical mixture	8.40 ± 0.08	9.89 ± 0.16
Water granulated mixture	15.27 ± 0.17	13.03 ± 0.15
Granules containing 14.28% Surelease	16.03 ± 0.38	13.45 ± 0.34
Granules containing 25% Surelease	15.03 ± 0.05	13.62 ± 0.45
Granules containing 33.33% Surelease	15.90 ± 0.16	16.01 ± 0.12

10.3.2 RELEASE OF METOCLOPRAMIDE HYDROCHLORIDE FROM MATRICES PREPARED BY WET GRANULATION

The addition of Surelease caused a dramatic decrease in the amount of metoclopramide hydrochloride released from matrices compared to those granulated with water (Figure 10.1). The release rates were slightly higher for the mixture granulated with water compared to the physical mixture (Table 9.4). The release rates considerably decreased as the amount of Surelease increased in the granules (Table 10.3). Square-root kinetics was probably the most applicable model for matrices containing 14.28% and 25% Surelease. However for matrices containing 33.33% Surelease, the square-root, first-order and Hixon Crowell models gave the close values of correlation coefficients (Table 10.3). When the data were fitted to equations 1.6 and 1.7, equation 1.7 gave the best fit (Table 10.5). The values of exponent n were in the range of $0.46 < n < 0.62$ indicating both erosion and

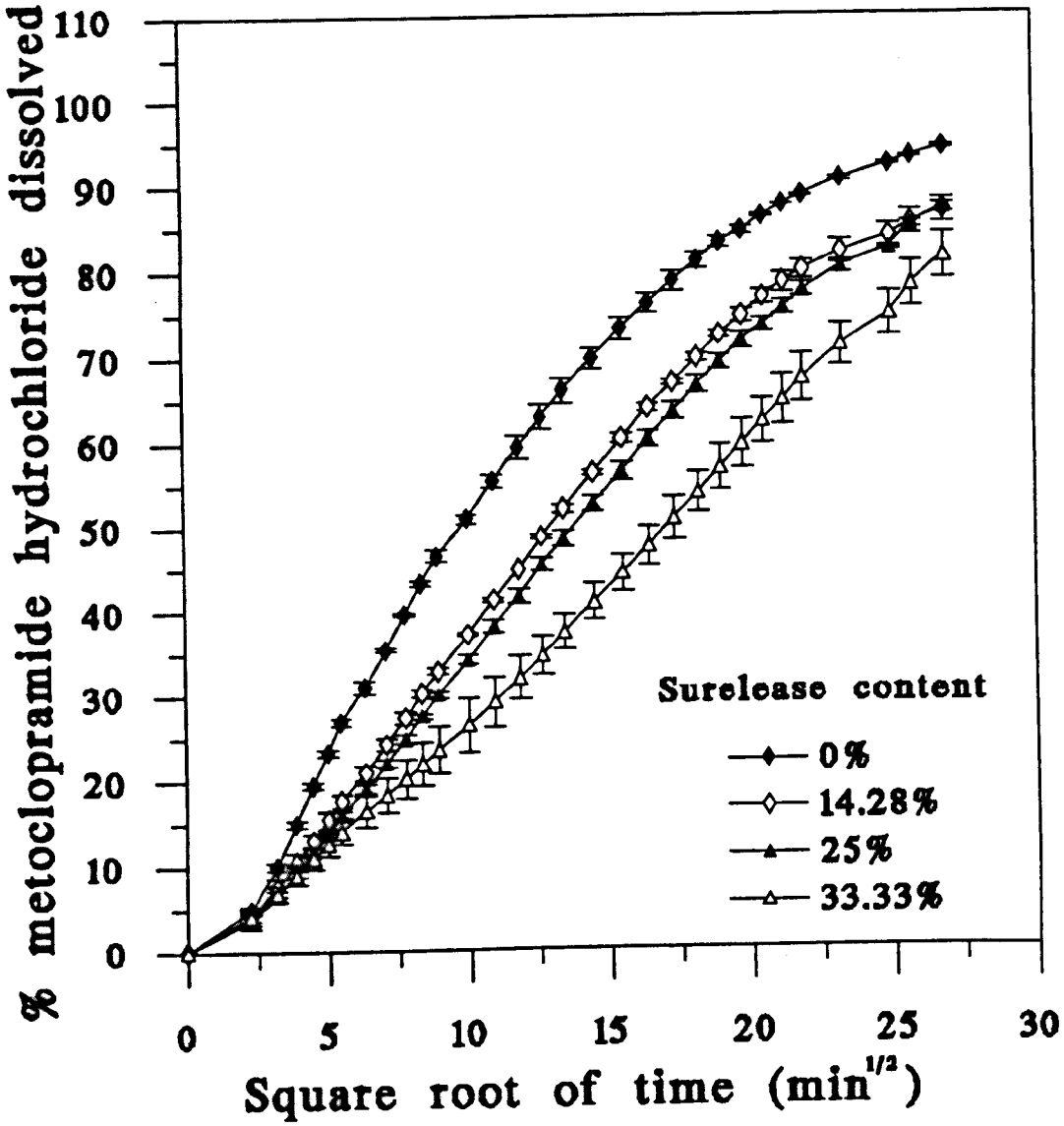


Figure 10.1. The effect of Surelease content on the release of metoclopramide hydrochloride from matrices containing 1:5 drug:HPMC K4M prepared by wet granulation.

Table 10.3. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of metoclopramide hydrochloride from 1:5 drug:HPMC K4M matrices containing different amounts of Surelease prepared by wet granulation, using equations 1.1-1.4.

Model	*	Percent of Surelease in the granules			
		0% (water granulated)	14.28%	25%	33.33%
Zero-order (Equation 1.1)	K_1	0.33 ± 0.01	0.20 ± <0.01	0.17 ± <0.01	0.12 ± 0.01
	r	0.967	0.985	0.987	0.993
	P<	0.001	0.001	0.001	0.001
	t1	-44.6 ± 0.8	-69.5 ± 0.9	-76.93 ± 0.9	-110.1 ± 15.2
Square-root (Equation 1.2)	K_2	5.5 ± 0.1	4.3 ± 0.1	4.1 ± <0.1	3.2 ± 0.3
	r	0.996	0.999	1	0.998
	P<	0.001	0.001	0.001	0.001
	t2	0.7 ± <0.1	1.9 ± 0.1	2.5 ± 0.1	2.5 ± 1.7
First-order (Equation 1.3)	K_3	0.0057 ± 0.0002	0.0034 ± 0.0001	0.0029 ± 0.0002	0.0021 ± 0.0002
	r	0.991	0.998	0.998	0.999
	P<	0.001	0.001	0.001	0.001
	t3	-20.1 ± 1.4	-26.7 ± 0.4	-29.9 ± 0.8	-44.7 ± 8.9
Hixon-Crowell (Equation 1.4)	K_4	0.0074 ± 0.0002	0.0045 ± 0.0001	0.0039 ± <0.0001	0.0027 ± 0.0003
	r	0.985	0.995	0.996	0.998
	P<	0.001	0.001	0.001	0.001
	t4	-28.4 ± 2.5	-40.3 ± 1.0	-44.65 ± 0.8	-65.2 ± 11.1

* Key: The units of release constants are: K_1 ($\%min^{-1}$), K_2 ($\%min^{-1/2}$), K_3 (min^{-1}), K_4 ($\%^{1/3}min^{-1}$) and the units of the lag times corresponding to different equations (1.1-1.4) t_1, t_2, t_3 and t_4 are min. P is the degree of significance.

diffusion contributed to the control of drug release. The release exponent increasedas the Surelease content of the granules increased suggesting a shift of release mechanism towards erosion.

10.3.3 RELEASE OF DICLOFENAC SODIUM FROM MATRICES PREPARED BY WET GRANULATION

Incorporation of Surelease had little retarding effect on the release rate of diclofenac sodium from matrices compared to those prepared using water as a granulating agent (Figure 10.2 and Table 10.4). The release rates of tablets prepared from mixtures granulated with water were similar to those of physical mixtures (Table 9.8). Again due to close values of (r) it for the square-root, first-order and Hixon-Crowell model it was not possible to consider one model as the best fit.

The values of exponent n (equation 1.7) were in the range of $0.51 < n < 0.60$ indicating both erosion and diffusion controlled drug release mechanism (Table 10.6). The release exponents were similar for tablets containing different amounts of Surelease. These values also resembled those obtained for physical mixtures of the drug and HPMC K4M (1:5 drug:HPMC K4M; Table 9.16).

10.4 GENERAL DISCUSSION

Comparison of the release rates for tablets prepared from water-granulated mixtures with those of directly compressed mixtures (chapter 9) shows that former mixtures exhibited similar release rates for diclofenac sodium and slightly faster rate for

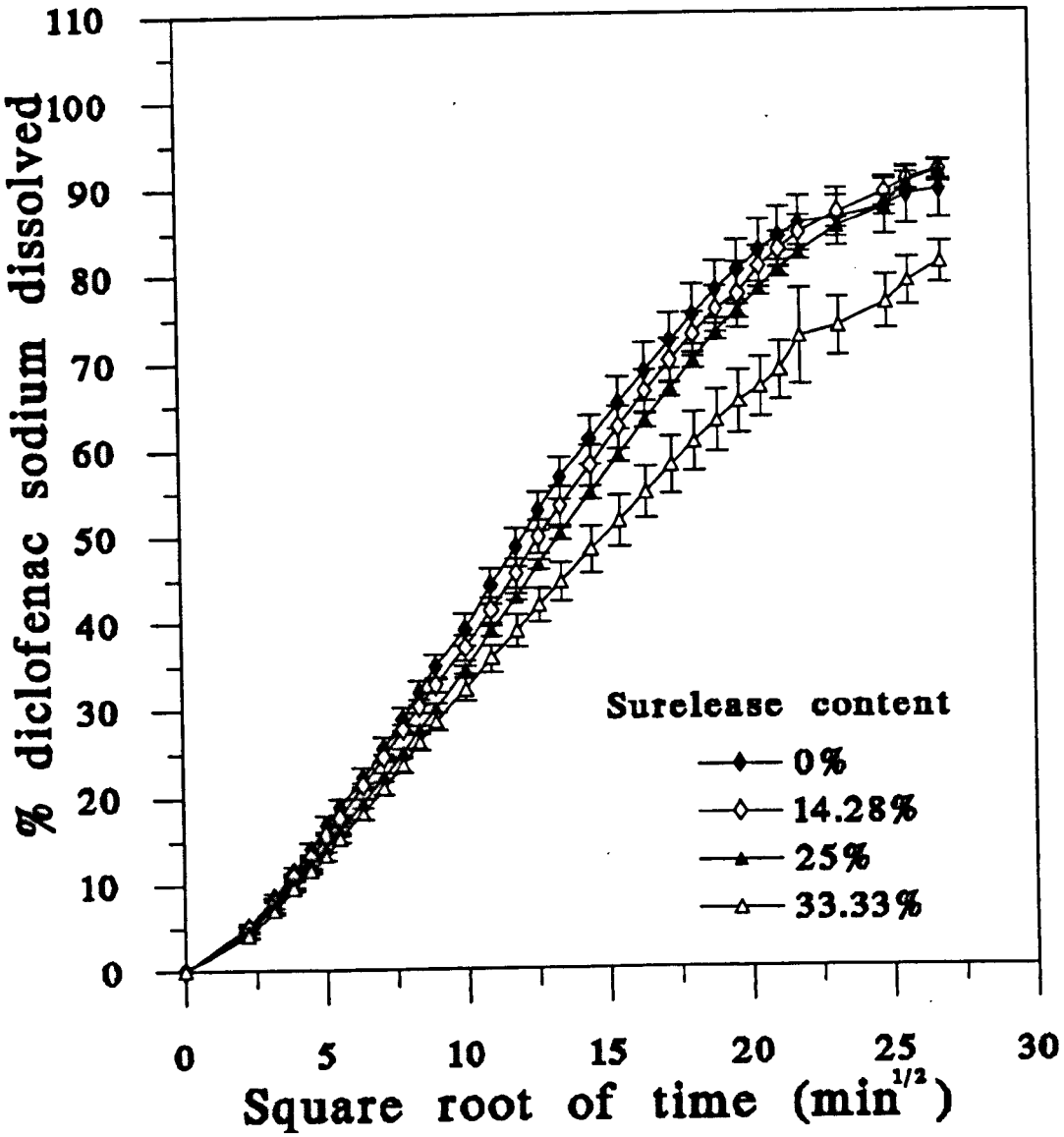


Figure 10.2. The effect of Surelease content on the release of diclofenac sodium from matrices containing 1:5 drug:HPMC K4M prepared by wet granulation.

Table 10.4. Values of release constants (K), correlation coefficients (r) and lag times (t) obtained from data corresponding to 15-60% release of diclofenac sodium from 1:5 drug:HPMC K4M matrices containing different amounts of Surelease prepared by wet granulation, using equations 1.1-1.4.

Model	*	Percent of Surelease in the granules			
		0% (water granulated)	14.28%	25%	33.33%
Zero-order (Equation 1.1)	K_1	0.24 ± 0.01	0.22 ± 0.01	0.20 ± <0.01	0.14 ± 0.01
	r	0.987	0.990	0.991	0.981
	P<	0.001	0.001	0.001	0.001
	t1	-52.6 ± 2.7	-57.4 ± 3.5	-58.3 ± 1.7	-112.6 ± 8.9
Square-root (Equation 1.2)	K_2	4.7 ± 0.2	4.5 ± 0.2	4.3 ± <0.1	3.5 ± 0.2
	r	0.998	0.998	0.998	0.999
	P<	0.001	0.001	0.001	0.001
	t2	2.3 ± 0.4	2.4 ± 0.7	3.2 ± 0.3	1.1 ± 0.6
First-order (Equation 1.3)	K_3	0.0041 ± 0.0002	0.0037 ± 0.0002	0.0034 ± 0.0001	0.0025 ± 0.0002
	r	0.999	0.999	0.999	0.997
	P<	0.001	0.001	0.001	0.001
	t3	-18.9 ± 3.4	-22.9 ± 4.1	-22.4 ± 2.7	-50.7 ± 10.7
Hixon-Crowell (Equation 1.4)	K_4	0.0053 ± 0.0004	0.0048 ± 0.0003	0.0044 ± <0.0001	0.0031 ± 0.0003
	r	0.997	0.997	0.998	0.994
	P<	0.001	0.001	0.001	0.001
	t4	-30.4 ± 2.4	-33.3 ± 3.9	-32.3 ± 0.7	-68.6 ± 9.2

* Key: See table 10.3.

metoclopramide hydrochloride. These findings are not in agreement with those reported by Mandal (1995) who stated that the amount of drug dissolved from wet granulated HPMC tablets were considerably higher than from directly compressed matrix formulations. The slight increase in the release rate of metoclopramide hydrochloride after granulation seen in this study, could be due to the higher porosity of the tablets prepared from granules (Table 10.2).

The release rates of metoclopramide hydrochloride were slower than diclofenac sodium from Surelease granulated matrices at equivalent Surelease content. On the other hand incorporation of Surelease into the HPMC matrix had little effect on the release of diclofenac sodium from granulated matrices while the release of metoclopramide hydrochloride was considerably affected by the amount of Surelease added. Kawashima et al (1989) reported that different release patterns could be observed from matrices containing different drug types and prepared using aqueous dispersions of Eudragit. Kawashima et al (1989) showed that although Eudragit NE 30D was an effective polymer in retarding the release of theophylline from matrices prepared by wet granulation, it was less effective in matrix tablets containing propranolol hydrochloride. Klinger et al (1990) showed that the incorporation of 5.2% Surelease into a matrix formulation containing theophylline and hydrous lactose prolonged the drug release. In another part of their study, increasing the amount of Surelease from 4.2% to 16.6% in a formulation containing chlorpheniramine maleate and dicalcium phosphate dramatically decreased the release rate of the drug.

As mentioned before, Surelease contains 0.8-1% w/w ammonia. It was shown in section 8.3.2.1 that metoclopramide hydrochloride precipitated in the 0.5% ammonia solution as a metoclopramide base. Additionally the passage of metoclopramide hydrochloride through a dialysis tube reduced to a great extent in the presence of Surelease (8.3.2.2.1) while no significant difference was evident for the passage of diclofenac sodium in the presence of Surelease. Therefore it may be concluded that the slow release of metoclopramide from Surelease granulated tablets compared to the water granulated tablet was due to the formation of metoclopramide base.

Comparison of the exponent n for metoclopramide hydrochloride or diclofenac sodium release from granulated matrices showed that drug release mechanism for both drugs from Surelease granulated mixtures was non-Fickian diffusion. In other words coupling of diffusion and erosion contributed to the release. The release exponent n for metoclopramide hydrochloride shifted to a higher value when the Surelease content reached 33.33% (Table 10.5). This may be explained by the fact that the highly water soluble metoclopramide hydrochloride was converted to its base form upon addition of Surelease which has a much lower solubility (Pitre and Stradi, 1987). Decrease in drug solubility meant that the role of erosion in the release mechanism increased. However Dabbagh et al (1996) showed that the value of n remained unchanged as the proportion of ethycellulose powder in the admixtures of HPMC and ethylcellulose increased. For diclofenac sodium matrices, the increase in Surelease content in the granules had no apparent effect on the drug release mechanism.

Table 10.5 The values of K_1, n based on equation 1.6 and K_2, n, l, based on equation 1.7 calculated in the range of 15-60% metoclopramide hydrochloride release, from matrices of 1:5 drug:HPMC K4M containing different amounts of Surelease and prepared by wet granulation. The values of the sums of squares of errors (ss) and Schwartz criteria are also given.

Percent Surelease in matrix	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	n	l*	ss	Schwartz
0	4.16	0.54	55.00	65.52	6.69	0.45	7.94	6.83	36.94
14.28	2.45	0.59	9.93	44.69	3.32	0.53	6.88	1.33	13.40
25	2.18	0.59	7.70	40.36	2.96	0.54	7.93	1.19	11.51
33.33	1.85	0.58	3.88	34.54	1.47	0.62	-7.62	0.96	8.47

* Key: The unit of K_1 and K_2 are $\%min^{-n}$ and the unit of l is min.

Table 10.6 The values of K_1, n based on equation 1.6 and K_2, n, l, based on equation 1.7 calculated in the range of 15-60% diclofenac sodium release, from matrices of 1:5 drug:HPMC K4M containing different amounts of Surelease and prepared by wet granulation. The values of the sums of squares of errors (ss) and Schwartz criteria are also given.

Percent Surelease in matrix	Equation 1.6				Equation 1.7				
	K_1^*	n	ss	Schwartz	K_2^*	n	l*	ss	Schwartz
0	2.41	0.60	5.77	33.59	2.96	0.57	4.35	2.84	25.04
14.28	2.25	0.61	2.86	22.36	2.72	0.57	4.02	0.73	3.24
25	1.96	0.62	1.82	15.80	2.22	0.60	2.79	0.83	5.35
33.33	2.44	0.55	11.40	52.11	3.31	0.51	9.06	1.97	21.66

* Key: See table 10.5.

10.5 CONCLUSIONS

The incorporation of Surelease into HPMC matrices affected the release of metoclopramide hydrochloride and diclofenac sodium to different extents. However, zero-order release was not obtained for either drug. The release of metoclopramide hydrochloride decreased as the Surelease content in the granules increased. The release of diclofenac sodium was less affected by incorporation of Surelease into the HPMC K4M matrices.

The release mechanism for both drugs was a combination of diffusion and erosion. Incorporation of Surelease into the matrices shifted the mechanism of release of metoclopramide hydrochloride to a more erosion-controlled system compared to water granulated matrices. However, the mechanism of release of diclofenac sodium was hardly affected by use of Surelease.

CHAPTER 11. GENERAL DISCUSSION

11.1 INTRODUCTION

One of the greatest opportunities in the field of pharmaceutical industry lies in conversion of standard solid oral dosage forms to safer, more convenient or more effective controlled-release formulations. Today several types of oral controlled-release products have been designed to release the drug at various rates. They are mainly classified either as multiparticulate systems such as pellets or single-unit systems such as tablets. Basically in all these systems the release of drug is controlled by diffusion either through a membrane (reservoir devices) or within a carrier (matrix systems) and/or dissolution of the membrane or carrier.

Polymeric materials are considered to be essential for achieving controlled delivery of drugs. Cellulose ethers are the most commonly used polymers in the preparation of oral controlled-release formulations. Among the cellulose ethers, hydroxypropylmethylcellulose and ethylcellulose are used extensively as diffusion barriers in the fabrication of all types of controlled release formulations.

This study investigated the application of the hydrophilic polymer, hydroxypropylmethylcellulose of different viscosities, and the hydrophobic polymer, ethylcellulose (as an aqueous dispersion) and their mixtures in the preparation of controlled-release pellets and matrices using two structurally different model drugs metoclopramide hydrochloride and diclofenac sodium. The effects of polymer content

on the release rates and mechanisms of release were investigated for each system. In addition the rates and mechanisms of release of both drugs were compared.

11.2 DRUG RELEASE FROM PELLETS

11.2.1 APPLICATION OF HPMC IN COATED PELLETS

Metoclopramide hydrochloride-layered pellets were coated with HPMC E5 or HPMC E15 up to a coating load of 20% w/w. As these polymers produced similar release profiles for the release of metoclopramide hydrochloride, pellets layered with diclofenac sodium were therefore only coated with HPMC E15 up to the 20% w/w coating load. The release of either drug was dependent, to a large extent, on the total content of the polymer present in the coat. Wan et al (1995b), similarly, demonstrated that the release of chlorpheniramine maleate from pellets decreased as the coating load of HPMC (Metolose 60-SH, 400 mPa.s) increased. All the HPMC coated-pellets disintegrated during the dissolution test and no gel like structure remained at the end of dissolution studies indicating that complete erosion of the membrane and the pellets had taken place, even at the 20% w/w coating load.

The reduction in the release rates with increased coating load was attributed to the increased diffusional path length. On the other hand, with increasing coating thickness, the resulting gel would become thicker and therefore its resistance to penetration by water and to erosion would increase (Wan and Lai, 1991). This would lead to a decrease in the release rate of the drug out of the gelled coat. Although the increasing coating load of HPMC E5 or HPMC E15 decreased the release rates of

both drugs, the majority of both drugs (> 90%) was released within approximately 1 h, even at the 20% w/w coating load of HPMC E5 or HPMC E15, indicating that the release was not controlled by applying a HPMC membrane.

Comparison of the release data for metoclopramide hydrochloride and diclofenac sodium pellets coated revealed that diclofenac sodium was released slightly more slowly than metoclopramide hydrochloride at equivalent coating loads. This was attributed to the higher water solubility of the metoclopramide hydrochloride than diclofenac sodium.

In order to understand the mechanism of drug release, data were fitted to two mathematical models (equations 1.6 and 1.7). In all cases equation 1.7, proposed by Ford et al (1991a), gave the better fit than equation 1.6, proposed by Korsmeyer et al (1983a). The value of exponent n was in the range of $0.42 < n < 0.50$ and $0.42 < n < 0.54$ for the release of metoclopramide hydrochloride from HPMC E5 and HPMC E15 coated pellets, respectively, indicating that diffusion was the predominant mechanism controlling drug release. The corresponding values for diclofenac sodium were $0.42 < n < 0.55$ which again indicates that the release mechanism was predominantly diffusion controlled. The similar values of n for each drug indicated that drug solubility may have little effect on the mechanism of drug release from HPMC coated pellets.

11.2.2 APPLICATION OF SURELEASE IN COATED PELLETS

Metoclopramide hydrochloride or diclofenac sodium-layered pellets were coated with Surelease to different thicknesses up to 20% coating load. The coating load had a major effect on the ultimate rate of drug release and the duration of the lag times prior to controlled release. In other words the release rates of both drugs dramatically decreased as the coating load of Surelease increased. Similar results have been reported by other workers (Ghebre-Sellassie et al, 1988; Porter, 1989a; Ozturk et al, 1990; Maganti and Celik, 1994). All the pellets remained intact during the dissolution test indicating that the Surelease membrane controlled drug release.

Generally, in coated dosage forms the membrane properties and geometry, such as membrane porosity, internal structure (tortuosity) and the membrane thickness critically affect the release rate of a drug (Tojo and Miyanami, 1983). It was shown that the distribution of pores was greater at low coating loads of Surelease. Therefore, the permeability of both drugs through the coating was rather high when there was a small amount of coating because of coating imperfections. On the other hand, the coating layer was thicker as the load increased. Therefore, the path length for diffusion of the dissolution medium to enter the core and for the dissolved drug to come out through the coat would also be increased.

It has been claimed that the aqueous solubility of a drug plays an important role in the release of a drug from coated pellets. Highly water soluble drugs are generally released faster than poorly water soluble compounds (Ghebre-Sellassie et al, 1988;

Iyer et al, 1990). This has been reported to be mainly due to the different rates of migration of the drugs during the coating process. During film deposition, highly water soluble drugs dissolve in the sprayed droplets and remained embedded in the film after the evaporation of water. As more and more layers of film are applied, the migration of drug diminishes. Since the presence of the drug in the inner layers of the coating leads to a porous structure during dissolution, a thicker coat is required to generate a specific release profile than would be the case with poorly water soluble drugs (Ghebre-Sellassie et al, 1987).

It was thought that metoclopramide hydrochloride, due to its higher solubility, might migrate to a greater extent than diclofenac sodium into the Surelease coat during its application and therefore should be released faster than diclofenac sodium. However it was observed that when metoclopramide hydrochloride was added to ammoniated water containing similar amounts of ammonia to diluted Surelease, a precipitate was formed. The melting point of the precipitate corresponded to the melting point of metoclopramide base (Mitchell, 1985). However, diclofenac sodium is freely soluble at pH > 6. Therefore it might be more prone to migrate into the Surelease than metoclopramide hydrochloride.

A comparison of the release profiles for metoclopramide hydrochloride and diclofenac sodium coated with Surelease revealed that despite its solubility, diclofenac sodium showed faster release rates than metoclopramide hydrochloride at equivalent coating loads. For example the first-order release rate of diclofenac

sodium was 33% faster than the release rate of metoclopramide hydrochloride at the 20% w/w coating load. Therefore the results of this study indicated that water solubility may not be an important factor in controlling the release of drug from Surelease-coated pellets.

The drug release mechanism was evaluated by determining the release exponent n for both drugs. It was observed that the coating load of Surelease had no effect on the mechanism of the release of metoclopramide hydrochloride as the values of n were similar for all coating loads. The value of n was in the range of $0.54 < n < 0.62$ indicating that mechanism of release was mostly diffusion controlled. However the release mechanism of diclofenac sodium was dependent on the coating load of Surelease. The higher value of n for the 8% and 12% coating loads (1.02 and 0.75, respectively) indicates that the contribution of diffusion as a rate limiting step was reduced. This maybe attributed to the presenec of more pores at low coating loads of Surelease which facilitated the diffusion process. However at high coating loads diffusion mainly controlled the release of drug. The values of n for 16% and 20% coating loads were 0.50 and 0.55, respectively.

11.2.3 APPLICATION OF SURELEASE/HPMC E15 MIXTURES DIRECTLY ON DRUG-LAYERED PELLETS

The addition of water soluble polymers, such as HPMC, to ethylcellulose aqueous dispersions is used to increase the permeability of the resulting film (Ghebre-Sellassie et al, 1988; Gilligan and Po, 1991), although it has been shown that this

could result in flocculation of the ethylcellulose dispersion (Wong and Bodmeier, 1996). In this study, Surelease films containing 5%, 7.5% or 10% w/w HPMC E15 were applied onto drug-layered pellets up to the 20% w/w coating load. Again, coating load had a major effect on the rate of drug released. On the other hand increasing the HPMC content in the coats increased the release rates of both drugs at equivalent coating loads. For example, the first-order release rate of metoclopramide hydrochloride was more than three times faster when the HPMC content was 10% than when the HPMC content was 5% at a coating load of 20% w/w. High proportions of HPMC in the Surelease membrane caused a rapid release of both drugs even at high coating loads. Therefore the ratio of HPMC/Surelease had a major effect on the release rate. These results are in agreement with those reported by Kannikoski et al (1984) and Gilligan and Po (1991).

The durations of lag times increased with increasing coating load but they were reduced as the amount of HPMC in the coats increased. Neither variation in HPMC content of the film nor variation in coating thickness provided zero-order release of drugs.

Studies on free films suggested that the increase in the release rates upon inclusion of HPMC was probably due to the dissolution of HPMC which left pores in the coat for drug release. These results are different to those published by Donbrow and Samuelov (1980) who showed that hydroxypropylcellulose (HPC) remained in an ethylcellulose film and formed swollen hydrated channels in the coat. The difference

between the results of this study and those performed by Donbrow and Samuelov may be due to the differences in the types of cellulose ethers used. The reduced interaction of HPMC with ethylcellulose due to its increased substitution (Sakellariou et al. 1986) may be responsible for the leaching out of HPMC from these blends. The flocculation phenomena mentioned above, which could interfere with the film formation from a colloidal polymer dispersion (Wong and Bodmeier, 1996), may also account for the increased rate of drug release.

The inclusion of 5% HPMC considerably increased the release rate of diclofenac sodium while that of metoclopramide hydrochloride just showed a marginal increase. Additionally the lag time decreased to a greater extent than with metoclopramide hydrochloride. In general, diclofenac sodium release rates were faster than metoclopramide hydrochloride at similar HPMC contents in the film and coating loads suggesting that drug solubility again is not an important factor in the release from pellets coated with Surelease/HPMC mixtures.

These results ruled out the possibility that differences in the release rates of two drugs might be due to differences in their rates of diffusion through the Surelease coat. It might have been expected that diclofenac sodium with lower solubility, would have more affinity than metoclopramide hydrochloride for the hydrophobic ethylcellulose. Therefore, diclofenac sodium might diffuse more easily than metoclopramide hydrochloride through the Surelease film. If this were the case it would have been expected that where drug release occurred through the pores,

metoclopramide hydrochloride would be released faster than diclofenac sodium because of its higher water solubility. However, in pellets coated with Surelease/HPMC diclofenac sodium was again released faster than metoclopramide hydrochloride suggesting that differences in release rates of the two drugs were not related to the differences in their rates of diffusion through the coat.

Dialysis studies proved that the interaction of metoclopramide hydrochloride with the anionic surfactant, ammonium oleate, present in the Surelease resulted in the formation of a precipitate. This interaction is the most probable mechanism for the slower release of metoclopramide hydrochloride from Surelease coated pellets. The retarding effect of anionic surfactants on the release of cationic drugs from hydrophilic matrices (Ford et al, 1991b) and inert matrices (Wells and Parrott, 1992) has been reported. Complexation of drug with the surfactant decreased the solubility of the metoclopramide hydrochloride. In addition this complexation and subsequent precipitation provided a more tortuous pathway for drug release. The presence of HPMC would facilitate the formation of a precipitate between a cationic drug and an anionic surfactant (Ford et al, 1991b). This explanation may apply here to account for the marginal increase in the release rate of metoclopramide hydrochloride upon inclusion of 5% HPMC into the Surelease film compared to the marked increase in the release rate of diclofenac sodium.

For both drugs, coating load had no apparent effect on the value of n for each HPMC content in the film. Although the value of n for the release of

metoclopramide hydrochloride was in the range of $0.36 < n < 0.75$ the majority of the values of n were around 0.6. This indicates that, similar to pellets coated with Surelease, diffusion was the predominant mechanism controlling the release of metoclopramide hydrochloride from pellets coated with Surelease/HPMC E15.

However for diclofenac sodium, the values of n were in the range of $0.87 < n < 1.66$. A comparison of the value of the release exponent n with those obtained for pellets coated with Surelease solely showed that different mechanisms controlled release of diclofenac sodium from pellets coated with Surelease/HPMC blends and those coated with solely Surelease. The high value of n indicates the reduced contribution of diffusion as a rate limiting step in the release of drug. Therefore it is probable that the rate of pore formation controls drug release rate.

11.2.4 APPLICATION OF SURELEASE ON 2% HPMC E5 SEAL-COATED PELLETS

The application of a 2% seal-coat of HPMC to drug-layered pellets decreased the release rate of both drugs from Surelease coated pellets compared to pellets without a seal-coat at an equivalent coating load of Surelease. The retardation of drug release after application of a seal-coat has been reported and ascribed to the reduced drug migration during the application of the sustaining coat (Ghebre-Sellassie et al, 1987; Porter, 1989b; Yang and Ghebre-Sellassie, 1990). Application of a seal-coat had a profound effect on the release of diclofenac sodium from 4% Surelease coated pellets. While more than 70% of the drug was released in 5 min from 4% Surelease-

coated pellets without seal-coat, those pellets with a seal-coat, released only 20% of the drug in 5 min.

As the coating load of Surelease increased, the release rates progressively decreased. Similar to pellets coated with only Surelease, a lag time developed and became longer as the coating load increased. Although diclofenac sodium was released slightly more slowly than metoclopramide hydrochloride from seal-coated pellets at Surelease coatings of 4% and 8% w/w, at coating loads of ≥12% w/w, diclofenac sodium again showed higher release rates than metoclopramide hydrochloride. This indicates that the faster release of diclofenac sodium from Surelease-coated pellets at low coating loads was mostly due to the migration and/or interaction (coagulation of Surelease in the presence of Na^+) of the diclofenac sodium with Surelease during application. These findings are not surprising if we consider the high solubility of diclofenac sodium and also complete ionization of this drug at the high pH of the Surelease dispersion. However migration and/or interaction were not the only factors contributing to the faster release of diclofenac sodium from pellets coated with Surelease.

Additionally when the pellets with a 12% coating load of Surelease over a 2% seal-coat of HPMC E5 were cured at 60°C, the release rates of metoclopramide hydrochloride markedly increased while those of diclofenac sodium remained nearly unchanged. Opposite results were found by Bodmeier and Paeratakul (1994). These authors stated that marked increase in the release of the hydrophobic ibuprofen was

observed from Aquacoat coated pellets, while the release of hydrophilic chlorpheniramine maleate, depending on the plasticizer content in the film, decreased or remained unchanged, after curing. This was attributed to dissolution and diffusion of ibuprofen across the Aquacoat film following curing because of the high solubility of this drug in the film. In addition the low melting point of ibuprofen promoted the migration of drug into the coat during curing, while chlorpheniramine maleate did not diffuse into the coat due to its low affinity for the Aquacoat (Bodmeier and Paeratakul, 1994). The migration of metoclopramide hydrochloride into the Surelease coat, although unlikely to occur due to the hydrophilicity of this drug, was examined. No drug migration was observed for metoclopramide hydrochloride following curing.

The release of metoclopramide hydrochloride was faster than diclofenac sodium for 12% surelease coated pellets over a 2% seal-coat after curing.

After curing, the surfactant due to its unstable nature in heat is converted to its constituents. This may account for the increase in the release rate of metoclopramide hydrochloride after curing. The interaction of metoclopramide hydrochloride with ammonium oleate reduced as the concentration of surfactant decreased following curing. This led to faster release of metoclopramide hydrochloride after curing.

The values of the release exponent for metoclopramide hydrochloride were in the range of $0.51 < n < 0.69$ which resembled those of pellets coated with Surelease without any seal-coat. The corresponding values for diclofenac sodium were $0.56 <$

$n < 0.95$ which again were similar to those obtained for pellets coated with Surelease without a seal-coat. It should be mentioned that high values of n (~0.95) were only obtained for pellets with a low coating load of Surelease (8%), while for other coating loads the values of n were about 0.50-0.60 indicating that diffusion is the major mechanism controlling drug release. Therefore the presence of a 2% HPMC E5 seal-coat did not change the drug release mechanism for either drug compared to those coated with Surelease without a seal-coat.

11.2.5 APPLICATION OF SURELEASE ON DRUG-LAYERED PELLETS ALREADY COATED WITH 20% HPMC E15

The drug-layered pellets already coated with 20% w/w HPMC E15 were overcoated with Surelease up to a 12% w/w coating load. Drug release characteristics were completely different from pellets with a 2% seal-coat of HPMC E5. Pellets with a Surelease overcoat on 20% HPMC E15 undercoat released their drug at a faster rate than pellets with a 2% HPMC E5 seal-coat. The scanning electron micrographs of former pellets before and after dissolution tests revealed that there were big pores and cracks in the pellets undercoated with 20% HPMC E15 and overcoated with 12% Surelease. The presence of these cracks was attributed to the hydration and swelling of the HPMC undercoat which lead to the rupture of the Surelease overcoat. These cracks and pores accounted for the faster release rate from pellets with the 20% HPMC E15 undercoat than the 2% HPMC E5 seal-coat. The cracks penetrated the whole thickness of the Surelease coat for former pellets, therefore water solubility could play an important role in drug release. The comparison of

metoclopramide hydrochloride or diclofenac sodium release rates from pellets already coated with 20% HPMC and overcoated with Surelease showed that metoclopramide hydrochloride was released faster than diclofenac sodium.

The faster release of metoclopramide hydrochloride in this case could be due to its higher solubility in water than diclofenac sodium in water. The faster release of metoclopramide hydrochloride may also be ascribed to the build-up of a higher osmotic pressure in the core due to the higher solubility of this drug. In addition these drugs affect the swelling properties of HPMC in different manners. Diclofenac sodium reduces the cloud point of HPMC and dehydrates this polymer (Rajabi-Siahboomi et al, 1994a) while hydrochloride salts of organic compound increase the cloud point of HPMC and facilitate hydration of this polymer (Mitchell et al, 1993c). Therefore HPMC may swell to a greater extent in the presence of metoclopramide hydrochloride than in the presence of diclofenac sodium. The greater extent of swelling may create more cracks and therefore increase the release rate of metoclopramide hydrochloride to higher degree than diclofenac sodium.

The values of n were 0.64 and 0.73 for the release of metoclopramide hydrochloride from pellets with 8% and 12% w/w coating loads of Surelease, respectively. The corresponding values for diclofenac sodium were 0.85 and 1.18. These values of n are slightly higher than those obtained for pellets with a 2% seal-coat of HPMC E5 at equivalent Surelease coating loads. This suggested that the contribution of diffusion as a rate limiting step was reduced in these pellets. This may be explained

by the ease of diffusion due to the presence of the cracks in the Surelease coat and also the increased role of erosion of HPMC undercoat on drug release mechanism.

11.3 DRUG RELEASE FROM MATRICES

Hydroxypropylmethylcellulose E15, when used in a matrix, produced better control of drug release than when used as a coat on drug-layered pellets. For example the zero-order release rate of metoclopramide hydrochloride from 1:5 drug:HPMC E15 matrices was 0.48 $\%min^{-1}$ compared to 2.1 $\%min^{-1}$ for the 20% coating load of HPMC E15 (where the drug:HPMC E15 ratio is approximately 1:5). This was attributed to the faster dissolution of HPMC E15 applied on a large surface area of the pellets.

Generally, the release rates from HPMC matrices decreased as the polymer content in the matrices increased irrespective of the grade of polymer used. These findings are similar to findings of Ford et al (1985b), Ranga Rao et al (1990) and Mitchell et al (1993b).

Drug release from HPMC matrices was dependent on the viscosity of the HPMC used in the formulation. The rank order in HPMC release rate was HPMC E15> HPMC K100> HPMC K4M ≈ HPMC E4M. These results are in accord with those reported by Daly et al (1984), Liu et al (1992) and Gao et al (1996). However Salomon et al (1979), Ford et al (1985a, b) and Baveja et al (1988) stated that the viscosity of HPMC did not affect the release rate of a drug. Gao et al (1996)

considered that the viscosity of HPMC affects the matrix dissolution rate and development of the gel layer thickness only below a critical value of viscosity. They showed for matrices composed of HPMC above a limiting viscosity grade (HPMC K4M), gel composition and thickness were identical while for matrices composed of low viscosity grades of HPMC (HPMC K100 LV), swelling was inhomogeneous due to rapid erosion.

Release rates were faster for the more soluble metoclopramide hydrochloride than the less soluble diclofenac sodium at similar drug:HPMC ratio and equivalent HPMC grade. However, Zhang et al (1990) reported that there were no differences between the release rates of theophylline and chlorpheniramine maleate from HPMC E5 matrices. They claimed that in erodible devices containing polymers such as HPMC E5, drug release is independent of drug solubility.

Mathematical modelling showed that both diffusion and erosion contributed to the release of both drugs. The values of n were between, 0.53-0.64 for metoclopramide hydrochloride release from HPMC matrices with different viscosity grades. These values are similar to those obtained by Ford et al (1987) for the release of soluble drugs from HPMC K15M matrices (0.65-0.71).

The values of n for diclofenac sodium release from HPMC matrices with different viscosities were in the range of 0.59-0.80. Ford et al (1987) found the value of $0.61 < n < 0.67$ for release of theophylline from HPMC K15M matrices. Diclofenac

sodium although more soluble than theophylline showed similar values of n for release from HPMC K100, HPMC K4M or HPMC E4M matrices.

Release exponents for metoclopramide hydrochloride were generally lower than that of diclofenac sodium. This indicates that for the release of the less water soluble diclofenac sodium, the contribution of erosion to the overall mechanism of release was more than that of metoclopramide hydrochloride. This is in agreement with findings of Ford et al (1987) Skoug et al (1993), Pham and Lee (1994) and Tahara et al (1996) who stated that the release of water soluble drugs was controlled mainly by diffusion while for water insoluble drugs, release was predominantly erosion controlled.

It has been reported that HPMC K4M gel may have a greater diffusional resistance to water within the inner gel region than other grades (Rajabi-Siahboomi et al, 1996). However the results of this study indicated that the performance of HPMC K4M and HPMC E4M were similar for the release of metoclopramide hydrochloride or diclofenac sodium. These results are in agreement with those published by Mitchell et al (1993a) who reported that substitution type had little effect on the dissolution of propranolol hydrochloride.

11.4 APPLICATION OF SURELEASE IN HPMC K4M MATRICES

Surelease has been demonstrated to be an effective wet granulation binder for the production of matrix controlled release tablets (Colorcon technical data). The

Surelease was included in the matrices containing 1:5 drug:HPMC K4M using wet granulation. The prepared granules contained 1:5:1, 1:5:2 or 1:5:3 drug:HPMC K4M:Surelease.

The porosities of the tablets prepared from granules were higher than those prepared from physical mixtures. Correspondingly the crushing strengths of the tablet decreased following granulation of HPMC matrices with water or Surelease. Similarly Liu et al (1993) showed that increasing the amount of water used in the granulation of HPMC decreased the hardness of the resultant tablets.

The release rates of metoclopramide hydrochloride were greatly reduced by incorporating Surelease into the HPMC K4M matrices. However the release rate of diclofenac sodium was less affected by incorporation of Surelease. Previously Klinger et al (1990) reported that increasing the amount of Surelease from 4.2% to 16.6% in a formulation containing chlorpheniramine maleate and dicalcium phosphate dramatically decreased the release rate of the drug.

The slow release of metoclopramide from Surelease granulated matrices was attributed to the conversion of highly water soluble metoclopramide hydrochloride to metoclopramide base with much lower solubility at high pH of Surelease. Therefore care must be taken when using Surelease as granulating agent as its high pH may affect the solubility of the drugs which are sensitive to high pH.

The values of exponent n for metoclopramide hydrochloride were in the range of $0.46 < n < 0.62$ indicating both erosion and diffusion controlled release. The release exponent increased as the Surelease content of the granules increased. This suggests that erosion controlled mechanism become more important for granules containing higher amounts of Surelease compared to those containing lesser amounts of Surelease or water granulated matrices. Decrease in drug solubility may account for the increased role of erosion in the release mechanism.

The values of the exponent n for diclofenac sodium were in the range of $0.51 < n < 0.60$. For diclofenac sodium matrices the increase in Surelease content in the granules had no apparent effect on the drug release mechanism.

CHAPTER 12. CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE STUDIES

12.1 CONCLUSIONS

Hydroxypropylmethylcellulose, hydrophilic polymer, and commercially available ethylcellulose aqueous dispersion (Surelease) as hydrophobic polymer were used in the preparation of coated pellets as well as matrix tablets to provide controlled release of metoclopramide hydrochloride as a cationic very water soluble drug and diclofenac sodium as an anionic drug with lower water solubility.

Drug release from pellets coated with low viscosity grades of HPMC was decreased with increasing coating load of polymer but, overall, drug release was fast and the majority of both drugs was released in less than 1 h even at high coating load (20% w/w). Diclofenac sodium was released more slowly than metoclopramide hydrochloride from pellets coated with HPMC.

The coating load of Surelease had a great retarding effect on the release of both drugs either when directly applied on drug-layered pellets or applied onto a 2% seal-coat of HPMC E5. The release of either drug was sustained over 12 h at high coating loads of Surelease. No improvement in the release pattern towards zero-order release was observed with increasing coating load of Surelease. Incorporation of HPMC into the Surelease film increased the release of both drugs. The Surelease:HPMC ratio had a major effect on the release rate of both drugs. Drug solubility was not an important factor in the release of drug from Surelease or

Surelease/HPMC coated pellets. Diclofenac sodium was released faster than metoclopramide hydrochloride despite its lower solubility. Thermal treatment of Surelease-coated pellets increased the release of metoclopramide hydrochloride but did not have any profound effect on the release of diclofenac sodium. The different release behaviour of these two drugs was attributed mostly to the interaction between cationic metoclopramide hydrochloride with anionic surfactant in situ.

When Surelease was applied on the pellets already coated with 20% HPMC E15 release rates of either drug were higher than when Surelease was applied onto 2% HPMC E5 coated pellets. The development of cracks due to the swelling of HPMC accounted for the higher release rates.

Drug release from HPMC matrices was dependent on the solubility of the drug, polymer content and viscosity. When Surelease incorporated into HPMC K4M matrices, it retarded the release of metoclopramide hydrochloride to greater extent than diclofenac sodium. This was attributed to the precipitation of metoclopramide hydrochloride as its base form.

12.2 RECOMMENDATION FOR FUTURE STUDIES

1. The interaction between metoclopramide hydrochloride and ammonium oleate was proposed as a possible mechanism for the slower release of this drug than diclofenac sodium from Surelease-coated pellets. Thorough investigation of this interaction and the resulted precipitate is recommended.

2. As the ammonium oleate is an unstable surfactant it would be interesting to study the effect of aging and storage of the pellets in different conditions of temperature and humidity on the release of drugs from both cured and uncured pellets.

3. It would be interesting to compare sodium or hydrochloride salts of other drugs for their potential interaction with Surelease.

4. In this study an Accela-Cota (a perforated coating pan) was used to apply coating formulation. Since the drying efficiency of the coating pans is low it is recommended to use other coating techniques such as fluidized bed devices and investigate the drug release characteristics.

5. It would also be useful to compare other commercially available ethylcellulose aqueous dispersions (eg. Aquacoat) which contain sodium lauryl sulphate as an anionic surfactant to see whether or not the differences between the release of these two drugs are maintained.

6. In this study the application of Surelease on pellets already coated with 20% HPMC E15 was studied. It would be interesting to investigate the potential of Surelease coat to provide zero-order release of these two drugs from their matrices using different contents and viscosity grades of HPMC.

ABBREVIATIONS

ΔH_f	Enthalpy of Fusion
ε	Porosity
µm	Micrometer
τ	Tortuosity
BDH	British Drug Houses
C	Concentration
C_s	Solubility
D	Diffusion coefficient
DS	Degree of substitution
DSC	Differential Scanning Calorimetry
EC	Ethylcellulose
g	Gram
h	Hour
HPMC	Hydroxypropylmethycellulose
HPMCP	Hydroxypropylmethycellulose phthalate
J	Joule
K_a	Rate of absorption
kg	Kilo gram
kN	Kilo Newton
kp	Kilo Pound
K_r	Rate of release
kV	Kilo Volt
M	Mole
mg	Milligram
min	Minute
ml	Millilitre
mm	Millimetre
mN	mili Newton
nm	Nanometre
PEG	Polyethylene glycol

pK_a	Negative logarithm of the Dissociation constant
psi	Pounds per square inch
r	Correlation Coefficient
SD	Standard Deviation
SEM	Scanning Electron Microscopy
ss	Sums of squares of errors
T_g	Glass transition temperature
T_m	Melting point
TMA	Thermomechanical analysis
T_s	Softening point
USP	United State Pharmacopoeia
UV	Ultraviolet
w/w	Weight in Weight

REFERENCES

Abrams, J. *Am. J. Med.* 75 (1984) 38-46.

Adeyeye, C.M. and Li, P.K. In *"Analytical Profiles of Drug Substances"*. (Ed) Florey, K. Academic Press, San Diego. 19 (1990) 123-144.

Alderman, D.A. *Int. J. Pharm. Tech. Prod. Mfr.* 5 (1984) 1-9.

Alpar, H.O. and Walters, V. *J. Pharm. Pharmacol.* 33 (1981) 419-422.

Arwidsson, H., Hjelstuen, O., Ingason, D. and Graffner, C. *Acta. Pharm. Nord.* 3 (1991) 65-70.

Aulton, M.E. and Abdul-Razzak, M.H., Hogan, J.E. *Drug Dev. Ind. Pharm.* 7 (1981) 649-668.

Bain, J.C., Tan, S.B., Ganderton, D. and Solomon, M.C. *Drug Dev. Ind. Pharm.* 17 (1991) 215-232.

Baker, R.W. In *" Controlled Release of Biologically Active Agents"*. (Ed) Baker, R.W. John Wiley and Sons, New York. (1987) 1-21.

Baveja, S.K., Ranga Rao, K.V. and Padmalatha Devi, K. *Int. J. Pharm.* 39 (1987) 39-45.

Baveja, S.K., Ranga Rao, K.V., Singh, A. and Gombar, V.K. *Int. J. Pharm.* 41 (1988) 55-62.

Bechgaard, H. *Acta Pharm. Tech.* 28 (1982) 149-157.

Bechgaard, H. and Nielsen, G.H. *Drug Dev. Ind. Pharm.* 4 (1978) 53-67.

Benita, S. and Donbrow, M. *Int. J. Pharm.* 12 (1982) 251-264.

Bertelsen, P., Christensen, F.N., Holm, P. and Jorgensen, K. *Int. J. Pharm.* 111 (1994) 117-125.

Bettini, R., Colombo, P., Massimo, G., Catellani, P.L. and Vitali, T. *Eur. J. Pharm. Sci.* 2 (1994) 213-219.

Bianchini, R., Bruni, G., Gazzaniga, A. and Vecchio, C. *Drug dev. Ind. Pharm.* 19 (1993) 2021-2041.

Bianchini, R. and Vecchio, C. *Boll. Chim. Farm.* 126 (1987) 441-448.

Bodea, A., Bakri, A., Jeannin, C. and Leucuta, S.E. *Proceed. 1st World Meeting*

APGI/APV. (1995) 261-262.

Bodmeier, R. and Paeratakul, O. *Pharm. Res.* 6 (1989) 725-731.

Bodmeier, R. and Paeratakul, O. *Int. J. Pharm.* 70 (1991) 59-68.

Bodmeier, R. and paeratakul, O. *Drug Dev. Ind. Pharm.* 20 (1994) 1517-1533.

Bonferoni, M.C., Rossi, S., Ferrari, F., Bertoni, M. and Caramella, C. *Proceed. 14th Pharm. Tech. Conference.* 1a (1995) 438-446.

Borodkin, P. and Tucker, F.E. *J. Pharm. Sci.* 63 (1974) 1359-1364.

Borodkin, P. and Tucker, F.E. *J. Pharm. Sci.* 64 (1975) 1289-1294.

Brown, G.L. *J. Polym. Sci.* 22 (1956) 423-434.

Caramella, C., Gazzaniga, A., Iamartino, P. and Ravelli, V. *Pharm. Tech. Eur.* February (1995) 18-26.

Catellani, P., Vaona, G., Plazzi, P., Colombo, P. *Acta. Pharm. Technol.* 34 (1988) 38-41.

Chambliss, W.G. In *"Pharmaceutical pelletization technology"*. (Ed) Ghebre-Sellassie, I. Marcel Dekker, New York. (1989) 15-38.

Chang, R.K. and Hsiao, C. *Drug Dev. Ind. Pharm.* 15 (1989) 187-196.

Chang, R.K., Hsiao, C.H. and Robinson, J. *Pharm. Tech.* 11 (1987) 56-68.

Chang, R.K. and Robinson, J.R. In *"Pharmaceutical Dosage Forms: Tablets"*. Vol III. (Eds) Liberman, L. and Schwartz, J.B. Marcel Dekker, New York. (1990) 199-302.

Chang, R.K., Price, J.C. and Hsiao, C. *Drug Dev. Ind. Pharm.* 15 (1989) 361-372.

Cheong, L.W.S., Heng, P.W.S. and Wong, L.F. *Pharm. Res.* 9 (1992) 1510-1514.

Chow, M.S.S. *U.S. Pharmacist.* February (1987) 58, 63-65, 68-70, 130.

Coletta, V. and Rubin, H. *J. Pharm. Sci.* 53 (1964) 953-955.

Colombo, P. *Advanced Drug Delivery Reviews*, 11 (1993) 37-57.

Colombo, P., Bettini, R., Santi, P., De Ascentiis, A. and Peppas, N.A. *J. Control. Rel.* 39 (1996) 231-237.

Connie, J.W. and Hadley, H.R. *Drug. Cos. Ind.* 90 (1970) 38-41.

Conte, U., Maggi, L., Colombo, P. and La Manna, A. *J. Control. Rel.* 26 (1993) 39-47.

Dabbagh, M.A. *"Performance and Characteristics of Controlled Release Matrices Composed of Hydroxypropylmethylcellulose and Other Polymers"*. Ph.D thesis. Liverpool John Moores university (1995).

Dabbagh, M.A., Ford, J.L., Rubinstein, M.H., Hogan, J.E. *Int. J. Pharm.* 140 (1996) 85-95.

Dahl, T.C. Calderwood, T., Bormeth, A. and Trimble, K. *J. Control. Rel.* 14 (1990) 1-10.

Daly, P.B., Davis, S.S. and Kennerley, J.W. *Int. J. Pharm.* 18 (1984) 201-205.

Dansereau, R., Brock, M. and Redman-Furey, N. *Drug Dev. Ind. Pharm.* 19 (1993) 793-808.

Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R. and Wilson, C.G. *Int. J. Pharm.* 21 (1984) 167-177.

de Labouret, A., Thioune, O., Fessi, H., Devissaguet, J.P. and Puisieux, F. *Drug Dev. Ind. Pharm.* 21 (1995) 229-241.

Devereux, J.E., Newton and Short, M.B. *J. Pharm. Pharmacol.* 42 (1990) 500-501.

Dillon, R.E., Matheson, L.A. and Bradford, E.B. *J. Colloid. Sci.* 6 (1951) 108-117.

Doelker, E. In *"Hydrogels in Medicine and Pharmacy"*. Vol. II polymers. (Ed) Peppas, N.A. CRC press, Philadelphia. (1987) 115-160.

Donbrow, M. and Benita, S. *J. Pharm. Pharmacol.* 34 (1982) 547-551.

Donbrow, M. and Friedman, M. *J. Pharm. Pharmacol.* 27 (1975) 633-646.

Donbrow, M. and Samuelov, Y. *J. Pharm. Pharmacol.* 32 (1980) 463-470.

Dressman, J.B., Derbin, G.M., Ismailos, G., Jarvis, C., Ozturk, A., Palsson, B.O. and Wheatley, T.A. *J. Control. Rel.* 36 (1995) 251-260.

Dyer, A.M., Khan, K.A. and Aulton, M.E. *Drug Dev. Ind. Pharm.* 21 (1995) 1841-1858.

El-Mahrouk, G.M., Al-Meshal, M.A., Al-Angary, A.A. and Mahrous, G.M. *Drug Dev. Ind. Pharm.* 19 (1993) 1903-1916.

Eskilson, C. *Manuf. Chem.* 56 (1985) 33-39.

Feely, L. and Davis, S.S. *Int. J. Pharm.* 41 (1988a) 83-90.

Feely, L. and Davis, S.S. *Int. J. Pharm.* 44 (1988b) 131-139.

Fiese, E.F. and Hagen, T.A. In *" The Theory and Practice of Industrial Pharmacy"*. (Eds) Lachman, L., Liberman, H.A. and Kanig, J.L. Lea & Febiger, Philadelphia. (1986) 179-180.

Fites, A.L., Banker, G.S. and Smolen, V.F. *J. Pharm. Sci.* 59 (1970) 610-613.

Flament, M.P., Leterme, P., Gayot, A., Gendrot, E., Bruna, E. and Cousin, G. *Pharm. Tech. Eur.* February (1994) 19-25

Follonier, N. and Doelker, E. *S.T.P. Pharma. Sci.* 2 (1992) 141-158.

Ford, J.L., Rubinstein, M.H. and Hogan, J.E. *Int. J. Pharm.* 24 (1985a) 327-338.

Ford, J.L., Rubinstein, M.H. and Hogan, J.E. *Int. J. Pharm.* 24 (1985b) 339-350.

Ford, J.L., Rubinstein, M.H. and Hogan, J.E. *J. Pharm. Pharmacol.* 37 (1985c) 115p.

Ford, J.L., Rubinstein, M.H., McCaul, F., Hogan, J.E. and Edgar, P.J. *Int. J. Pharm.* 40 (1987) 223-234.

Ford, J.L., Mitchell, K., Rowe, P., Armstrong, D.J. Elliott, P.N.C., Rostron, C. and Hogan, J.E. *Int. J. Pharm.* 71 (1991a) 95-104.

Ford, J.L., Mitchell, K., Sawh, D., Ramdour, S., Armstrong, D.J., Elliott, P.N.C., Rostron, C. and Hogan, J.E. *Int. J. Pharm.* 71 (1991b) 213-221.

Ford, J.L. and Timmins, P. In *"Pharmaceutical thermal analysis techniques and applications"*. (Eds) Ford, J.L. and Timmins, P. Ellis Horwood Limited, Sussex. (1989) 1-24.

Friedman, M. Donbrow, M. and Samuelov, Y. *Drug Dev. Ind. Pharm.* 5 (1979) 407-424.

Gamlen, M.J. *Manuf. Chem.* 56 (1985) 55-59.

Ganderton, D. *Manuf. Chem.* 56 (1985) 27-31. .

Gao, P., Skoug, J.W., Nixon, P.R., Ju, T.R., Stemm, N.L. and Sung, K.C. *J. Pharm. Sci.* 85 (1996) 732-740.

Gazzaniga, A., Busetti, C., Moro, L., Lombardi, C. and Giordano, F. *Proceed. 1st World Meeting APGI/APV.* (1995) 286-287.

Ghebre-Sellassie, I. In *"Pharmaceutical pelletization technology"*. (Ed) Ghebre-Sellassie, I. Marcel Dekker, New York. (1989) 1-13.

Ghebre-Sellassie, I., Gordon, R.H., Fawzi, M.B. and Nesbitt, R.U. *Drug Dev. Ind. Pharm.* 11 (1985) 1523-1541.

Ghebre-Sellassie, I., Gordon, R.H., Middleton, D.L., Nesbitt, R.U. and Fawzi, M.B. *Int. J. Pharm.* 31 (1986) 43-54.

Ghebre-Sellassie, I., Gordon, R.H., Nesbitt, R.U. and Fawzi, M.B. *Int. J. Pharm.* 37 (1987) 211-218.

Ghebre-Sellassie, I., Iyer, U., Kubert, D. and Fawzi, M.B. *Pharm. Tech.* 12 (1988) 96-106.

Gilligan, C.A. and Li Wan Po, A. *Int. J. Pharm.* 73 (1991) 51-68.

Good, W.R. *Drug Dev. Ind. Pharm.* 9 (1983) 647-670.

Goodhart, F.W., Harris, M.R., Murthy, K.S. and Nesbitt, R.U. *Pharm. Technol.* 8 (1984) 64-71.

Govender, T., Dangor, C.M. and Chetty, D.J. *Drug Dev. Ind. Pharm.* 21 (1995) 1303-1322.

Grass, G.M. and Robinson, J.R. In *"Modern Pharmaceutics"*. (Eds) Banker, G.S. and Rhodes, C.T. Marcel Dekker, New York. (1990) 635-671.

Greminger, G.K. and Krumel, K.L. In *"Handbook of Water Soluble Gums and Resins"*. (Ed) Davidson, R.L. Academic Press, San Diego. (1980) 1-25.

Griffin, A. and Grattan, T.J. *Proceed. 13th pharm. Tech. Conference.* 2 (1994) 14-21.

Guo, J.H. *Drug Dev. Ind. Pharm.* 20 (1994) 1883-1893.

Haluska, R.J. Helms, D.S. and Porter, S.C. *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.* 19 (1992) 12-13.

Harland, R.S., Dubernet, C., Benoit, J.P. and Peppas, N.A. *J. Control. Rel.* 7 (1988) 207-215.

Harris, M.R. and Ghebre-Sellassie, I. In *"Aqueous polymeric coatings for pharmaceutical dosage forms"*. (Ed) McGinity, J.W. Marcel Dekker. New York. (1989) 63-78.

Hasan, M., Najib, N., Suleiman, M., El-Sayed, Y. and Abdel-Hamid, M. *Drug Dev. Ind. Pharm.* 18 (1992) 1981-1988.

Hernandez, J.I., Ghaly, E.S., Malave, A. and Marti, A. *Drug Dev. Ind. Pharm.* 20 (1994) 1253-1265.

Higuchi, T. *J. Pharm. Sci.* 52 (1963) 1145-1149.

Hixon, A.W. and Crowell, J.H. *Ind. Eng. Chem.* 23 (1931) 923-931.

Hogan, J.E. *Int. J. Pharm. Tech. & Prod. Mfr.* 3 (1982) 17-20.

Huber, H.E. and Chrsitensen, G.L. *J. Pharm. Sci.* 57 (1968) 164-166.

Hui, H.W., Robinson, J.R., and Lee, V.H.L. In *"Controlled Drug Delivery: Fundamental and Applications"*. (Eds) Robinson, J.R. and Lee, V.H.L. Marcel dekker, New York (1987) 373-432.

Hussain, A., Kimura, R., Huang, C.H. and Mustafa, R. *Int. J. Pharm.* 21 (1984) 289-294.

Hutchings, D.E. and Sakr, A. *J. Pharm. Sci.* 83 (1994) 1386-1390.

Iannuccelli, Coppi, G. and Cameroni, R. *Proceed. 1st World Meeting APGI/APV.* (1995) 379-380.

Iley, W.J. *Powder. Tech.* 65 (1991) 441-445.

Iyer, R.M., Augsburger, L.L. and Parikh, D.M. *Drug Dev. Ind. Pharm.* 19 (1993) 981-998.

Iyer, U., Hong, W.H., Das, N. and Ghebre-Sellasie, I. *Pharm. Tech.* 14 (1990) 68-86.

Jackson, I.M., Roberts, S., Timmins, P. and Sen, H. *Pharm. Tech. Int.* November/December (1989) 29-32.

Jambhekar, S.S., Breen, P.J and Rojanasakul, Y. *Drug Dev. Ind. Pharm.* 13 (1987) 2789-2810.

Johnson, K., Hathaway, R., Leung, P. and Franz, R. *Int. J. Pharm.* 73 (1991) 197-208.

Jones, D.M. In *"Pharmaceutical Pelletization Technology"*. (Ed) Ghebre-Sellassie, I. Marcel Dekker, New York. (1989) 145-164.

Kallstrand, G. and Ekman, B. *J. Pharm. Sci.* 72 (1983) 772-775.

Kannikoski, A. *Acta Pharm. Fenn.* 93 (1984) 147-157.

Kannikoski, A., Fock, H., Marttila, E. and Uotila, J. *Acta Pharm. Fenn.* 93 (1984) 135-145.

Katikaneni, P.R., Upadrashta, S.M., Neau, S.H. and Mitra, A.K. *Int. J. Pharm.* 123 (1995) 119-125.

Kawashima, Y., Takeuchi, H., Handa, T., Thiele, W.J., Deen, D.P. and McGinity, J.W. In *"Aqueous Polymeric Coating for Pharmaceutical Dosage Forms"*. (Ed) McGinity, J.W. Marcel Dekker, New York. (1989) 363-397.

Kawashima, Y., Takeuchi, H., Hino, T., Niwa, T., Lin, T.L., Sekigawa, F. and Ohya, M. *Int. J. Pharm.* 99 (1993) 229-238.

Kim, C.J. *J. Pharm. Sci.* 84 (1995) 303-306.

Klinger, G.H., Ghali, E.S., Porter, S.C. and Schwartz, J.B. *Drug Dev. Ind. Pharm.* 16 (1990) 1473-1490.

Knoch, A. In *"Multiparticulate Oral Drug Delivery"*. (Ed) Ghebre-Sellassie, I. Marcel Dekker, New York. (1994) 35.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A. *Int. J. Pharm.* 15 (1983a) 25-35.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A. *J. Pharm. Sci.* 72 (1983b) 1189-1191.

Kruger-Thiemer, K. and Eriksen, S.P. *J. Pharm. Sci.* 55 (1966) 1249-1253.

Kumar, V. and Banker, G.S. *Drug Dev. Ind. Pharm.* 19 (1993) 1-31.

Laicher, A., Lorck, C.A., Grunenberg, P.C., Klemm, H. and Stanislaus, F. *Pharm. Ind.* 55 (1993) 1113-1116.

Langer, R. *Chem. Eng. Comm.* 6 (1980) 1-48.

Langer, R.S. and Peppas, N.A. *Biomaterials.* 2 (1981) 201-215.

Lapidus, H. and Lordi, N.G. *J. Pharm. Sci.* 55 (1966) 840-843.

Lapidus, H. and Lordi, N.G. *J. Pharm. Sci.* 57 (1968) 1292-1301.

Lehmann, K. and Dreher, D. *Pharm. Tech.* 3 (1979) 53-99.

Lehmann, K. and Petereit, H.U. *Drugs Made. Ger.* 37 (1994) 19-21.

Li, S.P., Feld, K.M. and Kowarski, C.R. *Drug dev. Ind. Pharm.* 15 (1989a) 1137-1159.

Li, S.P., Jhawar, R., Mehta, G.N., Hardwood, R.J. and Grim, W.M. *Drug Dev. Ind. Pharm.* 15 (1989b) 1231-1242.

Li, S.P., Feld, K.M. and Kowarski, C.R. *Drug Dev. Ind. Pharm.* 17 (1991) 1655-1683.

Li, S.P., Mehta, G.N., Buehler, J.D., Grim, W.M. and Harwood, R.J. *Pharm. Tech. Int.* 2 (1990) 48-52.

Li, S.P., Pendharkar, C.M., Mehta, G.N., Karth, M.G. and Feld, K.M. *Drug Dev. Ind. Pharm.* 19 (1993) 2519-2537.

Li, H.K., Robinson, J.R. and Lee, V.H.L. In *"Controlled Drug Delivery: Fundamental and Applications"*. (Eds) Robinson, J.R. and Lee, V.H.L. Marcel Dekker, New York (1987) 4-94.

Lindholm, T. and Juslin, M. *Pharm. Ind.* 44 (1982) 937-941.

Lindholm, T., Juslin, M. and Kekalainen, S. *Pharm. Ind.* 44 (1982) 1093-1098.

Lindholm, T., Lindholm, B.A., Niskanen, M. and Koskiniemi, J. *J. Pharm. Pharmacol.* 38 (1986) 686-688.

Lippold, B.C., Lippold, B.H., Sutter, B.K. and Gunder, W. *Drug Dev. Ind. Pharm.* 16 (1990) 1725-1747.

Lippold, B.H., Sutter, B.K. and Lippold, B.C. *Int. J. Pharm.* 54 (1989) 15-25.

Liu, C.H., Chen, S.C., Kao, Y.H., Kao, C.C., Sokoloski, T.D. and Sheu, M.T. *Int. J. Pharm.* 100 (1993) 241-248.

Liu, C.H., Kao, Y.H., Chen, S.C., Sokoloski, T.D. and Sheu, M.T. *J. Pharm. Pharmacol.* 47 (1995) 360-364.

Lordi, N.G. In *"The Theory and Practice of Industrial Pharmacy"*. (Eds) Lachman, L., Liberman, H.A. and Kanig, J.L. Lea & Febiger, Philadelphia. (1986) 430-456.

Madan, P.L. *Pharm. Manuf.* February (1985a) 23-27.

Madan, P.L. *Pharm. Manuf.* May (1985b) 41-45.

Maffione, G., Iamartino, P., Guglielmini, G. and Gazzaniga, A. *Drug Dev. Ind. Pharm.* 19 (1993) 2043-2053.

Maganti, L. and Celik, M. *Int. J. Pharm.* 103 (1994) 55-67.

Mandal, T.K. *Drug Dev. Ind. Pharm.* 21 (1995) 1389-1397.

Masilungan, F.C. and Lordi, N.G. *Int. J. Pharm.* 20 (1984) 295-305.

Mathieu, C., Huet de Barochez, B. and Cuine, A. *Proceed. 1st World Meeting APGI/APV.* (1995) 381-382.

Mehta, A.M. *Inter. Symp. Control. Rel. Bioac. Mater.* 12 (1985) 155-156.

Mehta, A.M. *Pharm. Manuf.* 3 (1986) 23-29.

Mehta, A.M. In *"Pharmaceutical Pelletization Technology"*. (Ed) Ghebre-Sellassie. I. Marcel Dekker, New Yrok. (1989) 241-265.

Mehta, A.M. and Jones D.M. *Pharm. Tech.* 9 (1985) 52-60.

Miller, R.A. and Vadas, B.E. *Drug Dev. Ind. Pharm.* 10 (1984) 1565-1585.

Millili, G.P. and Schwartz, J.B. *Drug Dev. Ind. Pharm.* 16 (1990) 1411-1426.

Mitchell, A.G. *J. Pharm. Pharmacol.* 37 (1985) 601-604.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Hogan, J.E. and Rostron, C. *Int. J. Pharm.* 100 (1993a) 143-154.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Rostron, C. and Hogan, J.E. *Int. J. Pharm.* 100 (1993b) 155-163.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Hogan, J.E. and Rostron, C. *Int. J. Pharm.* 100 (1993c) 165-173.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Hogan, J.E. and Rostron, C. *Int. J. Pharm.* 100 (1993d) 175-179.

Moffat, A.C., Jackson, J.V., Moss, M.S. and Widdop, B. In *"Clarke's Isolation and Identification of Drugs"*. (Eds) Moffat, A.C., Jackson, J.V., Moss, M.S. and Widdop, B. Pharmaceutical Press, London. (1986) 533-534, 776-777.

Moore, K.L. In *"Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms"*. (Ed) McGinity, J.W. Marcel Dekker, New York. (1989) 303-315.

Mosquera, M.J., Cuna, M., Souto, C., Concheiro, A., Martinez-Pacheco, R. and Gomez-Amoza, J.L. *Int. J. Pharm.* 135 (1996) 147-149.

Muhammad, N.A., Boisvert, W., Harris, M.R. and Weiss, J. *Drug Dev. Ind. Pharm.* 17 (1991) 2497-2509.

Munday, D.L. and Fassihi, A.R. *Int. J. Pharm.* 52 (1989) 109-114.

Murthy, K.S. and Ghebre-Sellassie, I. *J. Pharm. Sci.* 82 (1993) 113-126.

Nagai, F., Sekigawa, F. and Hushi, N. In *"Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms"*. (Ed) McGinity, J.W. Marcel Dekker, New York. (1989) 81-104.

Najib, N. and Suleiman, M.S. *Drug Dev. Ind. Pharm.* 11 (1985) 2169-2181.

Narisawa, S., Yoshino, H., Hirakawa, Y. and Noda, K. *Chem. Pharm. Bull.* 42 (1994) 1485-1490.

Navarro, A. and Ballesteros, M.P. *S.T.P. Pharma. Prat.* 4 (1994) 108-115.

Nesbitt, R.U., Mahjour, M. and Fawzi, B. *Abs 39th National Mtg AphA Academy of Pharm. Sci.* Minneapolis, MN, (1985) 111.

Nesbitt, R.U., Mahjour, M., Mills, N.L. and Fawzi, B. *J. Control. Rel.* 32 (1994) 71-77.

Nishihata, T., Liversidge, G. and Higuchi, T. *J. Pharm. Pharmacol.* 35 (1983) 616-617.

Niskanen, M., Niskanen, T., Yliruusi, J.K. and Kristofferson, E. *Pharm. Tech. Int.* 2 (1990) 22-28.

Onions, A. *Manuf. Chem.* 57 (1986a) 55-59.

Onions, A. *Manuf. Chem.* 57 (1986b) 66-67.

Osterwald, H.P. *Pharm. Res.* 2 (1985) 14-18.

Ozturk, A.G., Ozture, S.S., Palsson, B.O., Wheatley, T.A. and Dressman, J.B. *J. Control. Rel.* 14 (1990) 203-213.

Park, K., Wood, R.W. and Robinson, J.R. In *"Medical Application of Controlled Release"*. Vol. I (Eds) Langer, R.S. and Wise, D.L. CRC Press, Philadelphia. (1984) 159-201.

Parrott, E.L. In *"The Theory and Practice of Industrial Pharmacy"*. (Eds) Lachman, L., Liberman, H.A. and Kanig, J.L. Lea & Febiger, Philadelphia. (1986) 27-28.

Peppas, N.A. *Pharm. Acta Helv.* 60 (1985) 110-111.

Peppas, A.N. and Sahlin, J.J. *Int. J. Pharm.* 57 (1989) 169-172.

Pham, A.T. and Lee, P.I. *Pharm. Res.* 11 (1994) 1379-1384.

Pitre, D. and Stardi, R. In *"Analytical Profiles of Drug Substances"*. (Ed) Florey, K. Academic Press, San Diego. 16 (1987) 327-360.

Porter, S.C. *Drug Dev. Ind. Pharm.* 15 (1989a) 1495-1521.

Porter, S.C. In *"Aqueous Polymeric Film Coatings for Pharmaceutical Dosage Forms"*. (Ed) McGinity, J.W. Marcel Dekker, New York. (1989b) 317-362.

Porter, S.C. and Bruno, C.H. In *"Pharmaceutical Dosage Forms: Tablets"*. Vol III. (Eds) Liberman, H.A., Lachman, L. and Schwartz, J.B. Marcel Dekker, New York. (1990) 115-120.

Porter, S.C. and D'Andrea, L.F.D. *Proceed. Inter. Symp. Control. Bioact. Mater.* 12 (1985) 41-42.

Porter, S.C. and Ghebre-Sellassie, I. In *"Multiparticulate Oral Drug Delivery"*. (Ed) Ghebre-Sellassie, I. Marcel Dekker, New York. (1994) 217-284.

Ragnarsson, G. and Johansson, M.O. *Drug Dev. Ind. Pharm.* 14 (1988) 2285-2297.

Ragnarsson, G., Sandberg, A., Johansson, M.O., Lindstedt, B. and Sjogren, J. *Int. J. Pharm.* 79 (1992) 223-232.

Rajabi-Siahboomi, A.R., Davis, M.C., Melia, C.D. *Proceed. Int. Symp. Control. Rel. Bioact. Mater.* 21 (1994a) 264-265.

Rajabi-Siahboomi, A.R., Bowtell, R.W., Mansfield, P., Henderson, A., Davis, M.C. and Melia, C.D. *J. Control. Rel.* 31 (1994b) 121-128.

Rajabi-Siahboomi, A.R., Bowtell, R.W., Mansfield, P., Davis, M.C. and Melia, C.D. *Pharm. Res.* 13 (1996) 376-380.

Ranga Rao, K.V. and Padmalatha Devi, K. *Int. J. Pharm.* 48 (1988) 1-13.

Ranga Rao, K.V., Padmalatha Devi, K. and Buri, P. *Drug Dev. Ind. Pharm.* 14 (1988) 2299-3220.

Ranga Rao, K.V., Padmalatha Devi, K. and Buri, P. *J. Control. Rel.* 12 (1990) 133-141.

Rekhi, G.S. and Jambhekar, S.S. *Drug Dev. Ind. Pharm.* 21 (1995) 61-77.

Rekhi, G.S., Mendes, W., Porter, S.C. and Jambhekar, S.S. *Pharm. Tech.* 13 (1989) 112-124.

Rekhi, G.S., Porter, S.C. and Jambhekar, S.S. *Drug Dev. Ind. Pharm.* 21 (1995) 709-729.

Ritger, P.L. and Peppas, N.A. *J. Control. Rel.* 5 (1987) 37-42.

Robinson, J.R. and Eriksen, S.P. *J. Pharm. Sci.* 59 (1970) 1796-1800.

Robinson, J.R. and Eriksen, S.P. *J. Pharm. Sci.* 55 (1966) 1254-1263.

Rowe, R.C. *Acta pharm. Suec.* 19 (1982) 157-160.

Rowe, R.C. *Pharm. Int.* 1 (1985a) 14-17.

Rowe, R.C. *Pharm. Int.* 6 (1985b) 119-123.

Rowe, R.C. *Int. J. Pharm.* 29 (1986) 37-41.

Russo, E.J. *Pharm Tech.* 8 (1984) 46-56.

Sakellariou, P., Rowe, R.C. and White, E.F.T. *Int. J. Pharm.* 34 (1986) 93-103.

Salomon, J.L., Doelker, E. and Buri, P. *Pharm. Ind.* 41 (1979) 799-802.

Sarisuta, N. and Punpreuk, K. *J. Control. Rel.* 31 (1994) 215-222.

Sarisuta, N. and Sirithunyalug, J. *Drug Dev. Ind. Pharm.* 14 (1988) 683-687.

Schmidt, P.C. and Niemann, F. *Drug Dev. Ind. Pharm.* 19 (1993) 1603-1612.

Schwartz, G. *Ann. Stat.* 6 (1978) 461-464.

Schwartz, J.B. and Ando, H.Y. *American Druggist.* July (1983) 41-45.

Schwartz, J.B., Nguyen, N.H. and Schnaare, R.L. *Drug Dev. Ind. Pharm.* 20 (1994) 3105-3129.

Shah, N.B. and Sheth, B.B. *J. Pharm. Sci.* 61 (1972) 412-415.

Sheskey, P.J., Cabelka, T.D., Robb, R.T. and Boyce, B.M. *Pharm. Tech.* 18 (1994) 133-150.

Sheu, M.T., Chou, H.L., Kao, C.C., Liu, C.H. and Sokoloski, T.D. *Int. J. Pharm.* 85 (1992) 57-63.

Singh, J. and Robinson, D.H. *Drug Dev. Ind. Pharm.* 14 (1988) 545-560.

Skoug, J.W., Mikelsons, M.V., Vigneron, C.N. and Stemm, N.L. *J. Control. Rel.* 27 (1993) 227-245.

Story, M.J. *Proceed. Capsugel Symposium.* (1989) 32-37.

Stratford, R.E., Yang, D.C., Redell, M.A. and Lee, V.H. *Int. J. Pharm.* 13 (1983) 263-272.

Suryakusuma, H. and Jun, H.W. *J. Pharm. Pharmacol.* 36 (1984) 497-501.

Tahara, K., Yamamoto, K., Nishihata, T. *J. Control. Rel.* 35 (1995) 59-66.

Tahara, K., Yamamoto, K., Nishihata, T. *Int. J. Pharm.* 133 (1996) 17-27.

Tice, T.R. and Cowsar, D.R. *Pharm. Technol.* 8 (1984) 26-36.

Timmins, P., Delargy, A.M., Howard, J.R. and Rowlands, E.A. *Drug Dev. Ind. Pharm.* 17 (1991) 531-550.

Tirkkonen, S. and Paronen, P. *Int. J. Pharm.* 92 (1993) 55-62.

Tojo, K. and Miyanami, K. *Powder. Tech.* 35 (1983) 89-96.

Twitchell, A.M., Hogan, J.E. and Aulton, M.E. *Proceed. 1st World Meeting APGI/APV.* (1995) 282-283.

Ueda, S., Hata, T., Asakura, S., Yamaguchi, H., Kotani, M. and Ueda, Y. J. *Drug Targetting*, 2 (1994) 35-44.

United States Pharmacopeia / The National Formulary. (1995). New York. 1950-1951, 2313.

Upadrashta, S.M., Katikaneni, P.R., Hileman, G.A. and Keshary, P.R. *Drug Dev. Ind. Pharm.* 19 (1993) 449-460.

Vanderhoff, J.W., Bradford, E.B. and Carrington, W.K. *J. Polym. Sci.* 41 (1973) 155-174.

Vanderhoff, J.W., Tarkowski, H.L., Jenkins, M. and Bradford, E.B. *J. Macromol. Chem.* 1 (1966) 361-397.

Voyutskii, S.S. *J. Polym. Sci.* 32 (1958) 528-530.

Wagner, T.C. and Keitel, S. *Proceed. 1st World Meeting APGI/APV.* (1995) 383-384.

Wan, L.S.C., Heng, P.W.S. and Wong, L.F. *Drug Dev. Ind. Pharm.* 19 (1993) 1201-1210.

Wan, L.S.C., Heng, P.W.S. and Wong, L.F. *Int. J. Pharm.* 116 (1995a) 159-168.

Wan, L.S.C., Heng, P.W.S. and Tan, Y.T.F. *S.T.P. Pharma. Sci.* 5 (1995b) 128-133.

Wan, L.S.C. and Lai, W.F. *Int. J. Pharm.* 72 (1991) 163-174.

Wan, L.S.C. and Lai, W.F. *Int. J. Pharm.* 94 (1993) 39-47.

Welling, P.G. *Drug Dev. Ind. Pharm.* 9 (1983) 1185-1225.

Welling, P.G. and Dobrinska, M.R. In *"Controlled Drug Delivery: Fundamental and*

Applications". (Eds) Robinson, J.R. and Lee, V.H.R. Marcel Dekker, New York. (1987) 257-291.

Wells, M.L. and Parrott, E.L. *J. Pharm. Sci.* 81 (1992) 453-457.

Wong, D. and Bodmeier, R. *Eur. J. Pharm. Biopharm.* 42 (1996) 12-15.

Wouessidjewe, D., Devissaguet, J.P. and Carstensen. J.T. *Drug Dev. Ind. Pharm.* 17 (1991) 7-25.

Yang, S.T. and Ghebre-Sellassie, I. *Int. J. Pharm.* 60 (1990) 109-124.

Yang, S.T., Savage, G.V., Weiss, J. and Ghebre-Sellassie, I. *Int. J. Pharm.* 86 (1992) 247-257.

Yotsuyanaagi, Y., Molokhia, S., Hwang, N.F., Flynn, G.L. and Higuchi, W.I. *J. Pharm. Sci.* 64 (1975) 71-76.

Yuen, K.H., Deshmukh, A.A. and Newton, J.M. *Drug Dev. Ind. Pharm.* 19 (1993) 855-874.

Zhang, G., Schwartz, J.B. and Schnaare, R.L. *Pharm. Res.* 8 (1991a) 331-335.

Zhang, G., Schwartz, J.B., Schnaare, R.L., Wigent, R.J. and Sugita, E.T. *Drug Dev. Ind. Pharm.* 17 (1991b) 817-830.

Zhang, G.H., Vadino, W.A. and Chaudry, I. *Proceed. Intern. Symp. Control. Rel. Biaoct. Mater.* 17 (1990) 333-334.

ATTENDANCE AT CONFERENCES

1- British Pharmaceutical Conference, Warwick, UK, September, 1995.

2- 15th Pharmaceutical Technology Conference, Oxford, UK, March, 1996.

3- The 1st and 2nd Seminars of Iranian Pharmacy Postgraduate Students, Manchester, UK, June and December, 1994.

4- Attending Postgraduate Research Seminars at the School of Pharmacy and Chemistry, Liverpool John Moores University.

PUBLISHED COMMUNICATIONS AND PRESENTATIONS

The following have been published or presented in advance of this thesis. Copies may be found in the pocket at the end of this thesis:

1- The effect of inclusion of HPMC on the release of metoclopramide hydrochloride from Surelease-coated pellets.

Sadeghi, F., Ford, J.L., Rubinstein, M.H., Rajabi-Siahboomi, A.R.

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2- Metoclopramide hydrochloride release from coated pellets.

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3- Effect of polymer type and coating load on drug release from coated pellets.

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4- Release behaviour from coated pellets: Effect of drug type.

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5- Effect of drug type on release behaviour from coated pellets.

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