Study of drug release behaviour from HPMC matrix tablets and EC coated matrix reservoir system

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SUMMARY

In the investigation on polymer particle in hydrophilic matrix system, hydroxypropyl methylcellulose (HPMC) mean particle size of 113 µm was identified as critical cut-off criterion for obtaining consistent sustained drug release profile. The mechanism of aspirin release from matrix tablets was studied. Polymer particles of similar mean particle sizes but of different size distributions were found to influence drug release rate but not the release mechanism. Drug release constant was found to be proportionally related to polymer mean particle size and relative number of polymer particles in the matrix system. This relationship could help to predict drug release performance from matrix systems with varying polymer content and particle sizes.

In reservoir dispersed matrix tablets, the release performances of water-soluble naproxen sodium and sparingly soluble aspirin from ethylcellulose (EC) coated HPMC matrix tablets were investigated. Drug release decreased as HPMC content in the core increased. Higher EC coating load led to lower drug release rate. Increase of Opadry (HPMC based coating system) concentration in EC coat increased drug release rate. Release profile of aspirin was more sensitive to EC coating level while that of naproxen sodium was influenced more significantly by HPMC content in the core. Impact of EC coat and Opadry on drug release kinetics were dependent on EC layer thickness. Release kinetics generally followed the zero order model at higher EC coating levels. At low EC coating level, an increase of Opadry ratio in

the EC coat modified the drug release kinetics to first order. The zero order release constants of naproxen sodium tablets coated with different EC coating formulations and at different coating levels showed a linear relationship with HPMC contents in the core. This relationship was not found with similarly prepared aspirin tablets.

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I. INTRODUCTION

A. Background

The oral route is the most convenient and commonly employed route for drug administration. In order to achieve and maintain the drug concentration within a therapeutically effective range, it is often necessary to consume a normal release drug dosage form several times a day at regular intervals. Besides the inconvenience, this also results in significant fluctuations of the plasma drug level. The development of extended release systems provides an ideal approach to deliver drug at a desired rate and maintain consistent / constant drug concentration over an extended period of time. Benefits of extended release systems that arise from the stable plasma drug level improve therapeutic efficacy and reduce side effects.

The term "extended release" implies a predictability and reproducibility in the drug release rate and kinetics. There is an extensive number of approaches available to achieve the above goals. The most often-used control methods employ monolithic or reservoir–type devices. For a monolithic device, the active ingredient is homogeneously dispersed in the rate-controlling polymer which forms either a lipophilic or hydrophilic matrix system where the release kinetics are governed by

diffusion or a combination of erosion and diffusion mechanisms. Polymers used for monolithic matrix systems include hydroxypropyl methylcellulose, ethylcellulose, chitosan and chitin. In the reservoir devices, the active drug and other ingredients are enclosed in a water-insoluble membrane formed by film coating. The rate-controlling membrane can be classified into two types: homogeneous and microporous.

B. Matrix Systems

1. Advantages

Hydrophilic matrix systems for extended release provide many advantages. Firstly, the matrix system is relatively easy to formulate. Secondly, production of the dosage form can use existing and conventional equipment and processing methods. In addition, the matrix system is economical, can be produced using a wide range of polymers, and is able to support high drug dose levels (Alderman, 1984 and Dabbagh et al., 1996). It is also less affected by variations in ingredients, production methods and end-use conditions than many other extended release systems, thus resulting in more uniform release profiles and high resistance to dose dumping (Ho et al., 1997 and Jovanovic et al., 1997).

2. Hydroxypropyl methylcellulose

The most popular polymer available for use in hydrophilic matrix systems is hypromellose, also known chemically as hydroxypropyl methylcellulose (HPMC). HPMC is a propylene glycol ether of methylcellulose, and therefore has a polymeric backbone of cellulose, a natural carbohydrate that contains repeating units of anhydroglucose. During the manufacturing process, cellulose fibers are first treated with caustic soda, followed by methyl chloride and/or propylene oxide. The end product obtained is then purified and ground to a fine powder.

There is a wide range of HPMC of different molecular weights and degrees of substitution. Being a semi-synthetic material derived from cellulose, the degree of HPMC polymerization can be varied during manufacture to provide a polymer with a range of desirable properties. The viscosity of HPMC is controlled by molecular weight. The ratio of the methoxyl ($-OCH_3$) and hydroxypropoxyl ($-OCH_2CHOHCH_3$) substituents influences the properties of the polymer such as organic solvent solubility, thermal gelation temperature of the aqueous solution and rate of hydration. The three major types of commercial HPMC classified according to the amount of methoxyl and hydroxypropoxyl substitutions in the polymer are listed as follows:

Type	% methoxyl	% hydroxypropoxyl
HPMC 2208 USP (Methocel K)	19-24	7-12
HPMC 2910 USP (Methocel E)	28-30	7-12
HPMC 2906 USP (Methocel F)	27-30	4-7.5

Methocel K has the fastest hydration rate, followed by Methocel E and Methocel F. Another major difference in the physical properties of these 3 types of HPMC is their cloud point. At temperatures below the cloud point, the polymer absorbs a large amount of water and gels rapidly. Above the cloud point, the polymer does not take up water. There is a gradual transition as the cloud point is approached, with the polymer losing more and more water of hydration and the speed of gelation in a hydrating matrix decreases (Mitchell et al., 1990).

HPMC is a widely accepted pharmaceutical excipient and is included in all major pharmaceutical compendia. It has a good safety record with low toxic effects and is also compatible with most drug substances.

3. Controlled release mechanisms

The mechanisms of extended release action of HPMC matrices are complex because the micro- and macro- structures of HPMC when

exposed to water are strongly time–dependent. To achieve extended release properties, it is essential that the chosen type of HPMC provides rapid hydration on contact with the dissolution medium, allowing the HPMC polymer chains to start to swell and form a continuous, gelatinous layer. This rapid formation of gel layer prevents fast penetration of water into the tablet core and tablet disintegration, which would otherwise occur. The viscous layer has another important role. It retards the rate of drug diffusion through the matrix to the exterior. The rate of erosion of the gel layer controls the rate of liberation of any insoluble active substance, which cannot be released by diffusion. Fast polymer hydration and gel layer formation are particularly critical when formulating with water-soluble drugs and water-soluble excipients (Mitchell et al., 1993b, Mitchell et al., 1993c and Ford et al., 1985a).

A swollen HPMC matrix can be divided into four components: dry glassy core, swollen glassy layer, gel layer and diffusion layer separating the matrix from the external medium. Within the dry glassy core, the polymer takes up most of the space, producing a completely unhydrated region. In the swollen glassy layer, solvent diffusion results in a small increase in water concentration, resulting in a more mobile network with very strong polymer chain entanglement. In the gel layer, due to the significant swelling that occurs, polymer concentration is lower than in the dry glassy and swollen glassy layers but strong chain entanglement is still

maintained. Finally, in the water rich diffusion layer, the polymer concentration is so low that chain entanglement becomes weak.

Gel strength is affected by type, viscosity and concentration of polymer employed. In general, the strength of the gel increases with increasing molecular weight, via the effect of polymer viscosity.

As HPMC is water soluble, the polymer matrix will gradually dissolve in water. Water penetrates the matrix and hydrates the polymer chains, which eventually detach from each other and disentangle from the matrix into the bulk solution, permitting erosion of the matrix to occur. It was proposed that surface erosion of the matrix is governed by two steps. The first step involves just the surface and depends on the rate of hydration. The second step involves the transport of polymer molecules from the surface across the aqueous diffusion layer, adjacent to the matrix and into the bulk solution (Reynolds et al., 1998).

Much research work has been done to model the erosion and diffusion mechanisms of swellable polymeric matrices. Attempts to separate the diffusional and erosional contributions to drug release have been reported. In one study, a linear correlation between drug release due to erosion and time was observed (Reynolds et al., 1998). The diffusional release rate

was a function of the molecular weight of the polymer, indicating that polymer erosion is dependent on polymer viscosity (Leszek , 1987).

Mathematical modeling has also been employed to describe the diffusion of a penetrant and a solute in a swellable polymer slab (Siepmann et al., 1998). According to the mathematical model, Equations 1 & 2, used to describe the mass transfer processes in the three component system, drug/polymer/water, the diffusion coefficients were strongly dependent on the concentration of water in the system. Hence, the free volume available for diffusion was a function of the water concentration.

$$D_1 = D_{1eq} \, exp(-\beta_1(1-c_1/c_{1eq})) \hspace{3cm} (1)$$
$$D_2 = D_{2eq} \, exp(-\beta_2(1-c_1/c_{1eq})) \hspace{3cm} (2)$$

where D_1 and D_2 are the diffusion coefficients for water and drug, β_1 and β_2 are dimensionless constants, c_1 is the water concentration and c_{1eq} is the water concentration at the equilibrium state. D_{1eq} and D_{2eq} are the respective diffusion coefficients of water and drug in the equilibrium swollen state of the system.

A semi-empirical equation (Equation 3) has been developed for the diffusion coefficient, D_p, of polymer within the diffusion layer adjacent to a matrix undergoing swelling and dissolution (Ju et al., 1997). This

equation was a key element in describing the swelling and dissolution of the polymer and the release of drug. For HPMC, D_p can be related to molecular weight, M, and polymer concentration. The parameter, C_p, defined as the polymer disentanglement concentration or the polymer concentration at the tablet diffusion layer interface, was found to be a key parameter in the mathematical model.

$$D_p = 7.24 * 10^{-5} M^{-0.6} [1 + 700 (M/96000)^{0.7} C_p/8]^{-2} \hspace{2cm} (3)$$

4. Influence of experimental parameters on drug release from HPMC matrix systems

During the formulation process of hydrophilic matrix tablets, the following factors must be taken into consideration.

a. Polymer content

The content of HPMC in the matrix had considerable impact on drug release rate (Baveja et al., 1988). Dissolution rate of ibuprofen decreased as HPMC content increased in the formula (Wan et al., 1991). When adinazolam mesylate was used as a model drug, researchers found that varying HPMC ratio produced a wide range of drug release curves (Sung et al., 1996). Low concentrations of HPMC led to tablet disintegration due

to lack of sufficient polymer in the system to form a uniform, continuous gel layer of appropriate strength.

b. Incorporation of other polymeric excipients

Combining different polymers with HPMC had been found to affect drug release mechanism and profile (Perez-Marcos et al., 1994 and Baveja et al., 1988). Mixing Carbopol with HPMC resulted in a decrease in the cloud point but increase in water content of the resultant gel, leading to reduction of viscosity. Incorporation of sodium carboxymethyl cellulose (NaCMC) into an HPMC matrix converted the release mechanism of oxprenolol hydrochloride and propranolol to zero order from non-linear release models. This phenomenon was ascribed to the difference in erosion rates of NaCMC and HPMC. Other investigations suggested that NaCMC is an ionic polymer that could retard the release of oppositely charged drugs, but the effect was not found to be dramatic. HPMC combined with non-ionic polymers, such as PEG 6000 and ethylcellulose was no more effective than the HPMC polymer itself in controlling the release rate of chlorpheniramine maleate from polymer matrices.

c. Polymer/ drug ratio

In a study on the release of propranolol hydrochloride and aminophylline from HPMC matrices, the drug / polymer ratio was found to be the major factor controlling the drug release. Similar release rates were obtained using Methocel K with viscosities of 4,000, 15,000 and 100,000 cp at the same drug: HPMC ratio (Ford et al., 1985a).

In another study, the diffusion rates for soluble drugs through HPMC gels were found to be dependent on the gel concentration. This was attributed to increased gel tortuosity with increasing concentration of polymer. Drug diffusion was however independent of the polymer molecular weight. Using propranolol hydrochloride, drug release from the matrix increased with increasing drug concentration. (Mitchell et al.,1993c).

d. Polymer viscosity

Change of polymer viscosity will affect drug release to some degree. Much research work was directed at exploring the relationship between polymer viscosity and drug release. Using propranolol hydrochloride as the model drug, it was observed that the square of dissolution $T_{50\%}$ varied proportionately with the solution viscosity (Wan et al., 1995). The release of acetazolamide from an HPMC matrix became slower when HPMC K4M (4,000 cp) was replaced with K15M (15,000 cp) (Dortung and Gunal, 1997). In one study, matrices were produced from 10 % HPMC having

viscosity values of 15, 860, 5000, 20,000 and 30,000 cp. A linear relationship between the reciprocal of release rate and the HPMC viscosity was observed. When the HPMC content was increased above 20 %, drug release was independent of viscosity (Campos-Aldrete and Villafuete-Robles, 1997).

e. Polymer particle size

Particle size can greatly influence polymer performance in the hydrophilic matrix systems (Mitchell et al., 1993a). In the study of the dissolution rate of propranolol hydrochloride from matrices containing different size fractions of HPMC K15M, it was found that the release rate decreased as the polymer particle size was reduced from > 355 μm to 150 - 210 μm. Further reduction in polymer particle size to 75 - 150 μm and < 75 μm caused no noticeable decrease in dissolution. Initial "burst" release of drug was seen at the highest level of polymer particle size > 355 μm and low content of HPMC.

The dissolution rate of metronidazole from matrix tablets containing 10 % HPMC exhibited a linear relationship with the cube of the diameter of the HPMC particles. When the HPMC concentration was increased to 20 % and above, release rate was not affected by the polymer particle size. An increasing burst effect occurred with increasing particle sizes of HPMC.

The particle size fractions of the HPMC used in the experiment were 163, 213, 335 and 505 μm respectively (Campos-Aldrete and Villafuete-Robles, 1997).

f. Drug solubility and type

Higher drug solubility generally result in faster release rates, due to the generation of higher diffusional driving forces. The effects of propranolol hydrochloride, tetracycline hydrochloride and indomethacin on the properties of gels and swelling characteristics of matrices containing HPMC had been evaluated. It was found that tetracycline hydrochloride and propranolol hydrochloride increased the cloud point of HPMC K15M (Mitchell et al., 1990). Tetracycline hydrochloride also interfered with the hydration process of HPMC on contact with water. Thermal analysis showed that propranolol hydrochloride affected the equilibrium water / HPMC content in HPMC gels. Water-soluble drugs also had an effect on the extent of gel swelling (Mitchell et al., 1993b).

g. Drug particle size

Impact of drug particle size on drug release from HPMC matrix systems varied according to drug type and polymer content level. It was reported that differences in drug particle size generally had little effect on drug

release rate when potassium chloride and promethazine hydrochloride were used as model drugs in HPMC matrices (Ford et al., 1985b). It was found that only at low HPMC: drug ratios, an appreciable effect was seen at a very large mean drug particle size. This was explained by the tendency of the matrix to be very "loose" and to disintegrate rapidly under these circumstances.

h. Surfactants

Addition of surfactants may affect drug release from a matrix system. It was observed that anionic surfactants could retard the release of cationic drugs such as chlorpheniramine maleate from extended release matrix tablets (Khan and Zhu, 1998 and Liam and Stanley, 1988). Sodium dodecyl sulphate, an anionic surfactant, was found to retard the release of propranolol hydrochloride (Ford et al., 1991).

The influence of ionic surfactants on drug release is concentration-dependent. The mechanism of this effect is via an ionic interaction between drug and surfactant. The ability of ionic surfactants to retard the release of drugs from HPMC matrices had been studied (Liam and Stanley, 1988). The concentration of surfactant within a matrix was reported to be an important parameter affecting release rate. The hydrocarbon chain length of surfactant did not appear to be a major factor

influencing drug release rate. It was found that the surfactant only had an effect when both it and the drug were ionized and had opposite charges. It was postulated that such complexes formed *in situ* within the HPMC matrix and that drug release from these systems would rely principally upon erosion (Liam and Stanley, 1998).

i. Filler solubility

The effects of the filler on drug release are dependent on the drug substance, polymer level and level of filler itself in a matrix system. Some researchers had indicated that theophylline release rate from matrix tablets was not affected by a switch between a soluble filler such as lactose and an insoluble filler such as tricalcium phosphate. (Veiga et al., 1997). Conversely, in the case of the model drug metoprolol tartrate, it was demonstrated that drug release rate increased when the filler was changed from dibasic calcium phosphate to lactose. Some experiments also indicated that the release of morphine from HPMC matrices was affected by the addition of lactose, which caused a concentration-dependent increase in the drug release rate (Bosca et al., 1995)

j. Production method and parameters

Production of matrix systems as a dosage form normally involves wet granulation or direct compression processes. Therefore, it is important to study the influence of production methods and parameters, such as mixing time of the ingredients and compression force on drug release behavior. The effect of compression force and subsequent tablet hardness on drug release was evaluated using a freely soluble drug centperazine and a polymer combination of HPMC and NaCMC. It was found that drug release was independent of tablet hardness in the range from 4 to 12 kg.cm^{-2} (Baveja et al., 1998). In the evaluation of the effect of lubricant mixing time on extended release matrix tablets, it was found that drug release rate was only slightly affected by the duration of mixing (Sheskey et al., 1995).

k. Tablet dimension and shape

Standard convex and capsule-shaped tablets were used to examine the effect of tablet size and shape (Siepmann et al., 2000). It was found that the larger the surface area, the faster was the release rate. Control of surface area-to-volume ratio offered an effective means of achieving the required release rates for different dose-sizes of the same formulation. Propranolol hydrochloride and chlorpheniramine maleate were used as model drugs. The effect of the initial matrix radius on release rate was found to be more pronounced than the effect of the initial thickness.

Research work also found that tablet shape significantly affected the rate of release of theophylline from matrix tablets (Veiga et al., 1997).

l. Dissolution medium

The dissolution medium employed may also affect drug release. It was found that addition of sodium or potassium chloride to the dissolution medium decreased the solubility of diclofenac sodium, with a resultant reduction in dissolution of the drug from an HPMC matrix system (Kurahashi et al., 1996). The effect of sodium chloride was greater than potassium chloride. Dissolution rate of the drug was also studied in a medium that simulated the changing pH of the pathway followed by the drug as it passed from the stomach to intestine (Perez-Marcos et al., 1994). Dissolution rate was found to be inversely related to the rate at which the pH was changed. This could be due to the deposition of an insoluble drug layer on contact with the acid medium. Increasing the viscosity of the HPMC used resulted in slower release rates.

5. Studies on the effects of HPMC particle properties

Matrices composed of propranolol hydrochloride and coarse particles (200 to 300 μm) of Methocel K exhibited premature drug release (Dabbagh et al., 1996 and Mitchell et al., 1993a). The release rate decreased as

polymer particle size was decreased. Coarse polymer particles above a critical size tended to result in failure of the matrix system, which was characterized by rapid matrix disintegration and immediate release of the drug. It was also found that polymer particle size had a greater influence on the dissolution of soluble drugs which require very rapid formation of a strong gel layer (Dabbagh et al., 1996).

HPMC particle size has been reported to affect the rate of dissolution of drug from a matrix tablet (Campos-Aldrete and Villafuete-Robles, 1997). Some authors had attributed this to the difference in water uptake and hydration rate between different particle size fractions. Rapid dissolution rates brought about by coarse fractions of HPMC were considered to be due to slow hydration of the polymer, allowing disintegration of the tablet before complete hydration of the external layers had occurred. It was considered that small size fractions of HPMC allowed more rapid and uniform hydration of the surface of the matrix, thereby effectively retarding release.

In contrast, some experimental results demonstrated that contrary to hydrating slowly, coarse particles bound water faster than finer particles (Mitchell et al., 1993a). After 60 minutes, bound water levels for coarse and fine particles were similar. However, it was the first few minutes of hydration that were the most important, corresponding to the period when

a protective gel coat was formed around the matrix. Hence, the differences in release rates should not be considered to be due to differences in the rates of hydration between the different particle size fractions of the polymer.

The effect of variations in drug release rate with varying polymer particle size was attributed to differences in surface area or differences in porosity of the controlled release gel layers. HPMC polymer fractions of smaller mean particle sizes had greater surface area to weight ratios than fractions of larger mean particle size. The greater surface area enhanced contact between polymer and water, thus increasing the overall rate at which polymer hydration and gelation occurred. This led to more effective formation of the protective gel barrier that was critical to the performance of hydrophilic matrix tablets (Campos-Aldrete and Villafuete-Robles, 1997).

There is limited information on the influence of HPMC particle size on drug release from matrix systems. It is therefore important and interesting to study this parameter in greater detail. Since raw material particle properties often vary from batch-to-batch, a full understanding of the variations caused by particle size and the mechanisms involved in these variations, is considered to be of practical usefulness.

6. Measurement of particle properties of HPMC powder

The determination and control of particle size is often a necessity in pharmaceutical analysis and formulations. This is particularly true in solid dosage forms. The size range and distribution of particles in a given product can influence its safety, efficacy, stability and viability of the manufacturing process (Randall, 1995).

In describing the particle diameter of a sample, three size parameters may be used: mean, median and mode. The mean is the sum of all diameters divided by the total number of particles. The median is the value above and below which 50% of the particles are found. The mode represents the size occurring most frequently. The mode is used less frequently than either mean or median. In a perfectly symmetrical distribution, mean, median and mode values are the same (Randall, 1995 and Weiner and Tscharnuter, 1987). Since most pharmaceutical substances comprise a range of particle sizes, it is important that the size distribution is determined.

A variety of techniques is available for sizing particles. The following methods are the most frequently used to characterize powders (Weiner and Tscharnuter, 1987 and Allen, 1990).

a. Microscopy

Despite the emergence of many methods for particle sizing, microscopy still remains a powerful tool. Advantages include direct visual representation of the particle being measured and the provision of information on particle shape. Only small samples are needed and the equipment is relatively inexpensive and simple to calibrate and maintain.

b. Sieving

Sieves provide mechanical barriers allowing separation of particles on the basis of size. Sieving is a rapid, convenient means of sizing larger particles in the dry state. In practice, a series of sieves is mounted with the largest mesh on top, followed by successively finer ones and finally a collecting pan. By placing a known amount of sample on the top sieve, shaking for a defined time, then collecting and weighing the material retained by each sieve and the collecting pan, the distribution of particles by size in the batch can be determined.

c. Electro-zone sensing

In such systems, sample particles are first suspended in an electrically conducting medium. The suspension containing the particles of interest

flows through a small orifice or aperture with an electrode on either side. The base resistance to the current between the electrodes is determined by aperture size and electrolyte strength. As each sample particle passes through the aperture, it displaces a volume of electrolyte solution equal to its own volume, momentarily changing the resistance and creating an electrical pulse. The magnitude of the electrical pulse is directly related to the size of the particle. This enables the particles to be sized and counted.

d. Light diffraction

This method is based on the theory of Fraunhofer diffraction, static light scattering or low-angle forward light scattering. This method can be applied to very small particles, as long as their dimensions are larger than the wavelength of the incoming light. Like microscopy and electro-zone sensing, it can be applied to the measurement of a wide range of particle types.

7. Particle size, size distribution and number of polymer particles

Particle size and size distribution are important physical properties of a polymer powder. Feret's, Martin's, projected area, specific surface,

stoke's and volume diameters are the various measurements that have been used to quantify particle size and size distribution.

Span of size distribution is an indication of the particle size spread between the 10% ($D_{10\%}$) and 90% ($D_{90\%}$) points of the cumulative distribution, scaled by the size of the 50% ($D_{50\%}$) point. It is described by the following equation:

$$Span = (D_{90\%} - D_{10\%}) / D_{50\%} \qquad (4)$$

In light diffraction measurement, the volume of particles in a particular size fraction with respect to the total volume of particles measured could be determined. The number of particles in the size fraction, which was referred to as the relative number of polymer particles, can be calculated using the following equation:

$$N_{polymer} = \Sigma \, 6 \, V_i / \pi \, d_i^3 \qquad (5)$$

where $N_{polymer}$ is the relative number of polymer particles for each size fraction, V_i is the relative volume of polymer particles in channel i in the light diffraction measurement, d_I is the diameter of the channel i.

C. Reservoir systems – membrane coating

For a reservoir system, the simplest and most effective method to achieve extended release is by the use of a membrane coating (Chen and Lee, 2001). Membrane coating can be carried out by the application of a polymer solution or dispersion onto the surface of the dosage form. As the solvent evaporates, polymer solidification occurs in the case of a solution or coalescence in the case of a dispersion. In either case, a porous membrane is formed and the pores or channels permit drug diffusion. Adjustment of the rate of water penetration and drug release is achieved by controlling membrane thickness or by addition of soluble pore/channel producers (Chen and Lee, 2001 and Kim et al., 2000).

Acrylic or water-insoluble cellulosic polymers have been extensively utilized as the film-former for reservoir systems. These may be applied from organic solution or preferably from aqueous dispersion. The method of application and processing conditions may influence the porosity of the coating and consequently the release mechanism (Parikh et al., 1993 and Narisawa et al., 1994b). Cellulose esters such as acetates and butyrates are often applied to produce insoluble but semi-permeable films. Some of the methacrylate polyester polymers are essentially insoluble throughout the gastrointestinal tract and may be useful in forming the membrane for enveloping reservoir systems.

1. Advantages of ethylcellulose (EC)

Among the film-formers used in pharmaceutical coating, ethylcellulose (EC) is probably the most widely used water-insoluble polymer (Narisawa et al., 1994a and Yang et al., 1992). EC is a cellulose ether produced by the reaction of ethyl chloride with an appropriate alkaline solution of cellulose. EC is an ideal polymer for extended release coating. It is odorless and tasteless, with good film-forming properties. The films formed are physicochemically and mechanically stable. The water channel within an EC membrane is the major pathway for drug diffusion (Narisawa et al., 1993 and Wesseling and Bodmeier, 1999).

2. EC coating

There are two methods to apply an ethylcellulose film. One method uses an organic solvent such as ethanol in which EC is soluble. An alternative method uses a plasticised aqueous dispersion system. The latter method is preferred due to safety and environmental pollution considerations as well as the ability to achieve high level of suspended solids without increasing the viscosity of the spray medium.

a. EC film formation

Ethylcellulose film formation from organic solutions occurs when evaporation of the solvent initiates an increase in polymer concentration.

At higher polymer concentrations, an intermediate gel-like stage is reached. Upon further evaporation of the solvent, a polymeric film is obtained (Ozturk et al., 1990).

Film formation from aqueous colloidal polymer dispersions is more complex (Antal et al., 1997). During coating, the polymer dispersion is sprayed onto solid particles in suitable equipment under process conditions which result in evaporation of water. As water evaporates, the colloidal particles are forced to move closer together to form a packed particulate film. Plasticisers are used to reduce the minimum film formation temperature (MFT) below the coating temperature. The combination of the close-packing of polymer particles and plasticity from operation above the MFT results in polymer coalescence and the establishment of a continuous film with suitable permeability to control drug release.

The choice and level of plasticiser are critical. A plasticiser promotes coalescence by reduction of the polymer glass transition temperature and thus MFT. Under-plasticisation of the polymer can result in incomplete film coalescence, while over-plasticisation can produce excessive tackiness (Kojima and Nakagami, 2002). The coalescence process, which may not be immediate, is dependent on the degree of plasticisation and the process temperature. In cases where coalescence is not immediate, a

post-coating curing process at elevated temperature is commonly recommended to ensure that a coherent stable film is formed.

The pore formation process of EC in the casting process has been investigated (Narisawa et al., 1993). Where an EC-ethanol–water ternary mixture was cast, a porous film was spontaneously formed via the process of coacervation and gelation of the polymer. Visual and microscopic observation revealed that pore formation proceeded on the basis of a phase separation mechanism, in which ethanol and water acted as solvent and non-solvent, respectively, for the polymer. The concentration of the solvents decreased gradually through evaporation. Gelation, which is an important process for establishment of the density of the resultant film, occurred when the decreasing ethanol concentration reached a critical concentration of approximately 62%. This value was almost constant, irrespective of polymer concentration and molecular weight. The density of the porous EC film was found to be affected by coating solution formulation variables, such as organic solvent : polymer ratio and organic solvent species. The permeation study of porous EC film was conducted using salicylic acid as the permeant.

b. Permeability enhancement

A coating composed of EC alone may provide excessive retardation of release with poorly water-soluble drugs, because of its dense structure, small degree of swelling (<4 % weight for pure polymer) and low water permeability (Sadeghi et al., 2001). In some circumstances, it is desirable to increase the permeability of an EC film and various microporous film-coating methods have been developed to achieve this. Some research work has demonstrated that it is possible to modify the porosity of the EC free film by varying the solvent / polymer ratio. It was reported that the use of different ratios of water and ethanol could control the permeability of EC films (Narisawa et al., 1993). The most frequently used method of permeability enhancement is by the incorporation of water-soluble ingredients into the coating dispersion (Yang et al., 1992 and Sadeghi et al., 2001). The inclusion of a hydrophilic polymer in EC coating film may increase the degree of swelling of the membrane so that drug permeation rate can be modified. In addition, a more swellable coating film may reduce the stress from the swollen core so that breakage of the coating film can be prevented even if some small flaws or cracks are present. Addition of a secondary polymer such as HPMC or polyethylene glycol (PEG) increases the hydrophilicity of the film and introduces pore and channel structures, thus promoting drug diffusion. Additives such as Span 20 may act as a carrier for salicylic acid through EC film. Tetrabutylammonium bromide may complex with salicylic acid, increasing its solubility in the membrane or increasing the diffusion coefficient. In

general, low viscosity methylcellulose (MC), HPMC, hydroxypropylcellulose (HPC) and PEG are commonly used additives in EC films.

Adding pore-forming agents to EC, to create more porous films, also has several other advantages (Narisawa et al., 1994c and Kim et al., 2000). Firstly, it reduces film tackiness, making application much easier. Secondly, for non-water soluble drugs, this pore forming agent enables an increased film-thickness, while achieving the same release rate, thus ensuring the relative uniformity of thickness of the applied film and reducing variation in dissolution performance.

c. Drug release mechanism

Several mechanisms have been proposed to explain the release behavior from EC film-coated systems (Chen and Lee, 2001; Narisawa et al., 1994c; Sajeev and Saha, 2001; Narisawa et al., 1993). One of the mechanisms involves the diffusion of solute molecules through the continuous plasticised polymer phase. This mechanism assumes that the polymer forms a continuous phase in which the plasticiser and other additives are homogeneously dispersed and the diffusion of solute molecules within the amorphous polymer phase is a dynamic process involving the cooperative movements of the penetrant through the polymer chain segments. In

effect, thermal fluctuations of chain segments allow sufficient local separation of adjacent chains to permit the passage of the penetrant. It is by this stepwise process that hindered molecular diffusion occurs. This behaviour has been described by the following mathematical equation:

$$P_a = P_m + P_p = (D\epsilon/\tau\beta)\,K + \epsilon_p\,D_p\,/\tau_p \qquad\qquad (6)$$

where P_a is the drug permeability through the coated tablet, P_m and P_p are the permeabilities in the polymer and aqueous phase respectively, D is the molecular diffusivity of drug, K is the distribution coefficient of drug between polymer membrane and water, τ is the tortuosity factor, ϵ is the volume fraction of polymer channels and β is the chain immobilization factor, reflecting the degree of cross-linking of crystallites in the polymer, D_p is the aqueous diffusivity of drug, ϵ_p is the volume fraction of aqueous channels, and τ_p is the tortuosity of the aqueous channels (Ozturk et al., 1990).

It was recognized that an osmotic pump mechanism also plays an important part in drug release from EC-coated systems. This has been demonstrated using coated spherical beads. Phenylpropanolamine hydrochloride (PPA) was used as a model drug. A plot of release rate against osmotic pressure revealed an inverse linear relationship with a non-zero intercept. The steep dependency of release rate on osmotic

pressure of the medium suggested that osmotically-driven release is a major mechanism for PPA pellets coated with an EC based film, while the non-zero intercept indicated some contribution from the diffusion mechanisms. A mathematical equation was derived to represent osmotically driven release:

$$J = \alpha \Delta\Pi(C_i - C_b) = k\ \sigma\Delta\Pi(C_i - C_b) \tag{7}$$

where α equals the product of k and σ, and is the osmotic driving force parameter, J is the flux of the solute (permeation rate per unit surface area) , k is the filtration coefficient, σ is the reflection coefficient, $\Delta\Pi$ is the osmotic pressure difference across the coating, and C_i and C_b are the core and bulk drug concentrations respectively (Ozturk et al., 1990).

D. Reservoir dispersed matrix system

Coating of tablets to achieve extended release properties can pose dosing problems, as cracks or non-uniformity of the coat can be detrimental to drug release, resulting in dose-dumping should the coat fail. A combination of matrix and coating, described as a reservoir dispersed matrix system, minimises this problem and gives greater flexibility in the achievement of the desired release kinetics and release rate (Sajeev and Saha, 2001). Reservoir dispersed matrix systems are composed of a

matrix-type core with a polymer coating having lower permeability than the core matrix. The coat serves as a rate-limiting barrier to drug release. The available factors for controlling of drug release include drug/polymer ratio of the core matrix tablet, thickness of coating applied to tablet and quantity and type of soluble additive present in the coating formulation. Such formulations exhibited dual control, where membrane coating controlled the release rate for the initial 3-4 hours of release and matrix structure controlled the release during the later phase. There had been very limited reported research work on the reservoir dispersed matrix systems and the release mechanism from such systems warrant further investigation.

1. Pre-plasticized EC dispersion

Aqueous EC dispersion systems had been reported to pose problems when used for extended release systems. Changes in drug release profile during storage or aging effects had been reported (Wesseling and Bodmeier, 1999 and Kojima and Nakagami, 2002). Aging effects had been attributed to incomplete coalescence during manufacture, followed by progressive coalescence of the colloidal polymer particles during storage. Drug release rate generally decreased upon storage. Each EC particle was composed of numerous polymer molecules or chains. It was proposed that polymer chains in adjacent particles diffuse across the particle

boundaries, resulting in progressive coalescence and disappearance of the particle contours. In such cases, a curing step after the coating process is recommended to accelerate the film formation process and avoid stability problems. The curing step involves thermal treatment at elevated temperatures above the MFT (Kojima and Nakagami, 2002).

Surelease (Colorcon, USA) is an example of an EC dispersion available commercially for film coating. It is a ready-to-use, plasticised and stabilised aqueous dispersion of EC. In film formation using pre-plasticised EC aqueous dispersions, the aging effect can be eliminated because complete coalescence of the film is achieved during the coating process. In addition, the curing step is not necessary (Sadeghi et al., 2001).

2. Equipment for coating application

Various types of equipment are employed for coating tablets, pellets and granules. In the selection of equipment, major considerations are given to the following factors. Efficient drying capacity, even distribution of coating material inside the coating chamber, effective flow of material to be coated without significant attrition, and rapid removal of dust and evaporated solvent generated from the coating process.

Commonly used equipment can be broadly divided into 3 categories: conventional coating pans, fluid bed coaters and side-vented pans.

The conventional coating pan was originally designed for sugar-coating which required low drying air flow volumes. Mixing of the tablet cores is generally poor. Without modification to the drying air system and improvement in mixing by the use of baffles, problems may arise if this type of equipment is used for film-coating.

Fluid bed coaters have high drying and mixing efficiencies. These are achieved by high air throughput, blowing from the bottom of coater. Fluid-bed coater is mainly used for granule or pellet coating but is less suitable for tablet coating due to attrition problems resulting from the intense tumbling action.

Side-vented pans are the most frequently used machine for film coating of tablets. Baffles are added to assist mixing and ensure even flow of tablets. Drying is achieved by air-flow penetrating through the tablet bed and coating is applied by spray guns onto the tablet bed surface. An even coating spray is achieved by atomising the coating solution to produce a dispersion of fine droplets.

E. Mathematical equations used to represent drug release kinetics

Different mechanisms of drug release have been proposed for various types of extended release product. The drug release mechanisms affect the release kinetics, which can be represented by mathematical equations or models. Hence, model fitting of drug dissolution results is commonly employed to elucidate the drug release mechanism of a product (Wan et al., 1992; Gao et al., 1996; Veiga et al., 1997). The following are commonly employed release models.

1. Korsmeyer-Peppas equation

$$\frac{M_t}{M_\infty} = Kt^n \tag{8}$$

where M_t/M_∞ is the fraction of drug released at time t, K is a constant and n is the exponent indicative of release mechanism. When n value is approximately 0.5, it indicates that release follows the Higuchi mechanism When n value is in between 0.5-1, the release mechanism is likely to follow first order kinetics. When n is approaching 1, release kinetics normally follows zero order.

2. Zero order equation

$$M = M_0 - K_0 t \qquad (9)$$

where M is the amount of drug remaining in the product at time t, M_0 is the initial amount of drug in the product, and K_0 is the zero order release constant.

3. First order equation

$$LnM = LnM_0 - K_1 t \qquad (10)$$

where K_1 is the first order release constant.

4. Higuchi square root equation

$$M_t = K_H t^{1/2} \qquad (11)$$

where M_t is the amount of drug released at time t and K_H is the Higuchi rate constant.

5. Hixson-Crowell cube root equation

$$M_t^{1/3} = M_0^{1/3} - K_c t \qquad (12)$$

where K_c is the Hixson-Crowell rate constant.

II. **OBJECTIVES**

The HPMC matrix system provides a convenient approach to sustain drug release. However, during formulation, scale-up and routine manufacture, it is often difficult to achieve reproducibility in drug release behaviour. One of the critical criteria is the polymer particle size. Differences in polymer particle size may lead to significant variations in drug release. In extreme situations, these variations could result in tablet disintegration and consequential dose dumping. Control of HPMC particle size is a common approach adopted to achieve batch to batch release consistency. In practice, it is unrealistic to control the HPMC powder to a very narrow particle-size range, due to cost and availability concerns. Our literature search has suggested that research on the impact of a wide range of polymer particle sizes and quantity of HPMC particles in the formulation on drug release profile and kinetics is limited and worthy of further investigation. Hence, the specific aims of the first part of the study were:

(a).   to investigate the effects of HPMC content (or quantity of HPMC particles) on drug release performance,

(b).   to investigate the effects of HPMC particle size on drug release behaviour, and

(c).   to evaluate the effects of HPMC particle size distribution on drug release.

Application of EC coating to matrix tablets is considered to be effective in modifying drug release kinetics and is especially useful in achieving time-independent extended release performance of the drug delivery system. The combination of EC coating and hydrophilic HPMC matrix systems is predicted to provide stable extended drug release with much reduced danger of dose dumping. In addition, it also enables greater formulation flexibility by provision of a greater number of release rate/release kinetics adjustment factors. The available information on this type of delivery system, including its mechanism of drug release, is very limited. Hence further study could help to provide useful knowledge for formulation and production of such sustained release dosage forms.

The aims of the second part of the study were:

(a).   to investigate the release performance of HPMC matrix tablets coated with EC, using model drugs of different solubilities,

(b).   to evaluate the effects of HPMC content on drug release from EC-coated matrix tablets,

(c).   to identify the effects of EC coating weight gain on drug release performance, and

(d).   to investigate the effects of varying quantities of soluble additive in the coating formulation on drug release rate and kinetics.

III. EXPERIMENTAL

Part I. Study of the effects of polymer particle properties on drug release from matrix tablets.

A. Materials

Aspirin (USP grade) was used as a model drug. Solubility of aspirin in water is 3 in 100 parts at 20 ºC. Aspirin was micronised using a pin mill (Retcsh ZM 1000, Germany) to a mean particle size of 79 μm. Anhydrous lactose (Pharmatose DCL 21, DMV, The Netherlands), dibasic calcium phosphate (Emcompress, Edward Mendell, USA) and magnesium stearate (Merck, Germany) were used as supplied.

Matrix polymer used was HPMC (K15M premium, 15,000 cps, Dow Chemical, USA). Using sieves, the HPMC powder was divided into the following sieve aperture size fractions for study: 20 μm – 30 μm, 40 μm – 50 μm, 70 μm – 80 μm, 100 μm – 120 μm and 160 μm – 200 μm. Unsieved powder was used as the control.

B. Methods

1. Milling of drug

Aspirin was comminuted using a pin mill (Retsch ZM 100, Germany). For the pin-milling process, the screen size selected for use was 500 micron with a 24-pin impeller rotating at a speed of 15000 rpm. The batches of milled aspirin powder were then combined.

2. Preparation of matrix tablets

The formulations of the matrix tablets used for evaluating the effects of HPMC particle size with fillers of different solubilities are given in Table 1-3. The batch weight of each formulation was 35 g. Weighed quantities of aspirin, HPMC and filler were first thoroughly mixed in a plastic bag for 15 min. The lubricant, magnesium stearate, was then added and mixed for a further 5 min. A 350 mg weighed portion of resultant mixture was then compressed into tablets of 3.9 mm thickness, using a single punch tablet machine (Manesty, E2, UK) with 9.5 mm diameter flat punches. Only tablets with weight deviation within 2 % of the theoretical weight were selected for study. The amount of aspirin in each matrix tablet was kept at a constant 120 mg, while the concentration of HPMC was varied. For the evaluation of polymer particle size effects, 5 different size fractions of HPMC were used at each concentration level. For evaluating the effects of filler solubility, unsieved HPMC was used with either lactose (soluble filler) or dibasic calcium phosphate (insoluble filler).

Table 1. Formulations of aspirin matrix tablets for evaluating the effects of HPMC particle size

Component	Formulation series				
	A	B	C	D	E
Aspirin (mg)	120	120	120	120	120
HPMC (sized)	5%	10%	20%	30%	40%
Lactose	QS	QS	QS	QS	QS
Magnesium stearate	1%	1%	1%	1%	1%

* Tablet weight was kept constant at 0.350 g. Five different size fractions of HPMC were used at each HPMC concentration level. QS, as much as was sufficient.

Table 2. Formulations of aspirin matrix tablets using unsieved HPMC K15 powder with lactose as the filler

Component	Formulation series					
	F	G	H	I	J	K
Aspirin (mg)	120	120	120	120	120	120
HPMC (unsieved)	0%	10%	20%	30%	40%	50%
Lactose	QS	QS	QS	QS	QS	QS
Magnesium Stearate	1%	1%	1%	1%	1%	1%

* Tablet weight was kept constant at 0.350 g. QS, as much as was sufficient.

Table 3. Formulations of aspirin matrix tablets using unsieved HPMC K15 powder with dibasic calcium phosphate (DCP) as the filler

Component	Formulation series					
	L	M	N	O	P	Q
Aspirin (mg)	120	120	120	120	120	120
HPMC (unsieved)	0%	10%	20%	30%	40%	50%
DCP	QS	QS	QS	QS	QS	QS
Magnesium Stearate	1%	1%	1%	1%	1%	1%

* Tablet weight was kept constant at 0.350 g. QS, as much as was sufficient.

3. Determination of drug content of matrix tablets

Randomly selected tablets were pulverized individually using a pestle and mortar. About 100 mg of the resultant powder was accurately weighed and transferred to a 250 ml volumetric flask. Phosphate buffer, pH 6.8 (USP) was added with continuous agitation to final volume. An aliquot sample was removed through a 0.45 μm filter and assayed for aspirin spectrophotometrically at 265 nm (Shimadzu, UV 1201, Japan). Each determination was carried out in triplicate and five tablets were analyzed for each formulation and the results averaged.

4. Dissolution test of matrix tablets

The dissolution test was carried out using the paddle apparatus (USP XXIII, method II, Hanson Research, 72-RL, USA) at 50 rpm and 37 ºC ± 1 ºC. Each tablet was accurately weighed and 3 tablets of each formulation were used. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8 (USP). At pre-selected time intervals, 4 ml samples were collected over eight hours using an automated sampler (Hanson Research, Dissotte 27-6A, USA). The samples removed were not replaced and the resultant loss in volume of the dissolution medium was compensated for in the calculation. The amount of drug released was determined by UV

spectrophotometry (Shimadzu, UV1201, Japan) at 265 nm. At least three replicated runs were carried out and the results were averaged.

5. Determination of polymer particle properties

HPMC K15M powder particle size properties were determined using a laser diffraction particle sizer (Coulter, LS230, USA). The measurement was based on the amount of laser light diffracted by particles. The sizer also provided submicron size information using the polarization intensity differential scattering (PIDS) method. The LS230 sizer employed laser light with a wavelength of 750 nm to size particles.

Part II. Study of the release performance of ethylcellulose coated matrix tablets

A. Materials

Aspirin (USP grade) was used as a poorly water-soluble model drug, while naproxen sodium (BP grade) was chosen as the soluble model drug and both were used as supplied.

HPMC (K4M, CR grade, Dow Chemical, USA) was used as the matrix polymer. α-lactose monohydrate (Pharmatose 200M, DMV, The

Netherlands) was used as the filler. In the case of aspirin, microcrystalline cellulose (Avicel PH 101, Asahi Chemical, Japan) was added as a binder to maintain reasonable tablet strength for the coating process. Stearic acid (Merck, Germany) was used as the lubricant in both cases.

Ethylcellulose, in the form of an aqueous dispersion (EC, Surelease E-7-19010, Colorcon, USA) was used as the coating polymer. Opadry (OY-7240 clear, Colorcon, USA) was used as a release channel agent in the coating formulation. Opadry is a water-soluble powder composed of HPMC E6 and PEG 4000 which acts as plasticiser.

B. Methods

1. Preparation of matrix tablets for coating

The formulations of naproxen sodium matrix tablets are shown in Table 4. The batch weight of each naproxen sodium formulation was 500 g. The weighed amounts of naproxen, HPMC, and lactose were first thoroughly mixed in the blender (Erweka, AR 401, Germany) for 30 min. The lubricant, stearic acid, was then added and mixed for a further 10 min. The resultant mixture was then compressed into 625 mg tablets, using a

Table 4. Formulations of naproxen sodium matrix tablets for EC coating

Component	Formulation series			
	1	2	3	4
Naproxen sodium (mg)	250.00	250.00	250.00	250.00
HPMC K4M (mg)	0.00	93.75	187.50	281.25
Pharmatose 200M (mg)	368.75	275.00	181.25	87.50
Stearic acid (mg)	6.25	6.25	6.25	6.25

single punch tablet machine (Manesty, E2, UK) with 9.5 mm diameter concave punches. The quantity of naproxen sodium in each matrix tablet was kept constant at 250 mg, while the concentration of HPMC was varied. For the evaluation of the impact of polymer content on drug release behaviour, polymer concentrations of 0 %, 15 %, 30 % and 45 % respectively were used.

The formulations of the aspirin matrix tablets are given in Table 5. The batch weight of each formulation was 500 g. The powder blend was prepared according to the procedure for naproxen sodium-HPMC matrix tablets. Similarly, the resultant mixture was then compressed into 350 mg tablets. The amount of aspirin in each matrix tablet was kept constant at 120 mg, while the concentration of HPMC was varied. Polymer concentrations of 0 %, 10 %, 15 % and 20 % were used to evaluate the effects of HPMC level on drug release performance.

2. Determination of drug content of matrix tablets

The drug content was determined according to the procedure described earlier (Experimental, Part I, Method B3). Aspirin was assayed spectrophotometrically at 265 nm while naproxen sodium at 332 nm.

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Table 5. Formulations of aspirin matrix tablets for EC coating

Component	Formulation series			
	5	6	7	8
Aspirin (mg)	120.00	120.00	120.00	120.00
HPMC K4M (mg)	0.00	35.00	52.50	70.00
Pharmatose 200M (mg)	156.50	121.50	104.00	86.50
Avicel PH101 (mg)	70.00	70.00	70.00	70.00
Stearic acid (mg)	3.50	3.50	3.50	3.50

3. Preparation of coating dispersion

The Surelease dispersion (as supplied) consisted of 25 % w/w solids content and was found unsuitable to be sprayed directly. Thus, dilution of Surelease dispersion was required. An amount of 66.7 g of distilled water was added to 100.0 g of Surelease dispersion with constant stirring for 30 min, and this reduced the level of solids to 15 % w/w.

A 15 % w/w Opadry solution was prepared separately by adding 15 g of Opadry in 85 g of distilled water. The mixture was stirred for 1 h to form a homogeneous solution. Appropriate amount of this solution were then added to the diluted Surelease dispersion to obtain final mixtures consisting of 10 %, 20 % and 30 % of the Opadry with respect to the total coating solids. The Surelease : Opadry mixtures were stirred thoroughly using a paddle stirrer at 200 rpm for another hour.

4. EC coating process

The matrix tablets were coated using a side-vented coating machine (O'Hara Technologies, Labcoat I, Canada). The side-vented pan had perforations and a coating capacity of 0.5 to 1 kg tablets. The coating parameters employed for naproxen sodium and aspirin are given in Tables 6 and 7 respectively.

Table 6. Coating parameters for naproxen sodium matrix tablets in the side-vented coater

Coating parameter	Opadry concentration in EC coating (%)			
	0	10	20	30
Tablet load (g)	680	700	710	690
Inlet air temperature (°C)	70	69	68	67
Bed temperature (°C)	47	47	47	49
Pan rotation speed (rpm)	12	12	13-15	12
Atomizing air pressure (bar)	2.1	2.1	2.1	2.1
Pattern air pressure (bar)	2.0	2.0	2.0	2.0
Pan pressure difference (mbar)	-0.3	-0.3	-0.2	-0.3

Table 7. Coating parameters of aspirin matrix tablets in the side-vented coater

Coating parameters	Opadry concentration in EC coating (%)			
	0	10	20	30
Tablet load (g)	680	700	700	700
Inlet air Temp. (°C)	57	59	56-63	56-63
Bed Temp. (°C)	43	39.7-43	39	40-45
Pan rotation speed (rpm)	10-12	12	12	12
Atomizing air pressure (bar)	1.4	1.3	1.4	1.4
Pattern air pressure (bar)	1.4	1.4	1.4	1.4
Pan pressure difference (mbar)	-0.9	-0.9	-0.9	-0.9

5. Determination of amount of coating applied to matrix tablets

Determination of the average coating weight gain applied to each batch was carried out by taking 40 accurately weighed yellow placebo tablets marked with a number from 1 – 40, and mixing together with white active tablets for coating. As the coating was transparent, the yellow colour and marking of the placebo tablets was not masked. The purpose of these placebo tablets was to enable calculation of the actual coating weight gain from each theoretical coating condition. The active tablets consisted of equal number of matrix tablets of different core formulations, differentiated by marking on the tablets. The tablets were coated together in a single batch to avoid variations due to uncontrollable differences in coating conditions. Tablets were coated to theoretical weight gains of 2 %, 4 %, 6 %, 8 % and 10 %. At each theoretical weight gain point, 10 of the marked placebo tablets were removed, accurately weighed and then returned back to the batch. Difference of weight before and after coating was divided by the original tablet weight. The percentage, representing actual coating percentage weight gain per tablet, was calculated and the ten individual tablet results were averaged.

6. Dissolution test of coated matrix tablets

The dissolution test was carried out according to the procedure described earlier (Experimental, Part I, Method, B4), aspirin was assayed spectrophotometrically at 265 nm and naproxen sodium at 332 nm.

IV. RESULTS AND DISCUSSION

Part I. Influence of HPMC particle properties on release of aspirin from HPMC matrix tablets

1. HPMC particle properties

HPMC K15M was divided into different size fractions using sieves of different mesh sizes. The mean particle size, median particle size, and volume distribution of each size fraction were determined. A total of 3 runs for each size fraction was carried out and the results were averaged (Table 8). Particle size properties of unsieved HPMC K15M are also listed in Table 8.

As shown in Table 8, the mean particle size of unsieved HPMC K15M was almost the same as that of the 70 - 80 μm sieve aperture size fraction, both around 110 μm. However, their size distribution patterns were very different. Distribution span for unsieved HPMC K15M was 2.34, about double the value of the 70 - 80 μm sieve aperture size fraction. This indicates that the particle size distribution of the unsieved HPMC powder was much wider compared to the sieved fraction.

Table 8. Particle characteristics of unsieved HPMC K15M and its different size fractions

Sieve aperture size	Mean particle size	Median particle size	Size distribution span	Number of particles per unit volume*	Volume percentage of counted particles
20 - 30 μm	34 μm	34 μm	1.39	604118	98.58 %
40 - 50 μm	58 μm	56 μm	1.37	341696	99.03 %
70 - 80 μm	113 μm	113 μm	1.24	126922	99.96 %
100 - 120 μm	180 μm	181 μm	1.02	35536	99.97 %
160 - 200 μm	309 μm	307 μm	0.996	4488	100.00 %
unsieved	112 μm	111 μm	2.34	197370	99.70 %

* Particles of size 1μm or larger.

The volume percentage of the HPMC particles in each size fraction was slightly less than 100 % because particles smaller than 1 μm were not included.

2. Effects of HPMC particle size on release of aspirin from matrix tablets

It was observed that the particle size of HPMC played an important role in determining the release of aspirin from the matrix tablet. The rate of aspirin released from the matrix tablet was affected by the particle size of HPMC to different extents (Figures 1-5). The drug release rate generally decreased as the HPMC mean particle size decreased, 309 μm > 180 μm > 113 μm > 58 μm = 34 μm. A markedly higher rate of drug release was observed when the mean particle size of HPMC was greater than 113 μm and the magnitude of the effect was also dependent on the concentration of HPMC in the matrix tablet. In contrast, less significant effects of particle size change on release rate were observed when HPMC of mean particle size 113 μm or smaller was employed within the range of polymer concentrations studied. Matrix tablets produced from HPMC with mean particle size of 180 μm or larger showed burst effects when HPMC
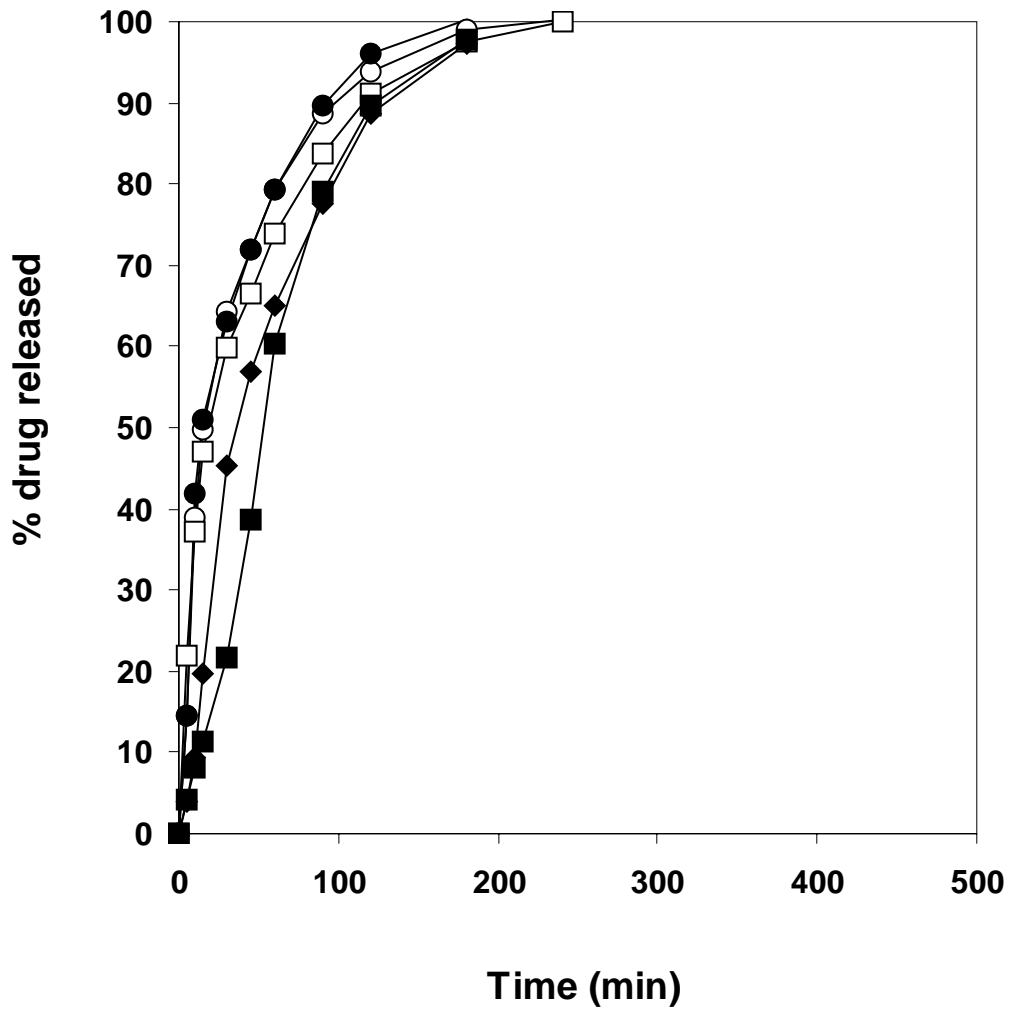
Figure 1. Effect of different HPMC K15M particle size fractions on aspirin release, at HPMC content of 5 %. Mean particle size : (○) 309 μm (●) 180 μm (□) 113 μm (■) 58 μm (◆) 34 μm
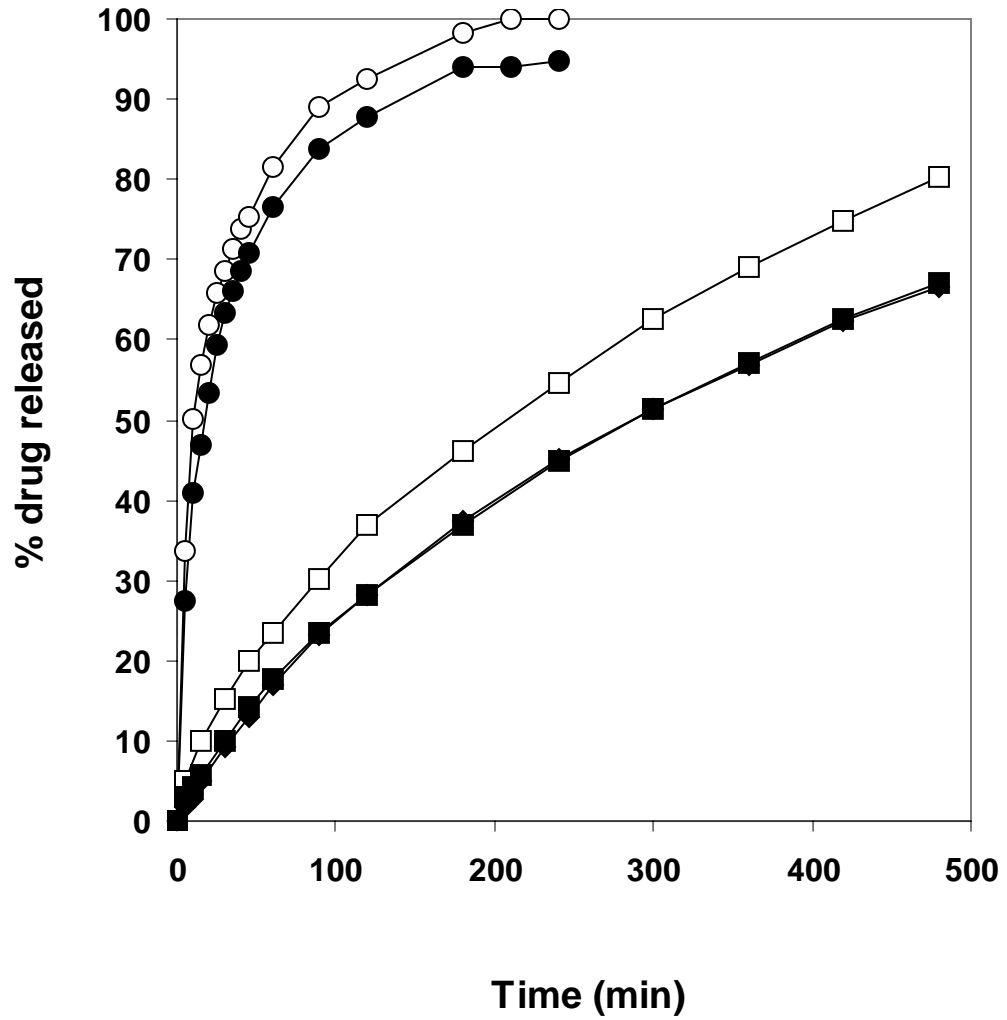
Figure 2. Effect of different HPMC K15M particle size fractions on aspirin release, at HPMC content of 10 %. Mean particle size: (O) 309 µm (●) 180 µm (□) 113 µm (■) 58 µm (◆) 34 µm
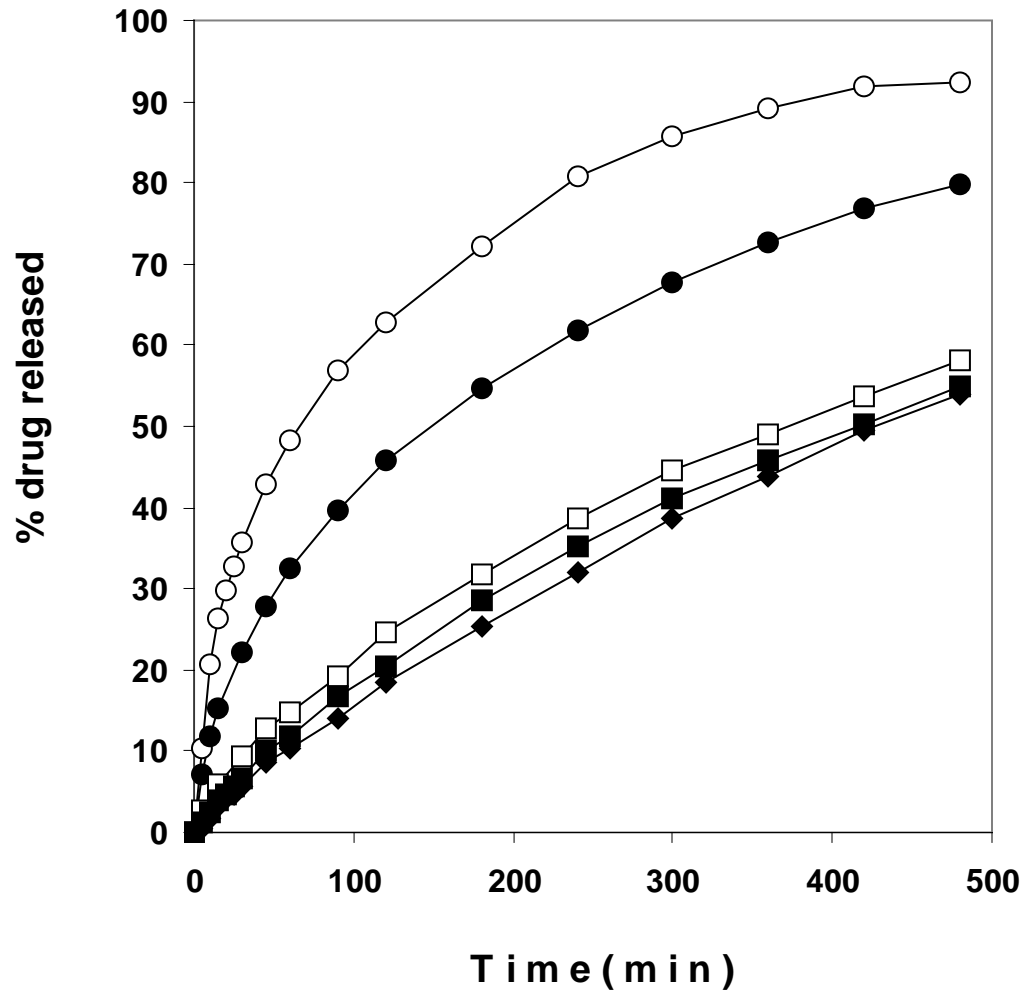
Figure 3. Effect of different HPMC K15M particle size fractions on aspirin release, at HPMC content of 20 %. Mean particle size: (O) 309 μm   (●) 180 μm (□) 113 μm (■) 58 μm (◆) 34 μm
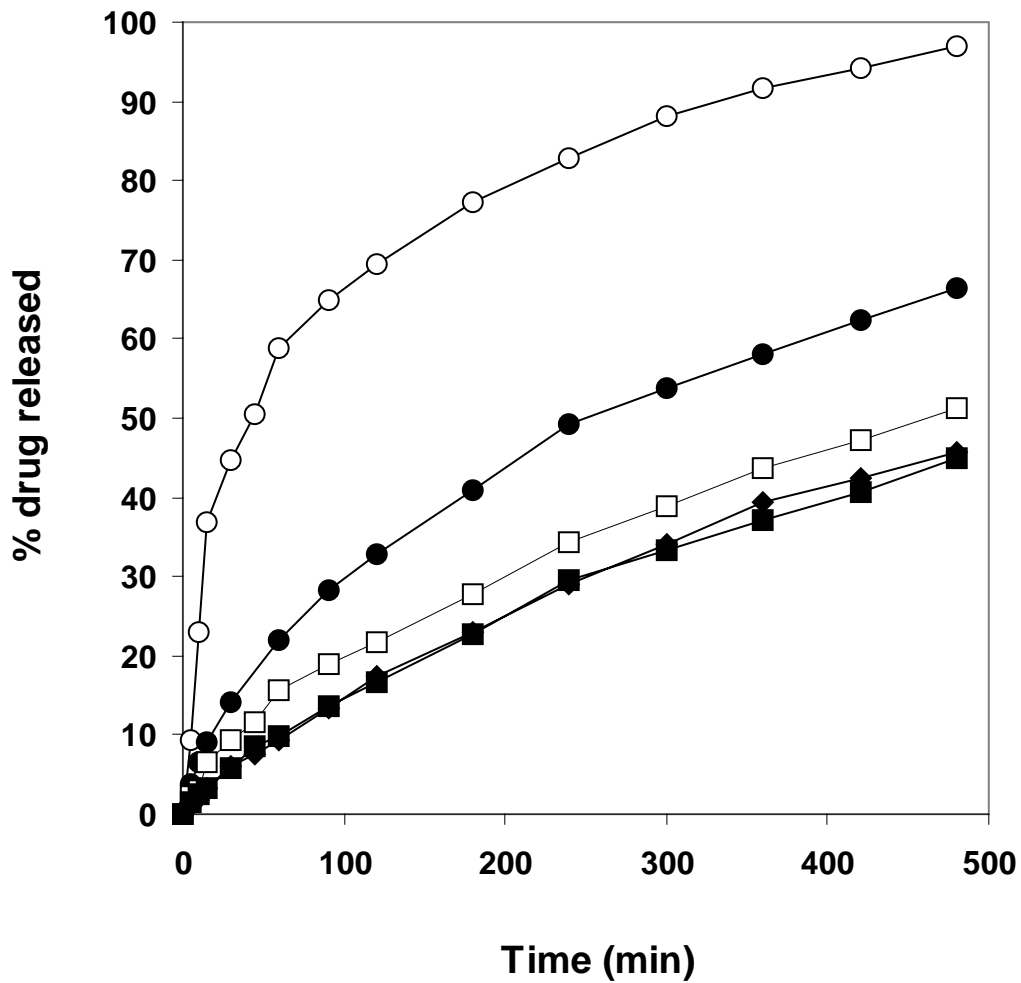
Figure 4. Effect of different HPMC K15M particle size fractions on aspirin release, at HPMC content of 30 %. Mean particle size: (O) 309 μm (●) 180 μm (□) 113 μm (■) 58 μm (◆) 34 μm
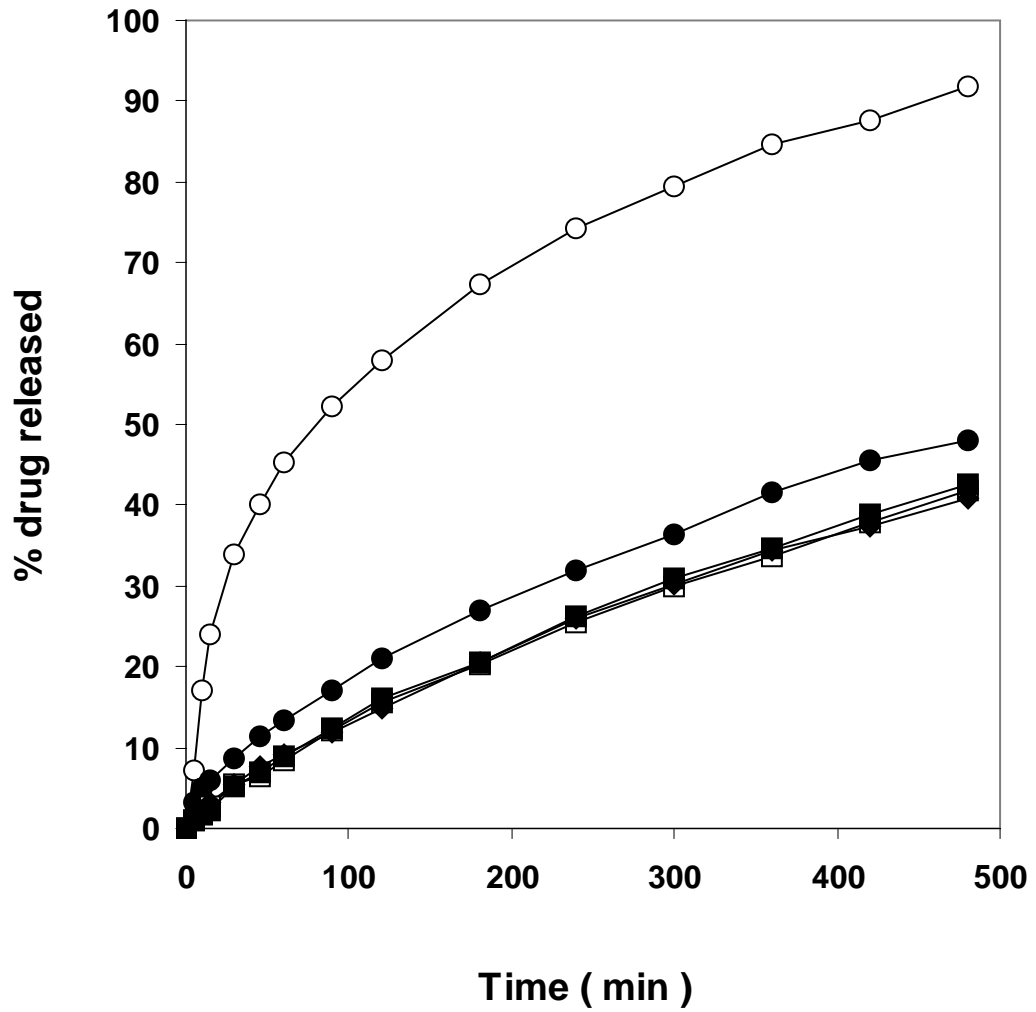
Figure 5. Effect of different HPMC K15M particle size fractions on aspirin release, at HPMC content of 40 %. Mean particle size: (O) 309 μm (●) 180 μm (□) 113 μm (■) 58 μm (◆) 34 μm
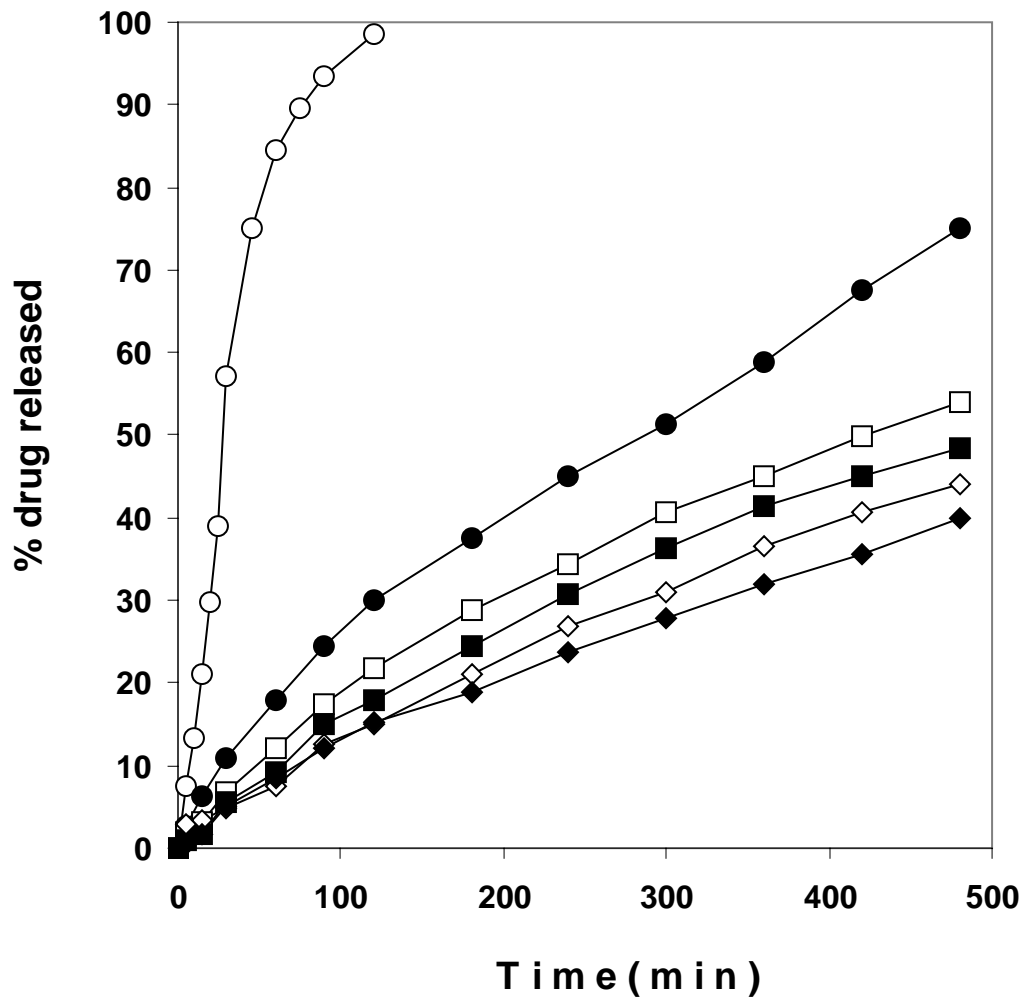
Figure 6. Effect of different concentrations of unsieved HPMC K15M on aspirin release from matrix tablets. HPMC concentration in the core : (○) 0 % (●) 10 % (□) 20 % (■) 30 % (◆) 40 % (◇) 50 %

content was less than 20 %. This effect was not observed with higher concentrations of HPMC.   Where HPMC particle size was larger than 180 μm, rapid drug release was seen at all the polymer concentrations studied. For polymer particles smaller than 113 μm, the burst effect was only apparent at the 5 % HPMC level. For all HPMC particle size fractions, it was found that aspirin release rate decreased as HPMC content increased in the formulation (Figures 1-6).

3. Effects of HPMC particle size on release kinetics of aspirin

In a polymer matrix system, segments of the polymer chain are continually in motion, thus creating voids. When the volume of these voids is of the same magnitude as the volume of a liquid molecule, these motions enable liquid molecules to pass through the polymer chains. This is how the hydration of the polymer and drug diffusion process is governed. Therefore, release kinetics expressing the diffusion of drugs from HPMC matrix is closely related to these motions. There are 3 possible situations governing drug release.

In situation I, HPMC in the matrix system is in the rubbery state and the chains adjust very quickly to the presence of a molecule of liquid. The rate of diffusion of the liquid is much less than the rate of relaxation of the polymer units, giving rise to Fickian diffusion. The amount of

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diffusing substance released at time *t* can be expressed by Higuchi release model.

In situation II, the polymer relaxation process is very slow or the volume of void is small compared with the rate of diffusion. The liquid diffuses through the polymer with a constant velocity showing an advancing front that marks the penetration limit of the liquid. Behind this advancing front, the polymer may transform into a swollen gel or rubbery polymer, while ahead of this front, the polymer free of liquid remains in the glassy state. The amount of drug released at time *t* follows zero order kinetics.

In situation III, the rates of diffusion of the liquid and relaxation of the polymer are of the same order of magnitude, giving rise to non-Fickian diffusion. This situation lies between situation I and situation II and the amount of drug released at time *t* follows first order release pattern.

In the current research work, HPMC mean particle size of 113 μm was identified as the threshold size for changes in drug release kinetics. Table 9 shows that the drug release mechanism was affected by HPMC mean particle size and HPMC concentration. When the HPMC mean particle size was 113 μm or smaller, the dissolution profiles generally gave a better fit with first order kinetics, which was observed for all the

Table 9. Kinetic parameters of aspirin release from matrix tablets formulated with different HPMC size fractions

Content of HPMC	Mean HPMC particle size	Korsmeyer-Peppas Equation		Zero Order Equation		First Order Equation		Higuchi Equation	
		n	R^2	K_0 (% min^{-1})	R^2	K_1 (min^{-1})	R^2	K_H (% min$^{-1/2}$)	R^2
5%	309 μm	0.2950	0.9509	*		0.0250	0.9822	*	
	180 μm	0.3070	0.9833	*		0.0269	0.9728	*	
	113 μm	0.3290	0.9844	*		0.0208	0.9715	*	
	58 μm	1.0130	0.9911	*		0.0170	0.9541	*	
	34 μm	0.8650	0.9853	*		0.0173	0.9887	*	
10%	309 μm	0.2046	0.9919	*		0.0278	0.9162	*	
	180 μm	0.2582	0.9506	*		*		*	
	113 μm	0.6085	0.9996	0.1947	0.8753	0.0034	0.9923	3.5378	0.9889
	58 μm	0.7053	0.9973	0.1602	0.9258	0.0024	0.9921	2.8764	0.9720
	34 μm	0.8114	0.9881	0.1596	0.9319	0.0024	0.9931	2.8593	0.9652
20%	309 μm	0.2809	0.9923	*		0.0073	0.9366	*	
	180 μm	0.5170	0.9911	*		0.0037	0.9450	3.8706	0.9923
	113 μm	0.6707	0.9993	0.1382	0.9185	0.0019	0.9834	2.4895	0.9746
	58 μm	0.8136	0.9954	0.1278	0.9602	0.0017	0.9942	2.2464	0.9445
	34 μm	0.8445	0.9967	0.1222	0.9808	0.0016	0.9991	2.1254	0.9241
30%	309 μm	0.3938	0.9919	*		0.0062	0.9348	4.9491	0.9264
	180 μm	0.5091	0.9962	0.1650	0.8436	0.0025	0.9604	3.0380	0.9942
	113 μm	0.6011	0.9970	0.1223	0.9014	0.0016	0.9668	2.2098	0.9821
	58 μm	0.7525	0.9985	0.1043	0.9548	0.0013	0.9868	1.8550	0.9547
	34 μm	0.8054	0.9977	0.1071	0.9668	0.0013	0.9905	1.8969	0.9492
40%	309 μm	0.3763	0.9935	*		0.0054	0.9477	4.6500	0.8962
	180 μm	0.5933	0.9990	0.1157	0.9005	0.0015	0.9634	2.0914	0.9841
	113 μm	0.8031	0.9977	0.0951	0.9682	0.0012	0.9917	1.6831	0.9447
	58 μm	0.8285	0.9947	0.0974	0.9686	0.0012	0.9923	1.7235	0.9435
	34 μm	0.7627	0.9983	0.0947	0.9610	0.0011	0.9878	1.6822	0.9509

*: R^2 too low, not applicable

HPMC concentrations studied. However, for HPMC mean particle size of 180 μm at HPMC concentration 20 % and above, the drug release mechanism gave best fit with the Higuchi kinetic model. At lower HPMC concentrations, the drug release mechanism was best described by the first order kinetics. The release mechanism for HPMC mean particle size of 309 μm at concentrations of 10 % and above did not fit with any of the models. This indicated that the magnitude of HPMC chain motion and volume of voids created were closely related to size of HPMC particles.

The effect of variation in polymer particle size distribution on drug release was also investigated by using sieved and unsieved HPMC powder of similar mean particle size. The unsieved HPMC powder had a mean particle size of 112 μm. Hence the 70 – 80 μm sieve aperture size fraction, which had a mean particle size of 113 μm was used in this study. Size distribution span of the unsieved HPMC powder was 2.34. In contrast, the size distribution of the 70 – 80 μm sieve aperture size fraction was narrower, with a distribution span of 1.24. Release profile and kinetic parameters for matrices prepared from the unsieved HPMC powders are shown in Figure 6 and Table 10. Changes in polymer size distribution generally did not affect the release mechanism within the HPMC concentration range studied. Drug release for both the sieved and unsieved polymer powders gave best fit with the first order release model.

However, as indicated by the release constant of the first order kinetics, K_1, differences in release rates were observed when the HPMC concentration was lower than 20 % (Tables 9 and 10). When the HPMC concentration was above 20 %, differences in release rate were not apparent.

The influence of polymer particle size could be explained by the binding efficiency of HPMC particles during gel layer formation. There are several basic factors governing the effective formation of HPMC extended release gel layer. Firstly, the polymer must hydrate sufficiently fast when wetted by the dissolution medium. Next, the hydrated polymer should swell and form a viscous gel. Finally, there must be sufficient adjoining HPMC particles present to provide contact and entanglement of the polymer chains, to produce a continuous and strong diffusion barrier on the surface of the matrix tablet. If the swelling polymer particles could not be in contact or bind with adjacent polymer particles, a strong and continuous release barrier would not be able to form. In addition, the matrix tablet would break-up readily as the pressure is generated within the tablet by swelling of the polymer particles with water uptake. Thus, drug would be released rapidly and the matrix tablet would be deemed as having failed. The potential for matrix system failure or burst release

Table 10. Kinetic parameters of aspirin release from the matrix tablets formulated with unsieved HPMC and different filler types

Filler type	HPMC content	Korsmeyer-Peppas Equation			Zero Order Equation		First Order Equation		Higuchi Equation	
		n	K	R^2	K_0 (% min^{-1})	R^2	K_1 (min^{-1})	R^2	K_H (% min$^{-1/2}$)	R^2
Lactose	0%	1.1052	1.074	0.9917	1.0850	0.8220	0.0315	0.9757	9.393	0.9091
	10%	0.7136	0.919	0.9981	0.1687	0.9436	0.0027	0.9869	3.046	0.9671
	20%	0.7394	0.594	0.9947	0.1265	0.9468	0.0017	0.9901	2.282	0.9619
	30%	0.8445	0.292	0.9958	0.1136	0.9680	0.0016	0.9983	2.033	0.9442
	40%	0.8302	0.277	0.9937	0.1011	0.9765	0.0013	0.9963	1.804	0.9370
	50%	0.8096	0.286	0.9725	0.0898	0.9621	0.0011	0.9875	1.613	0.9532
DCP	0%	0.3953	9.645	0.9730	*		*		*	
	10%	0.4546	4.531	0.9943	*		0.0029	0.8821	3.455	0.9835
	20%	0.6296	1.177	0.9926	0.1309	0.8629	0.0017	0.9496	2.238	0.9905
	30%	0.7377	0.506	0.9939	0.1040	0.9265	0.0013	0.9711	1.867	0.9711
	40%	0.7499	0.395	0.9897	0.0910	0.9603	0.0010	0.9809	1.618	0.9515
	50%	0.8005	0.289	0.9966	0.0884	0.9752	0.0011	0.9939	1.561	0.9385

*: R^2 too low, not applicable

depends on the matrix water uptake ability, extent of swelling, distance between adjacent polymer particles, as well as the strength of the diffusion gel layer formed.

The results obtained in this study suggested two possible phenomena to explain the bahaviour as polymer particle size was decreased. Firstly, for the same amount of polymer, reduction of particle size numerically increased the number of particles and hence the number of contact points available for binding of the swelling particle also increased. This would favour the formation of a continuous gel layer that would retard drug release, as well as inhibit further penetration of water into the tablet core. Secondly, a smaller polymer particle would produce a lower pressure differential on swelling when compared to a larger particle. Thus, the smaller polymer particles were less likely to cause disintegration of the matrix tablets. The above two effects aptly explained the lower release rate with decreasing HPMC particle size. Increasing HPMC content or reducing particle size could, to some degree, achieve similar drug release rate retarding effect. Depending on the concentration of HPMC in the tablet core, the release retarding effects due to particle size reduction leveled-off at a specific polymer particle size value. Further size reduction did not provide any significant change to the dissolution profile. At low HPMC concentrations, there are likely to be areas at the surface of the matrix tablet where there is no HPMC (Mitchell et al,

1993a). In their study, the smaller particles had approximately 3 times the surface area of the larger ones and spread more extensively over the entire matrix and reduced the size of the HPMC-free area.

From the current research, HPMC content was identified to be very important because of its influence on the effects of HPMC particle size and size distribution. It was observed that maintaining HPMC content above 20 % was helpful in developing a robust extended release matrix system. The matrix system prepared with 5 % HPMC released 80 % of the drug within 2 h and showed unpredictable release behaviour. Varying HPMC concentrations at levels below 20 % caused significant changes in the release rates, irrespective of the polymer mean particle size. Similarly, differing polymer size distribution exerted significant influence on drug release rate when the polymer level was less than 20 %. Hence, matrix systems with less than 20 % HPMC showed greater polymer particle size and size distribution sensitivity. When the polymer content was above 20 %, the influence of HPMC particle size and size distribution was significantly reduced.

With water insoluble drugs, hydrophilic matrix formulation might involve low HPMC concentrations. Therefore, it is essential that consideration be given to the influence of particle size and size distribution of the component polymer material, when developing matrix systems.

4. Quantitative relationship between drug release rate and HPMC particle properties

Several basic factors govern the formation and the extended release performance of a gel layer. Previous investigations proposed that the formation of the continuous gel layer was controlled by polymer hydration speed, polymer chain relaxation and swelling and availability of sufficient adjoining HPMC particles to provide contact and entanglement of polymer chains, thus producing a continuous barrier. It was also reported that increasing compression force could significantly affect tablet hardness and thickness, which would subsequently alter tablet porosity, tortuosity and surface area. However, minimal effects of compression force on drug release from HPMC tablets were observed (Baveja et al., 1988). This indicated that the initial surface area, porosity and tortuosity of the tablets had changed markedly during the process of polymer swelling and formation of the extended release gel layer or that drug release was independent of these tablet physical properties. Drug release performance is however expected to be more closely related to porosity and tortuosity of the gel barrier used to control the rate of drug diffusion, as well as the strength and viscosity of the gel layer to resist rapid erosion rather than the porosity of the original tablet matrix.

In this study, it appeared that polymer content, particle size, particle distribution and number of particles could directly influence the availability of adjoining particle contact points, viscosity, porosity and tortuosity of the gel layer. Increase in the size of particles of a constant total number or increase in the number of particles of equal size can both lead to higher degree of chain entanglement. This will result in a less porous and more tortuous diffusion barrier for drug release and water penetration into the tablet core.

With a higher polymer concentration per unit area, the resultant gel layer would be more viscous and consequently more resistant to erosion. For the layer containing polymer particles of similar size, the higher the total number of particles, the slower the drug release will be. For the same number of particles, the larger the polymer particles are, the slower the release will be.

For similar polymer content, reduction of particle size is accompanied by numerical increase in the polymer particle quantity. However, the effects of numerical increase in particle number were counteracted by the effects of particle size reduction.

According to the drug release models of the matrix tablets studied (Results and Discussions. Part I.3), the matrix tablet showed three

different release characteristics as particle size decreased: matrix disintegration at large particle size level, release by diffusion at medium size level and a combination of both erosion and release by diffusion at fine size level.

Within the polymer concentration range studied, large particles upon swelling could not effectively bind with adjacent ones due to insufficient availability of polymer particles at immediately adjacent locations. Thus, the isolated polymer particle functioned as a disintegrant rather than a release-retarding agent. Pressure from the individual isolated swelling polymer particles was relieved by the matrix disintegration process. The medium-sized particles occurred in larger numbers and were able to be formulated with statistical possibility of the presence of adjacent polymer particles for binding to form a continuous gel structure that controlled drug release by diffusion. Erosion of the hydrophilic gel structure had a considerably lower influence on drug release compared to the diffusion process. This was indicated by the better fit of the drug release kinetics to the Higuchi square root equation. Comparatively, the fine polymer particles formed a less porous and more tortuous gel structure. Therefore, release mechanism depended on a combination of both diffusion and erosion and followed first order kinetics. Thus, the *n* value of the Korsmeyer-Peppas equation was observed to increase with decrease in HPMC particle size (Table 9).

Diffusion rate is known to be directly proportional to pore size and pore number. According to Fick's law, diffusion rate decreases as the mean length of the diffusion route increases. Quantitative relationships between drug release and porosity or tortuosity of extended release barriers have been previously proposed (Robert and Donald, 1984). Drug release from porous matrices, which follow the Higuchi model, can be described by the following equation:

$$M_t = (D\varepsilon(2A - \varepsilon C_s)\ C_s\ t/\tau)^{1/2} \qquad (13)$$

where M_t is the amount of drug released at time t, D is the diffusion coefficient of drug in the solvent penetrating the matrix, A is the total amount of drug in the matrix sytem, C_s is the solubility of the drug in the solvent penetrating matrix substance, ε is the porosity and τ is the tortuosity of the matrix gel layer which is a measure of diffusional distance in excess of the linear path that the solute would travel. It has been suggested that the gel layer might show different viscosity values under different conditions (Leszek, 1987). According to Einstein and Stoke's equation, diffusion coefficient decreases proportionately as the viscosity increases (Leszek, 1987):

$$D = R.T\ /\ (6\pi.\ N.\ \gamma.\ \eta\ ) \qquad (14)$$

where D is the diffusion coefficient, R is the gas constant, T is the temperature, N is the Loschmidt's number, γ is the particle radius and η is the viscosity.

From the above findings in literature, factors affecting viscosity, porosity and tortuosity of the gel structure were found to have quantitative relationships with drug release rate. In the present study, it was also found that the drug release rate was affected by the polymer particle numerical quantity and particle size.

Consequently, a quantitative assessment of the effects of these two factors on drug release was carried out. As polymer particles were distributed in three dimensional space of the matrix, a cube root relationship between drug release constant and polymer particle quantity was expected. For each formulation, three dissolution runs were carried out and the mean value of the first order release constant K_I obtained. The release constants were plotted against the corresponding cube root of the relative number of polymer particles for different concentrations of the polymer employed (Figure 7). A good linear relationship was demonstrated within each size fraction. The R^2 values for the size fractions with mean particle size of 34, 58, 113, 180 and 309 μm and for the unsieved material (112 μm) were 0.9962, 0.9927, 0.9786, 0.9941, 0.9985 and 0.9708, respectively. The relationship across the different size fractions showed
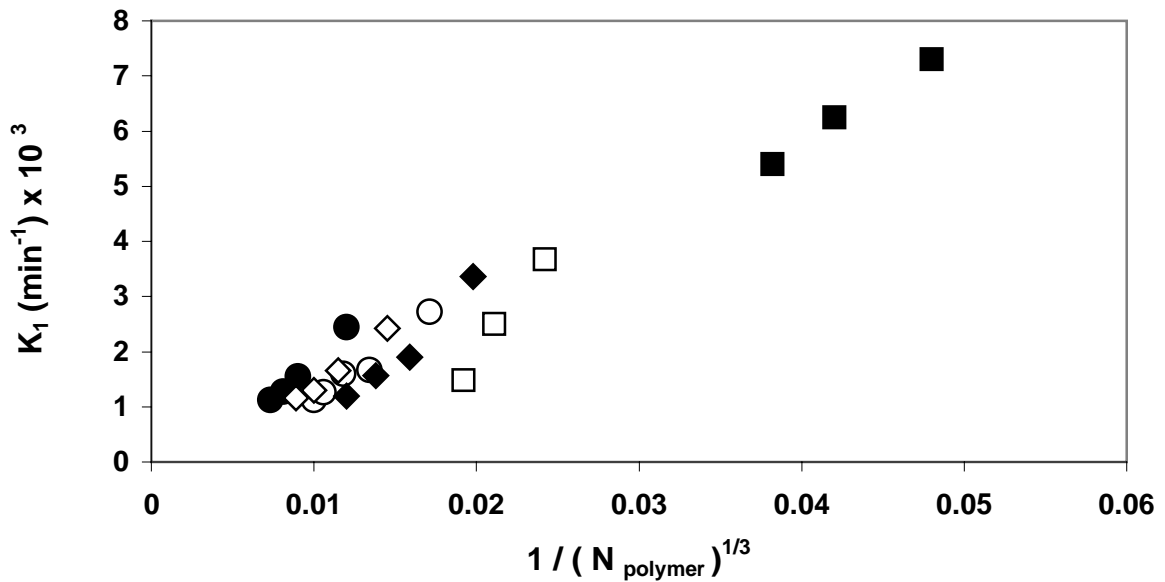
Figure 7. First order release constant K_1 versus number of HPMC particles. HPMC mean particle size: (■) 309 µm (□) 180 µm (◆) 113 µm (◇) 58 µm (●) 34 µm (○) unsieved (112 µm)
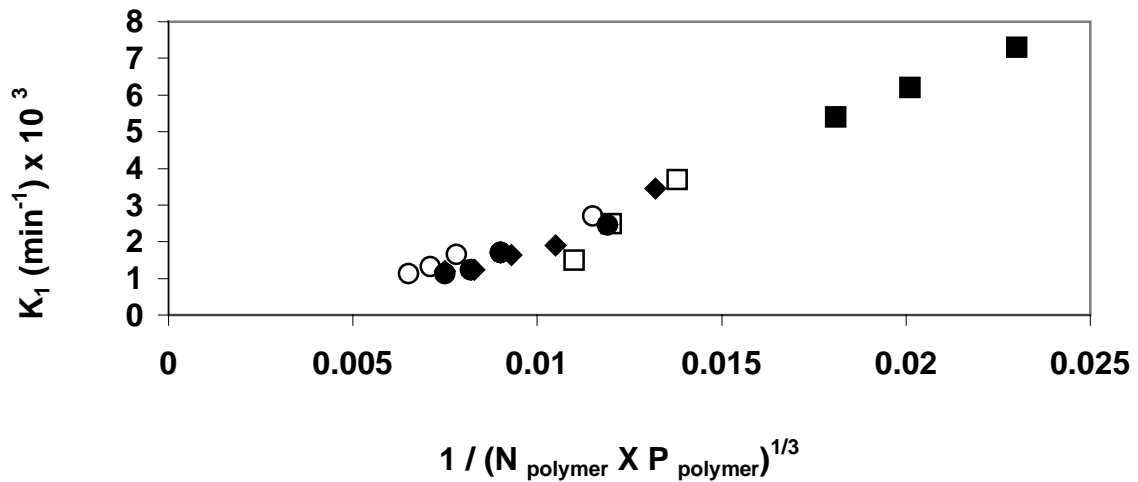
Figure 8. First order release constant K_1 versus number of HPMC particles and mean particle size. HPMC mean particle size : (■) 309 µm (□) 180 µm (◆) 113 µm (◇) 58 µm (●) 34 µm (○) unsieved (112 µm)

linearity with R^2 value of 0.9394. This indicated that the effects of polymer particle size on K_1 value were significant and should not be neglected. The summative effect of polymer particle size and relative particle number on the drug release constant is depicted in Figure 8. A good linear relationship (R^2 of 0.9698) represented by Equation 15 was demonstrated.

$$K_1 = d/ (N_{polymer} \; X \; P_{polymer})^{1/3} + a \qquad\qquad (15)$$

where $N_{polymer}$ refers to the relative number of polymer particles in the formula, $P_{polymer}$ is the mean particle size of the polymer powder and d is a constant indicating sensitivity of the matrix system to changes in particle size and polymer quantity. The value, a, is a release retarding constant. The values for d and a were found to be 0.3969 and -0.0020 respectively. The above relationship is applicable to matrix systems capable of forming an effective gel layer without disintegration and with release mechanism composed of erosion and diffusion.

The application of the equation was further verified by the use of a different matrix system consisting of insoluble dibasic calcium phosphate as filler instead of soluble lactose. The concentration of unsieved HPMC powder used was varied from 10-50 %. The mean value of K_1, obtained from three determinations was plotted against the corresponding $1/(N$

$_{polymer}$ X $P_{polymer})^{1/3}$. A good linear relationship between the two factors was demonstrated (R^2 0.9781, Figure 9). *d* and *a* values were found to be 0.4035 and −0.0018 respectively and were very close to the values obtained from the matrix system with lactose as the filler. This suggested that the type of fillers had little impact on drug release rate. Hence, no significant difference in the drug release rates between soluble filler and insoluble fillers was found. This finding agrees with earlier findings of other researchers (Gao et al., 1996 and Rekhi et al., 1999).

The findings of the current study have important practical applications. Firstly, it demonstrates that it is possible to achieve consistent batch-to-batch extended release performance for HPMC matrix systems of varied polymer particle size properties. One simple approach is to use polymer powder with particle size below that of the critical threshold. If the threshold size is very small and it becomes impractical and expensive to implement, the equation could be employed to achieve the same goal. By examining the polymer mean particle size and particle number per unit volume of each batch, the equation could be used to predict the actual polymer content needed for that particular batch to give the same K_1 value from the first batch. By this approach, the undesirable influence from variations of polymer particle size could be minimised. Secondly, the equation can help to predict drug release performance of systems with

varying polymer content and particle size and hence reduce the number of

trials in product development.
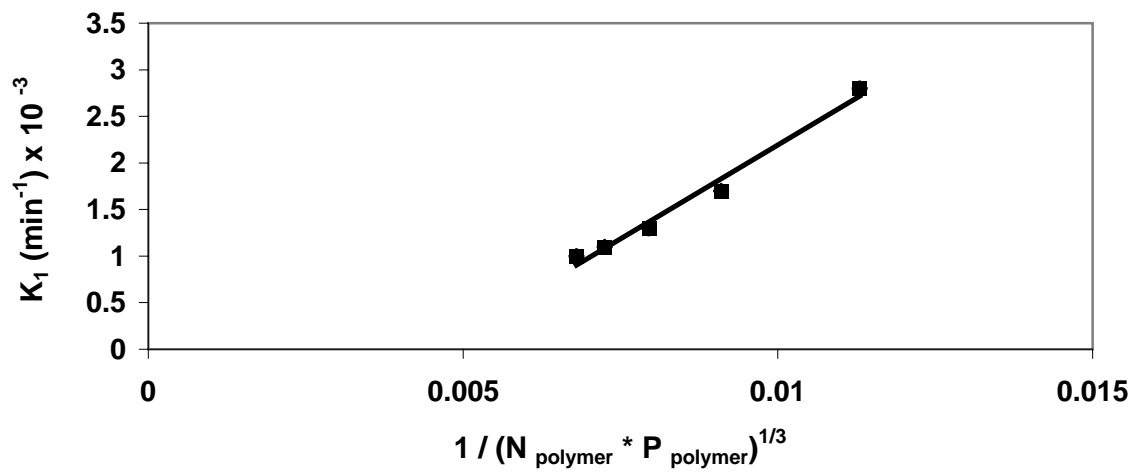
Figure 9. Effect of HPMC particle properties on first order release constant K_1 using dibasic calcium phosphate as filler.

Part II. Reservoir dispersed matrix tablets

1. EC coating level on matrix tablets

In this part of the study, the effect of EC coating level on drug release from matrix tablets was investigated. HPMC of a lower viscosity grade (K 4M) was employed to better observe the effect of the EC coating. For each batch, the active tablets were mixed together with 40 marked and pre-weighed placebo tablets of the same size and shape. As the Surelease (EC) coat is a clear membrane, the yellow placebo tablets were distinguishable from the active tablets. At each theoretical Surelease coating weight gain point, samples were removed for dissolution studies. Ten placebo tablets were also withdrawn, weighed and then returned back to the coating batch. The average weight increase of the placebo tablets against their original weights was considered as the actual weight of coating (expressed as a percentage) applied to the tablet batch at that point. The results are shown in Table 11.

2. Effects of HPMC content

2.1 Effects of HPMC content on drug release rate of uncoated matrix tablets

Figures 10 and 11 show that HPMC content had an effect on the release rates of both water-soluble naproxen sodium and less water-soluble aspirin. A higher HPMC content resulted in a slower release rate, which is in agreement with the findings presented in Part I. As more HPMC particles were available in the matrix with the increase of HPMC content, a faster and stronger polymer gel layer formation was expected.

For a poorly water soluble drug, in the HPMC concentration range studied, the following results were observed. Without HPMC in the tablet core, release of aspirin from the matrix tablet was completed within 2 h. However, increase of HPMC content to 20 % decreased aspirin release to less than 50 % within 8 h. The impact of HPMC content on the aspirin release rate was significant. 10 % HPMC in the matrix formulation was sufficient to give rise to 8 h controlled release.

For a water soluble drug like naproxen sodium, higher HPMC levels were needed to achieve the corresponding controlled release effect than for a poorly water soluble drug. The HPMC concentrations studied varied from zero to 45 %. Without HPMC in the core, more than 95 % of naproxen sodium was released within 30 min, much faster than that from the corresponding aspirin tablet. With HPMC level at 15 %, about 90 % of the drug was released into the dissolution media in 6 h. When the HPMC content was increased to 30 %, a marked drop in release rate was

Table 11. Amounts of coating applied to matrix tablets using dispersions of Surelease with varying amounts of Opadry

Matrix tablets							
Amount of Opadry in EC coating (%)							
0	10	20	30	0	10	20	30
Actual weight gain (%)							
Naproxen sodium				Aspirin			
*	*	*	*	1.78	2.26	1.60	1.78
2.87	2.65	2.91	2.41	3.36	4.06	3.79	3.71
4.50	5.45	5.44	4.50	6.04	6.28	6.09	5.78
6.82	6.68	6.58	5.78	7.24	8.38	7.92	7.86
8.83	9.26	9.12	8.09	10.04	10.23	10.28	9.11

* Coating level too low to show release difference for naproxen sodium tablet, therefore, no sampling done.
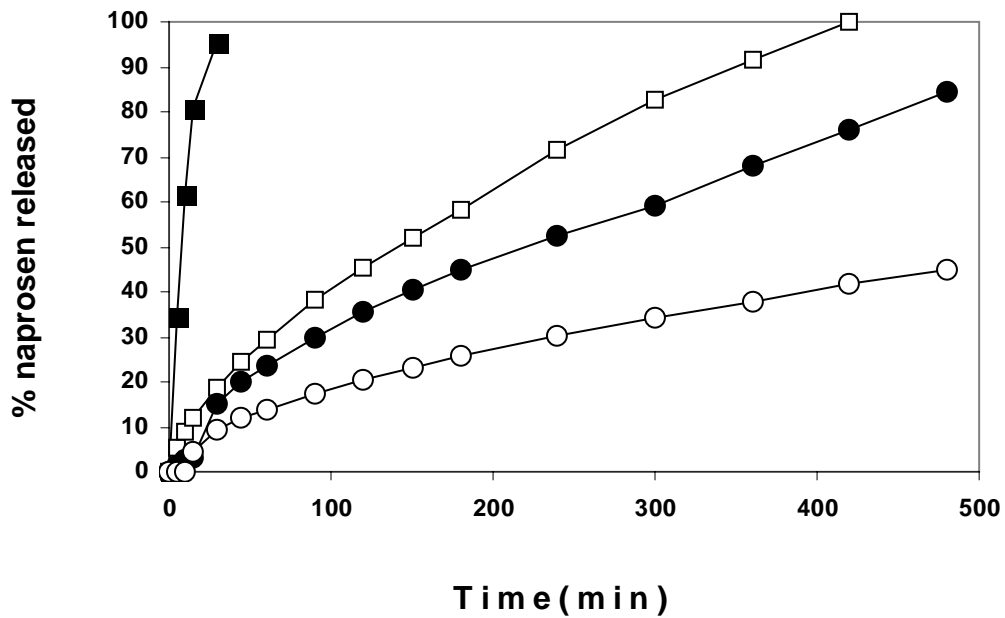
Figure 10. Effect of different HPMC levels on naproxen sodium release from uncoated matrix tablet. (■) 0 % HPMC (□) 15 % HPMC (●) 30 % HPMC (○) 45 % HPMC
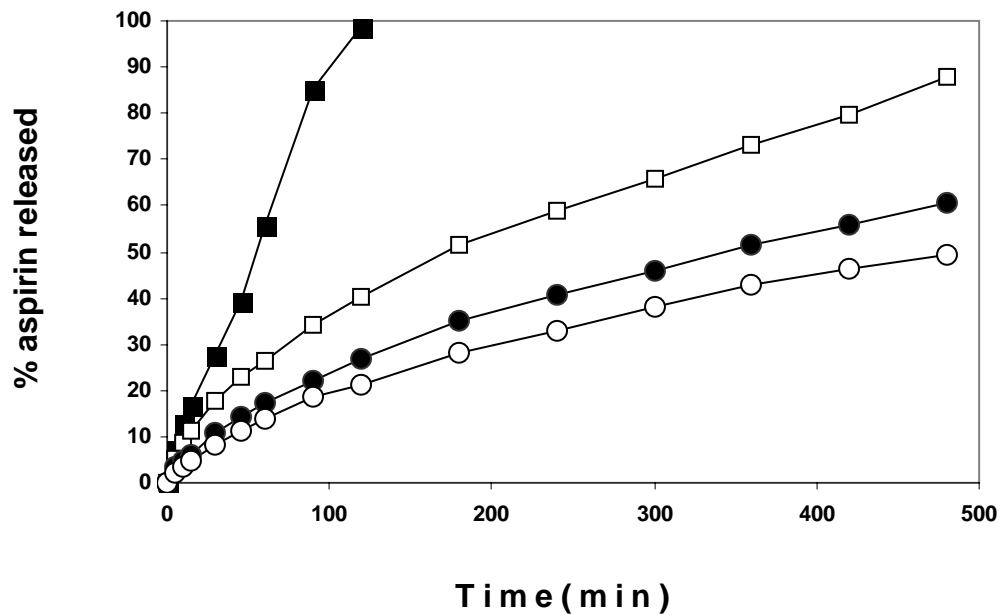
Figure 11. Effect of different HPMC levels on aspirin release from uncoated matrix tablet. (■) 0 % HPMC (□) 10 % HPMC (●) 15 % HPMC (○) 20 % HPMC

obtained, with only 65 % of drug released in 6 h. At 45 % of HPMC content, less than 50 % of drug was released within 8 h. Clearly, the water-soluble drug was sensitive to the HPMC content in the matrix.

2.2 Effects of HPMC content on drug release kinetics from uncoated tablets

The kinetic models of aspirin and naproxen sodium release profiles are shown in Tables 12 and 13.

When HPMC was not included in the formula, the release of aspirin followed zero order with R^2 of 0.9859. As HPMC content in the matrix increased to 10 %, 15 % or 20 %, release kinetics changed to Higuchi model, with R^2 of 0.9922, 0.9834 and 0.9799 respectively. Varying n value from the Korsmeyer - Peppas equation indicated a trend of release kinetic change with a increasing HPMC content.

Without HPMC, the release of naproxen sodium followed a first order model with R^2 of 0.9936. As HPMC content in the matrix increased to 15 %, release kinetics still fitted to first order model, with R^2 of 0.9887. When HPMC concentration was further increased to 30 % and 45 %, release pattern changed to Higuchi model, with R^2 of 0.9835 and 0.9896 respectively. However, n value obtained was constant at 0.6.

Table 12. Kinetic parameters of aspirin release from EC-coated HPMC matrix tablets

EC coating Level (%)	Opadry concentration in EC coat (%)	HPMC content in core tablet (%)	Zero order equation K_0 (% min^{-1})	R^2	First order equation K_1 (min^{-1})	R^2	Higuchi equation K_H (% min$^{-1/2}$)	R^2	Korsmayer- Peppas equation n	R^2
0	0	0	0.8814	0.9859	0.0173	0.8911	7.6304	0.8854	0.8320	0.9940
0	0	10	0.2089	0.7091	0.0040	0.9795	3.8161	0.9922	0.6035	0.9975
0	0	15	0.1449	0.7822	0.0020	0.9763	2.6268	0.9834	0.6499	0.9962
0	0	20	0.1191	0.8288	0.0015	0.9672	2.1511	0.9799	0.6957	0.9952
1.78	0	0	0.6870	0.9835	0.0097	0.9814	13.2110	0.9944	1.9618	0.9760
1.78	0	10	0.0618	0.9977	0.0007	0.9975	1.7155	0.9771	1.0579	0.9971
1.78	0	15	0.0552	0.9973	0.0006	0.9961	1.4759	0.9695	0.9100	0.9822
1.78	0	20	0.0408	0.9892	0.0004	0.9939	1.0792	0.9911	0.9879	0.9923
3.36	0	0	0.0201	0.9958	0.0002	0.9968	0.6330	0.9946	1.4512	0.9403
3.36	0	10	0.0118	0.9915	0.0001	0.9905	0.3885	0.9558	1.4994	0.9712
3.36	0	15	0.0132	0.9691	0.0001	0.9497	0.5033	0.9581	1.2653	0.9561
3.36	0	20	0.0109	0.9874	0.0001	0.9878	0.4092	0.9902	1.2414	0.9870
4.06	10	0	0.0153	0.9803	0.0002	0.9703	0.5135	0.9849	0.8686	0.9784
4.06	10	10	0.0141	0.9920	0.0001	0.9926	0.3179	0.9420	0.9909	0.9742
4.06	10	15	0.0095	0.9640	0.0001	0.8635	0.3080	0.9288	1.7266	0.9677
4.06	10	20	0.0256	0.9964	0.0003	0.9956	1.0003	0.9911	4.3370	0.9901
6.28	10	0	0.0134	0.9775	0.0001	0.9794	0.4034	0.9893	0.8452	0.9940
6.28	10	10	0.0082	0.9860	0.0001	0.9889	0.2407	0.9960	0.9559	0.9886
6.28	10	15	0.0079	0.9855	0.0001	0.9858	0.2183	0.9795	1.0419	0.9890
6.28	10	20	0.0008	0.9819	0.0001	0.9715	0.2230	0.9746	1.1330	0.9777

Table 12 (Continue). Kinetic parameters of aspirin release from EC-coated HPMC matrix tablets

EC coating Level (%)	Opadry concentration in EC coat (%)	HPMC content in core tablet (%)	Zero order equation K_0 (% min^{-1})	R^2	First order equation K_1 (min^{-1})	R^2	Higuchi equation K_H (% min$^{-1/2}$)	R^2	Korsmayer- Peppas equation n	R^2
1.60	20	0	1.4602	0.8981	0.0524	0.9945	13.6070	0.9088	2.1434	0.9651
1.60	20	10	0.1996	0.9793	0.0032	0.9941	4.7431	0.9987	0.8922	0.9881
1.60	20	15	0.1264	0.9749	0.0017	0.9983	3.0621	0.9948	0.7978	0.9994
1.60	20	20	0.1193	0.9772	0.0016	0.9978	2.9112	0.9942	0.8081	0.9993
3.79	20	0	0.6151	0.9785	0.0131	0.9933	10.2050	0.9672	1.9283	0.9048
3.79	20	10	0.2067	0.9871	0.0040	0.9892	4.6607	0.9752	1.2164	0.9572
3.79	20	15	0.0922	0.9996	0.0011	0.9900	2.5155	0.9774	1.0128	0.9988
3.79	20	20	0.0794	0.9982	0.0009	0.9942	2.1181	0.9752	0.9431	0.9988
6.09	20	0	0.0758	0.9873	0.0007	0.9571	1.5150	0.8728	2.1623	0.9965
6.09	20	10	0.0678	0.9566	0.0007	0.9156	1.9445	0.9316	1.3489	0.9576
6.09	20	15	0.0653	0.9798	0.0007	0.9698	2.2842	0.9555	2.2193	0.9792
6.09	20	20	0.0635	0.9944	0.0007	0.9890	2.2327	0.9790	2.1746	0.9960
7.92	20	0	0.0532	0.9813	0.0006	0.9772	0.9693	0.8876	1.2683	0.9878
7.92	20	10	0.0558	0.9581	0.0006	0.9554	1.2473	0.8267	2.6939	0.9409
7.92	20	15	0.0434	0.9594	0.0005	0.9518	1.5114	0.9280	2.4996	0.9975
7.92	20	20	0.0458	0.9873	0.0005	0.9841	1.7012	0.8381	1.3518	0.9598
10.28	20	0	0.0204	0.9896	0.0002	0.9858	0.5775	0.9642	0.9811	0.9910
10.28	20	10	0.0080	0.9785	0.0001	0.9664	0.1940	0.9561	1.0171	0.9548
10.28	20	15	0.0088	0.9893	0.0001	0.9789	0.2250	0.9251	1.1264	0.9845
10.28	20	20	0.0191	0.9769	0.0002	0.9754	0.7463	0.9652	2.0869	0.9640

Table 12 (Continue). Kinetic parameters of aspirin release from EC-coated HPMC matrix tablets

EC coating Level (%)	Opadry concentration in EC coat (%)	HPMC content in core tablet (%)	Zero order equation K_0 (% min^{-1})	R^2	First order equation K_1 (min^{-1})	R^2	Higuchi equation K_H (% min$^{-1/2}$)	R^2	Korsmayer-Peppas equation n	R^2
1.78	30	0	2.0600	0.9561	0.0691	0.9823	20.8080	0.8522	1.6370	0.9460
1.78	30	10	0.2141	0.9740	0.0039	0.9860	3.6373	0.9207	0.8381	0.9920
1.78	30	15	0.1423	0.9377	0.0020	0.9889	2.5591	0.9503	0.7451	0.9973
1.78	30	20	0.1301	0.9581	0.0018	0.9938	2.3290	0.9348	0.8516	0.9897
3.71	30	0	1.3467	0.9445	0.0589	0.9555	12.8660	0.7673	1.3315	0.9210
3.71	30	10	0.1963	0.9668	0.0035	0.9915	3.4966	0.9113	0.8644	0.9847
3.71	30	15	0.1317	0.9487	0.0017	0.9998	3.0403	0.9959	0.6701	0.9967
3.71	30	20	0.1191	0.9602	0.0016	0.9916	2.7785	0.9963	0.7069	0.9986
5.78	30	0	1.2864	0.9733	0.0421	0.9809	15.6290	0.8709	3.8888	0.9806
5.78	30	10	0.1412	0.9971	0.0022	0.9895	3.8749	0.9895	1.2210	0.9822
5.78	30	15	0.0896	0.9983	0.0011	0.9901	2.4955	0.9822	1.1089	0.9964
5.78	30	20	0.0833	0.9976	0.0010	0.9992	2.2463	0.9868	1.0154	0.9959
7.86	30	0	0.4976	0.9368	0.0150	0.9705	9.5851	0.9586	2.4498	0.9187
7.86	30	10	0.1579	0.9810	0.0026	0.9980	4.4159	0.9939	1.4905	0.9547
7.86	30	15	0.0896	0.9944	0.0012	0.9936	2.5408	0.9720	1.5603	0.9632
7.86	30	20	0.0915	0.9930	0.0012	0.9792	2.5697	0.9558	1.3367	0.9902
9.11	30	0	0.3607	0.9521	0.0096	0.9866	8.4267	0.9853	2.3470	0.9448
9.11	30	10	0.1901	0.9888	0.0037	0.9855	5.2710	0.9920	1.6690	0.9534
9.11	30	15	0.0725	0.9927	0.0009	0.9828	2.0145	0.9474	1.1285	0.9934
9.11	30	20	0.0665	0.9961	0.0008	0.9906	1.8398	0.9584	1.1714	0.9875

Table 13. Kinetic parameters of naproxen sodium release from EC-coated HPMC matrix tablets

EC coating Level (%)	Opadry concentration in EC coat (%)	HPMC content in core tablet (%)	Zero order equation K_0 ($\% \min^{-1}$)	R^2	First order equation K_1 ($\min^{-1}$)	R^2	Higuchi equation K_H ($\% \min^{-1/2}$)	R^2	Korsmayer-Peppas equation n	R^2
0	0	0	5.7329	0.9216	0.1034	0.9939	18.493	0.9149	0.6	0.9268
0	0	15	0.2928	0.8561	0.0051	0.9887	4.4522	0.9751	0.6	0.9985
0	0	30	0.2178	0.7270	0.0032	0.9629	3.3639	0.9835	0.6	0.9993
0	0	45	0.1244	0.6870	0.0015	0.8516	1.9261	0.9896	0.6	0.9998
2.87	0	0	2.7155	0.9579	0.1055	0.9555	28.8670	0.9749	2.5	0.9774
2.87	0	15	0.1668	0.9996	0.0031	0.9624	4.3503	0.9652	1.1	0.9915
2.87	0	30	0.1261	0.9939	0.0018	0.9982	3.1504	0.9791	1.1	0.9894
2.87	0	45	0.0951	0.9925	0.0012	0.9990	2.5203	0.9920	1.0	0.9974
4.50	0	0	2.1603	0.9848	0.0557	0.9543	24.9240	0.9714	3.5	0.9646
4.50	0	15	0.1561	0.9960	0.0027	0.9777	2.4052	0.7412	1.4	0.9816
4.50	0	30	0.1232	0.9856	0.0019	0.9693	1.9524	0.7414	1.5	0.9909
4.50	0	45	0.0888	0.9958	0.0011	0.9850	1.3436	0.7279	1.5	0.9941
6.82	0	0	1.5570	0.9185	0.0471	0.9817	23.8710	0.9477	5.6	0.9922
6.82	0	15	0.1376	0.9982	0.0021	0.9863	4.1650	0.9813	1.9	0.9810
6.82	0	30	0.1110	0.9980	0.0015	0.9925	3.1680	0.9743	1.8	0.9803
6.82	0	45	0.0682	0.9973	0.0008	0.9929	1.8965	0.9670	1.4	0.9961
8.83	0	0	1.5683	0.9779	0.0420	0.9453	23.6170	0.9733	4.5	0.9586
8.83	0	15	0.1290	0.9954	0.0018	0.9740	3.5480	0.9475	1.9	0.9903
8.83	0	30	0.1009	0.9978	0.0013	0.9900	2.8699	0.9670	1.7	0.9927
8.83	0	45	0.0632	0.9952	0.0007	0.9886	1.7560	0.9555	1.4	0.9983

Table 13 (Continue) . Kinetic parameters of naproxen sodium release from EC-coated HPMC matrix tablets

EC coating Level (%)	Opadry concentration in EC coat (%)	HPMC content in core tablet (%)	Zero order equation K_0 (% min^{-1})	R^2	First order equation K_1 (min^{-1})	R^2	Higuchi equation K_H (% $min^{-1/2}$)	R^2	Korsmayer- Peppas equation n	R^2
2.65	10	0	2.7435	0.9866	0.0761	0.9441	27.1440	0.9840	2.8	0.9854
2.65	10	15	0.1762	0.9895	0.0023	0.9988	3.6433	0.9900	1.1	0.9936
2.65	10	30	0.1405	0.9834	0.0020	0.9979	3.2061	0.9841	1.0	0.9942
2.65	10	45	0.1079	0.9893	0.0014	0.9991	2.7778	0.9920	1.0	0.9968
5.45	10	0	2.3342	0.9660	0.1044	0.8642	27.0830	0.9638	1.9	0.9229
5.45	10	15	0.1525	0.9946	0.0022	0.9927	3.3920	0.9726	1.1	0.9910
5.45	10	30	0.1135	0.9983	0.0015	0.9942	2.8170	0.9590	1.3	0.9874
5.45	10	45	0.0869	0.9986	0.0011	0.9971	2.4011	0.9803	1.3	0.9943
7.45	10	0	2.5307	0.9680	0.0752	0.9849	33.1730	0.9360	3.3	0.9248
7.45	10	15	0.1464	0.9970	0.0023	0.9758	3.6721	0.9345	1.7	0.9845
7.45	10	30	0.1033	0.9974	0.0013	0.9888	2.5106	0.9388	1.6	0.9839
7.45	10	45	0.0752	0.9990	0.0009	0.9943	2.0553	0.9719	1.4	0.9961
9.26	10	0	2.6452	0.9916	0.0650	0.9186	29.0090	0.9417	5.3	0.9473
9.26	10	15	0.1407	0.9926	0.0020	0.9544	3.4950	0.9179	1.6	0.9938
9.26	10	30	0.1088	0.9924	0.0014	0.9761	2.6517	0.9186	1.6	0.9909
9.26	10	45	0.0756	0.9916	0.0009	0.9857	2.1099	0.9475	1.6	0.9882
2.91	20	0	1.7595	0.9929	0.0637	0.9284	17.5780	0.9695	1.4	0.9960
2.91	20	15	0.2019	0.9552	0.0029	0.9986	3.8823	0.9931	0.9	0.9875
2.91	20	30	0.1568	0.9504	0.0023	0.9980	3.4307	0.9953	0.8	0.9924
2.91	20	45	0.1250	0.9463	0.0016	0.9909	2.7515	0.9954	0.9	0.9880

Table 13 (Continue) . Kinetic parameters of naproxen sodium release from EC-coated HPMC matrix tablets

EC coating Level (%)	Opadry concentration in EC coat (%)	HPMC content in core tablet (%)	Zero order equation K_0 (% min^{-1})	R^2	First order equation K_1 (min^{-1})	R^2	Higuchi equation K_H (% min$^{-1/2}$)	R^2	Korsmayer- Peppas equation n	R^2
5.44	20	0	2.3848	0.9718	0.0479	0.9933	21.2670	0.9693	2.1	0.8868
5.44	20	15	0.1835	0.9832	0.0026	0.9993	4.3746	0.9889	1.2	0.9795
5.44	20	30	0.1499	0.9803	0.0022	0.9995	3.5636	0.9897	1.1	0.9874
5.44	20	45	0.1146	0.9844	0.0015	0.9997	2.5036	0.9668	1.1	0.9919
6.58	20	0	2.6708	0.9839	0.0670	0.9693	31.0310	0.9983	3.8	0.9561
6.58	20	15	0.1726	0.9986	0.0025	0.9941	4.4863	0.9702	1.2	0.9905
6.58	20	30	0.1357	0.9986	0.0020	0.9861	3.3829	0.9681	1.2	0.9853
6.58	20	45	0.0990	0.9990	0.0013	0.9954	2.7236	0.9825	1.3	0.9895
9.12	20	0	2.8803	0.9940	0.0669	0.9137	30.1230	0.9767	4.2	0.9136
9.12	20	15	0.1446	0.9989	0.0020	0.9896	3.5166	0.9661	1.3	0.9849
9.12	20	30	0.1076	0.9965	0.0014	0.9977	2.6832	0.9676	1.2	0.9845
9.12	20	45	0.0882	0.9977	0.0011	0.9974	2.4329	0.9839	1.3	0.9831
2.41	30	0	2.1628	0.9842	0.0579	0.9701	20.3970	0.9802	1.1	0.9633
2.41	30	15	0.2157	0.9593	0.0037	0.9952	4.1384	0.9824	0.8	0.9948
2.41	30	30	0.1706	0.9299	0.0026	0.9952	3.4707	0.9903	0.8	0.9888
2.41	30	45	0.1268	0.9385	0.0017	0.9876	2.5984	0.9885	0.7	0.9950
4.50	30	0	1.4122	0.9897	0.0279	0.9313	15.1810	0.9768	1.4	0.9836
4.50	30	15	0.2107	0.9854	0.0050	0.9199	4.5702	0.9693	1.0	0.9876
4.50	30	30	0.1603	0.9607	0.0024	0.9984	3.6219	0.9959	0.9	0.9855
4.50	30	45	0.1221	0.9660	0.0016	0.9976	2.9543	0.9975	0.9	0.9873

Table 13 (Continue) . Kinetic parameters of naproxen sodium release from EC-coated HPMC matrix tablets

EC coating Level (%)	Opadry concentration in EC coat (%)	HPMC content in core tablet (%)	Zero order equation K_0 (% min^{-1})	R^2	First order equation K_1 (min^{-1})	R^2	Higuchi equation K_H (% min$^{-1/2}$)	R^2	Korsmayer- Peppas equation n	R^2
5.78	30	0	2.0535	0.9796	0.0528	0.9512	23.8190	0.9769	2.9	0.9755
5.78	30	15	0.1933	0.9907	0.0041	0.9258	4.8578	0.9799	1.0	0.9934
5.78	30	30	0.1374	0.9747	0.0019	0.9964	3.2481	0.9919	0.9	0.9891
5.78	30	45	0.1076	0.9741	0.0014	0.9970	2.6983	0.9983	0.9	0.9872
8.09	30	0	2.8076	0.9996	0.0625	0.9730	25.1260	0.9666	3.5	0.9516
8.09	30	15	0.1753	0.9980	0.0028	0.9793	4.5464	0.9771	1.2	0.9838
8.09	30	30	0.1305	0.9923	0.0018	0.9953	2.9539	0.9585	1.1	0.9819
8.09	30	45	0.0956	0.9937	0.0012	0.9993	2.6093	0.9932	1.2	0.9717

3. Effects of EC coating

3.1 Effects of EC coating on drug release

3.1.1 EC coating with no water-soluble additive

The release profiles of aspirin from the HPMC matrix tablets coated with different amounts of Surelease without any water-soluble component in the coating formulation, are shown in Figures 12 and 13.

It was observed that for a poorly water-soluble drug like aspirin, EC coating of matrix tablets had a considerable impact on drug release rate (Figures 12 and 13). Application of EC coating led to significant decrease in aspirin release rate. The higher the quantity of EC coating, the slower was the aspirin release rate. Release constants K_0 and K_1 were both inversely related to the EC coating quantity (Table 12).

The marked effect of EC coat could be clearly observed in aspirin tablets without HPMC in the core. Compared to the uncoated tablets which released 100 % of the drug in less than 180 min (Figure 11), aspirin tablets coated with 1.78 % of EC layer released only 75 % of the drug into the dissolution medium within 180 min (Figure 12). When EC coating weight was further increased to 3.36 %, aspirin release was less than 2 %
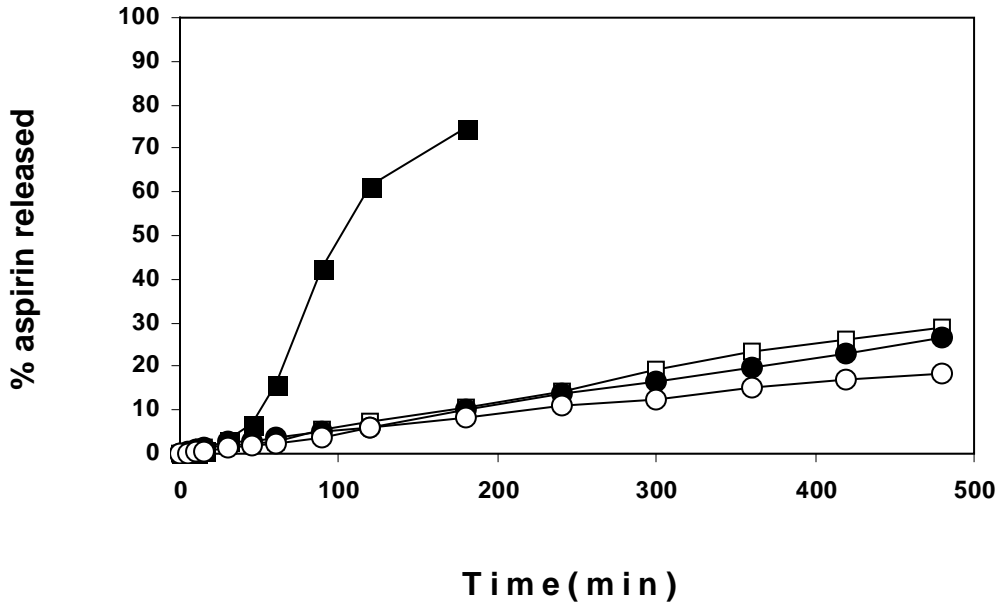
Figure 12. Effect of different HPMC levels on aspirin release from matrix tablet with 1.78 % EC coating without Opadry. (■) 0 % (□) 10 % (●) 15 % (○) 20 %
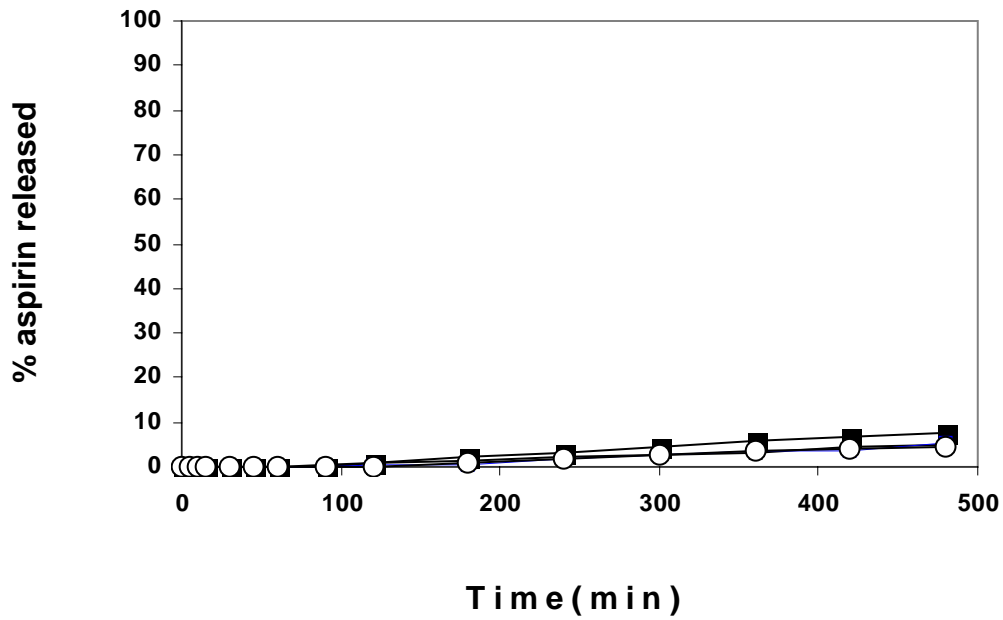

Figure 13. Effect of different HPMC levels on aspirin release from matrix tablet with 3.36% EC coating without Opadry. (■) 0 % (□) 10 % (●) 15 % (○) 20 %

in the same time interval and less than 10 % in 8 h (Figure 13). Further increase in EC coating amount led to practically no release. The same trend was noticed in aspirin tablets with 10 %, 15 % and 20 % HPMC in the core.

Difference in aspirin release rate due to variation in HPMC content decreased when EC coating was applied. When the coating reached a certain level, the effect of HPMC content was insignificant (Figure 12 and 13). The same result was seen from the K_0 or K_1 values at different HPMC contents (Table 12). At EC coating level of 1.78 % and 10 %, 15 % and 20 % HPMC contents in the core, aspirin K_0 values were 0.0618, 0.0552 and 0.0408 respectively. Increasing EC coating level to 3.36 %, aspirin K_0 values decreased to 0.0118, 0.0132 and 0.0109 respectively. At 3.36 % coating level, the amount of aspirin released within 8 h was close to 5 %, irrespective of the amount of HPMC in the matrix.

The research work reported under Part I indicated that the drug release through HPMC matrix is mainly via diffusion. In reservoir type devices, when the controlling membrane is microporous, the release controlling step is also by diffusion. Drug release from such devices is a function of drug concentration in the device as well as the thickness of the diffusion barrier (Chen and Lee, 2002). EC coating without soluble additives had very poor water permeability, hence only limited amount of water could

cross the coating barrier to enable dissolution of drug. A combination of EC coating with a poorly water-soluble drug like aspirin and a gel forming HPMC in the matrix core would dramatically retard drug release to very low rates. Therefore, drug release was low. When the EC coating level reached to certain amount, in this case around 4 %, the coat became almost completely impassable to water movement, hence, almost no drug release was observed.

In comparison to aspirin, naproxen sodium is freely soluble in water. The release profiles of naproxen sodium from the matrix tablets coated with different amounts of EC coating are shown in Figures 14-17. The release rate of naproxen sodium decreased as either EC coating level or HPMC content in the matrix was increased.

Release of naproxen sodium was considerably faster than that of aspirin, even at much higher EC coating level and HPMC content. This was noticed both from the release profile (Figures 12-17) and release constant obtained (Tables 12 and 13). Without HPMC in the core, at 4.50 % of EC coating, over 90% of the naproxen sodium was released within 60 min (Figure 15), zero order release constant K_0 was 2.1603. At 8.83 % EC coating, 8 h drug release from naproxen matrix containing 45 % HPMC still exceeded 25 % (Figure 17) with K_0 value at 0.0632. In comparison,

less than 10 % of aspirin was released in 8 h, even at 3.36 % EC coating and K_0 values were well below 0.025 regardless of HPMC content in the core (Table 12).

It was also observed that when HPMC was not included in the core tablet, the ability of EC coat layer to sustain the release of naproxen was significantly less than that for aspirin. On increasing EC coating amount from 2.87 % to 8.83 %, the time taken to release 90 % naproxen sodium extended from about 45 min to 90 min only. This suggested that the control of the water-soluble drug release by only the application of EC coating was poor.

 Varying HPMC content in the matrix demonstrated significant impact on release of naproxen sodium from EC coated tablet. Increasing HPMC content in the core from 15 % to 45 % led to a decrease of more than 25 % of drug released with 8 h. The decrease was greater at lower EC coating level. At 2.87 %, 6.82 % and 8.83 % of EC coating, the decrease in amount of naproxen released due to increase of HPMC level was 35 %, 28 % and 25 %, respectively (Figures 14-17). The release constants in Table 13 showed the same trend. At 2.87 % EC coating level, increase of HPMC content from 15 % to 45 % led to a significant decrease of K_0 value from 0.1668 to 0.0951. Further increase in EC coating to 6.82 %, K_0 value decreased from 0.1376 to 0.0682.
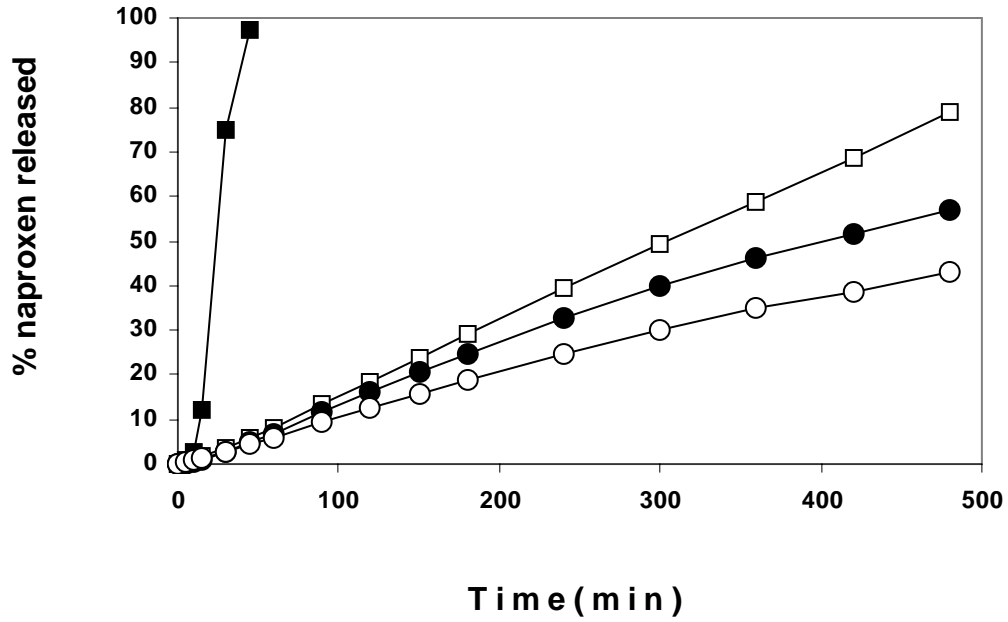
Figure 14. Effect of different HPMC levels on naproxen sodium release from matrix tablet with 2.87 % EC coating without Opadry. (■) 0 % (□) 15 % (●) 30 % (○) 45 %
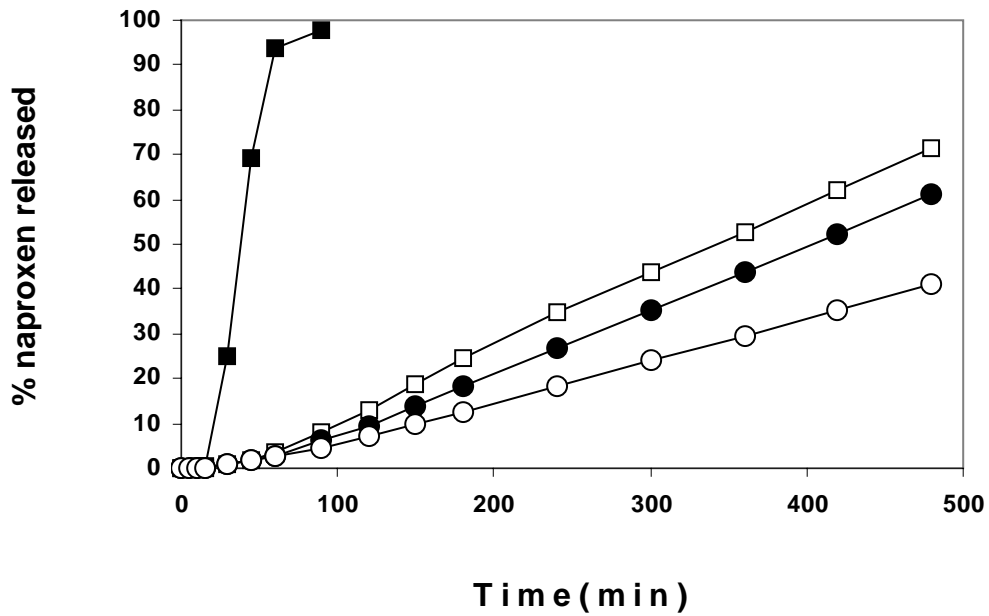

Figure 15. Effect of different HPMC levels on naproxen sodium release from matrix tablet with 4.50 % EC coating without Opadry. (■) 0 % (□) 15 % (●) 30 % (○) 45 %
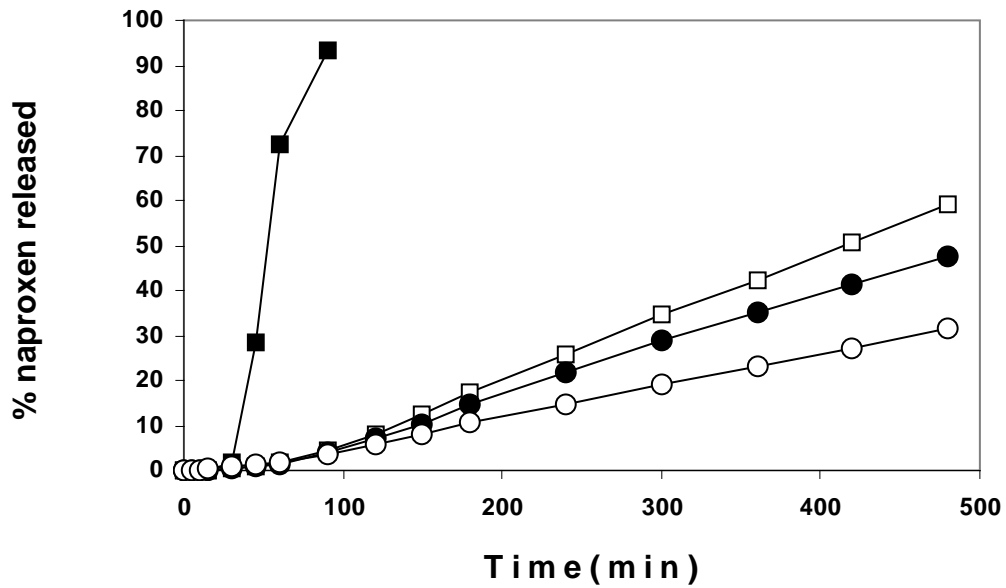
Figure 16. Effect of different HPMC levels on naproxen sodium release from matrix tablet with 6.82 % EC coating without Opadry. (■) 0 % (□) 15 % (●) 30 % (○) 45 %
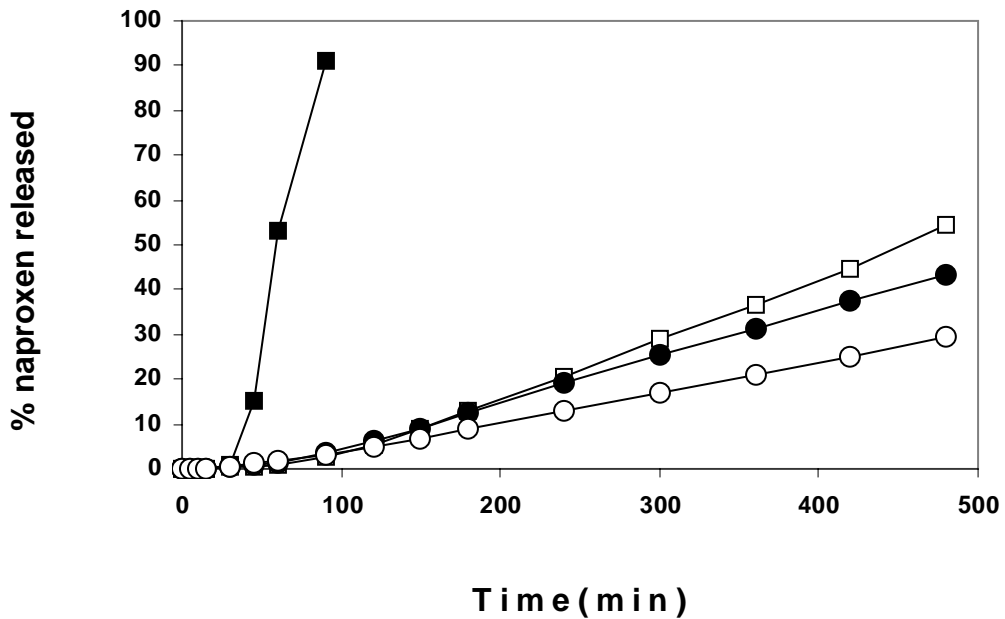

Figure 17. Effect of different HPMC levels on naproxen sodium release from matrix tablet with 8.83 % EC coating without Opadry. (■) 0 % (□) 15 % (●) 30 % (○) 45 %

Varying HPMC content in the matrix demonstrated significant impact on release of naproxen sodium from EC coated tablet. Increasing HPMC content in the core from 15 % to 45 % led to a decrease of more than 25 % of drug released with 8 h. The decrease was greater at lower EC coating level. At 2.87 %, 6.82 % and 8.83 % of EC coating, the decrease in amount of naproxen released due to increase of HPMC level was 35 %, 28 % and 25 %, respectively (Figures 14-17). The release constant in Table 13 showed the same trend. At 2.87 % EC coating level, increase of HPMC content from 15 % to 45 % led to a significant decrease of K_0 value from 0.1668 to 0.0951. Further increase in EC coating to 6.82 %, K_0 value decreased from 0.1376 to 0.0682.

From the above results, it was found that with HPMC in the naproxen tablet, both the HPMC content and EC coating level exerted significant contribution to the controlled release effect of the water-soluble drug. In comparison, without HPMC in the core, it was difficult to achieve controlled release effect by using only EC coating on the naproxen sodium tablets. The application of EC coating on HPMC matrix tablet offers an effective and precise approach to achieve the desired extended release for very water-soluble drugs. As demonstrated with the model drug, naproxen sodium, in the HPMC matrix, with core HPMC concentrations of 0 % to 45 %, and EC coating level of 0 % to about 9 %, 8 h controlled release profiles could be adjusted from over 90 % to almost 30 %, therefore

offering a wide range of formulation options. The release performance also suggested that the HPMC content in the core could be used as the key factor to modify drug release, with the EC coating for added leverage to more precise control of the release profile.

3.1.2 EC coating with water-soluble additive

It was noticed from the current work and earlier studies that the release profiles of poorly water–soluble aspirin and freely water-soluble naproxen sodium were affected by the constituent HPMC content in the core, as well as the thickness of EC coating applied. Compared to the freely water-soluble drug, the release of the poorly water-soluble drug was more sensitive to changes in the thickness of EC coating.

The amount of HPMC in the core formula can be precisely adjusted. However, the applied coating could vary slightly from batch-to-batch as slight changes in coating conditions could cause some variation in weight of coating applied. Consequently, very stringent control of the coating process is critical for minimal batch-to-batch variability and for reproducible drug release profiles. A method to minimize the problem is to add soluble channel - forming agent to the non - permeable EC coating as it would increase the porosity and permeability of the coating and

consequently, decrease the sensitivity of release behaviour to small variations in the amount of coating applied.

Opadry was chosen as the pore forming agent to be used and the effect of Opadry level in EC coating on aspirin release is depicted in Figures 18-21. For aspirin tablets, increase of Opadry level in the EC coating generally increased drug release. However, the magnitude of increase was more noticeable when Opadry concentration in EC coat was 20 % and above.

Adding 10 % Opadry to the EC coating did not contribute to significant difference in release performance over EC formulations without Opadry. At 4.06 % EC coating level, amount of drug released within 8 h was still below 10 % irrespective of the amount of HPMC in the core (Figure 18). This release performance was comparable to that of 3.36 % EC coating without Opadry (Figure 13). When the EC coating level was increased to 6.28 %, the amount of drug released within 8 h dropped below 5 % (Figure 19). As the release rate was low, there was little difference in 8 h aspirin release between tablets with different amounts of HPMC in the core.

When the amount of Opadry in the EC coating was increased to 20 %, an appreciable increase in aspirin release was observed compared to that with
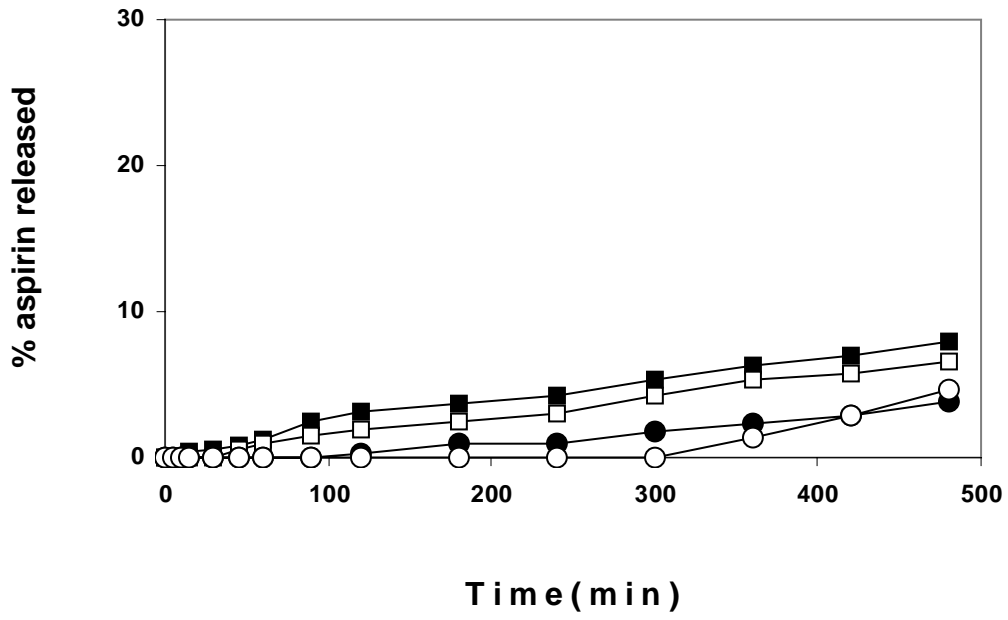
Figure 18. Aspirin release from matrix tablet of different HPMC levels, coated with 4.06 % EC layer with 10 % Opadry. (■) 0 %　(□) 10 %　(●) 15 %　(○) 20 %
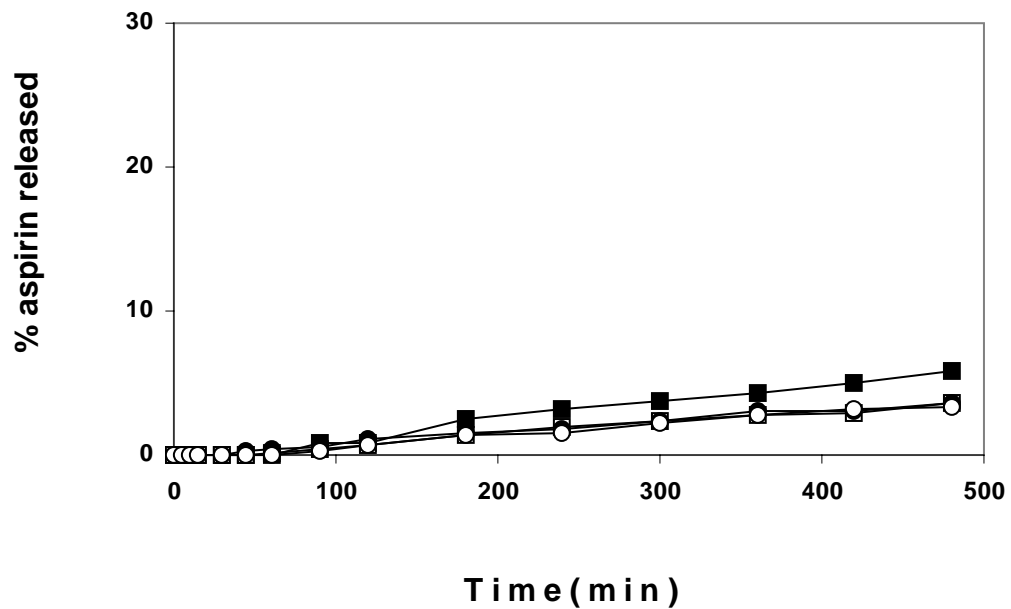

Figure 19. Aspirin release from matrix tablet of different HPMC levels, coated with 6.28 % EC layer with 10 % Opadry. (■) 0 %　(□) 10 %　(●) 15 %　(○) 20 %
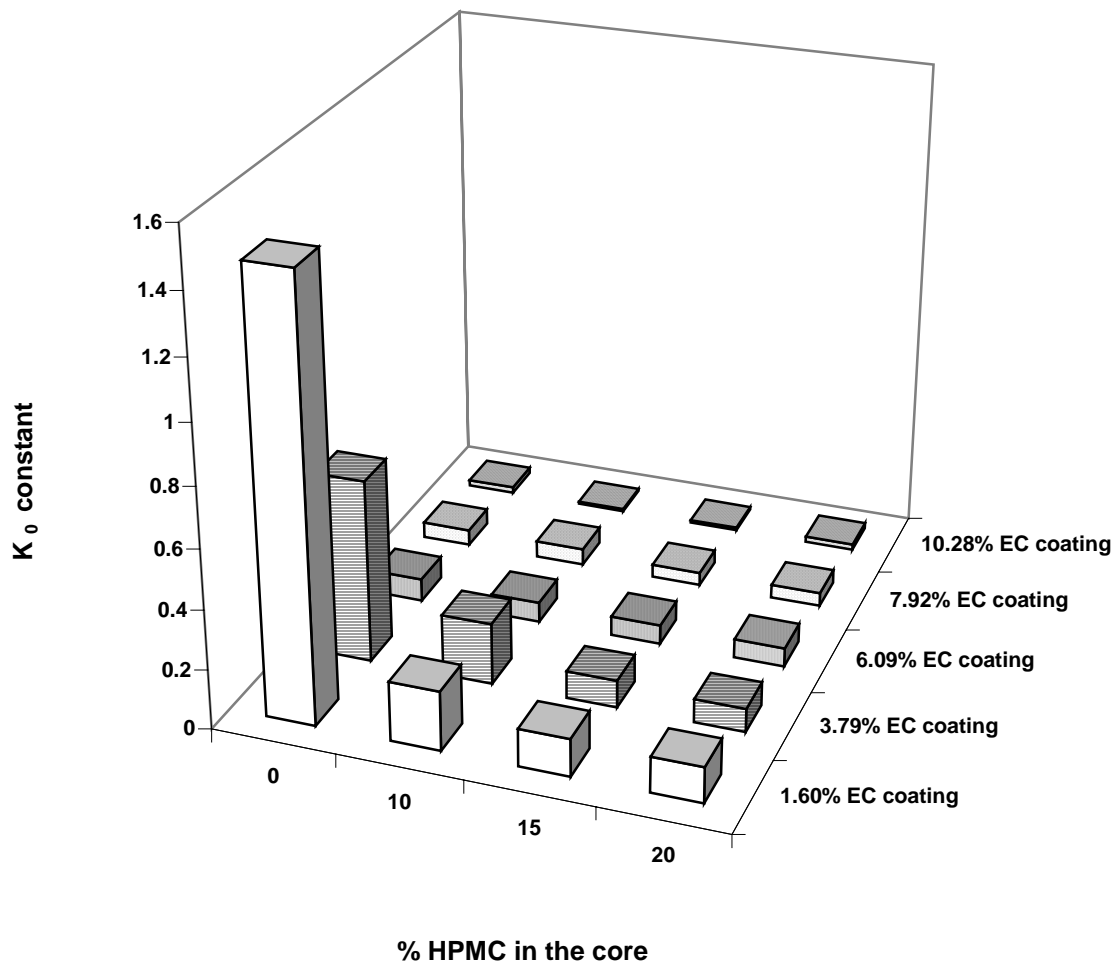
Figure 20. Effects of HPMC content in the matrix core and amount of EC coating with 20 % Opadry on aspirin release constant K_0.
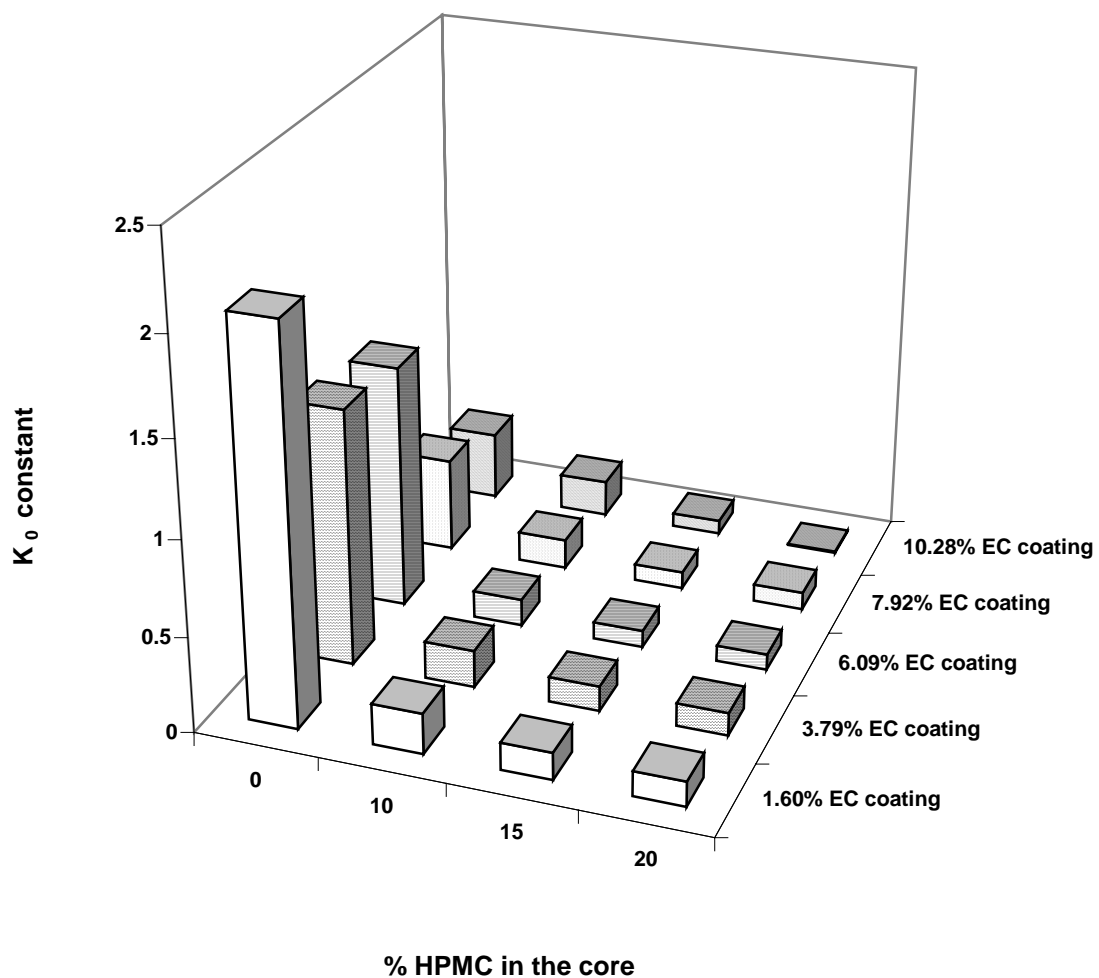
Figure 21. Effects of HPMC content in the matrix core and amount of EC coating with 30 % Opadry on aspirin release constant K_0,

no or 10 % Opadry (Table 12). Aspirin release rate decreased markedly with increase of EC coating level or HPMC content in the core, when EC coating amount was below 6.09 % (Figure 20). However, it was clearly seen that the influence of HPMC content on aspirin release decreased as the coating weight increased. No significant difference in aspirin release rate was observed from tablets with different HPMC content when EC coating was about 6.09 % and above. However, the aspirin release rate still decreased with increase in weight of EC coating amount to this level and above.

When Opadry level in the EC coating was increased to 30 % (Figure 21), it was noticed that drug release was only slightly faster than at the 20 % level (Figure 20), when EC coating level was below 6 %. However, significant difference in release rate was obtained, when the EC coating level was about 6 % and above.

Similar to EC coating with 20 % Opadry, both the HPMC content in the matrix and EC coating amount could be modified to offer a wider range of adjustment possibility to the controlled release performance, when Opadry level was increased to 30 %. Aspirin release rates varied from 92 % in 1 h to 32 % in 8 h at the HPMC / EC coat range studied. However, the sensitivity of aspirin release rate to EC coating level decreased as the concentration of the soluble additive was increased.

Release profiles for naproxen sodium at different Opadry concentration in EC coating are depicted in Figures 22-24. HPMC in the core still had a big impact on sustaining naproxen sodium release rate. Without HPMC in the matrix core, more than 90 % of naproxen sodium was released within 60 min, irrespective of the EC coating level and the Opadry concentration in the EC coat. As soon as 15 % of HPMC was incorporated into the matrix core, even at very low EC coating level and high Opadry ratio, controlled release effect were able to extend to 8 h. It was clearly seen that, without HPMC in the core, variation in EC coating load and Opadry concentration had limited impact on drug release rate.

Increasing Opadry level in the EC coating formulations increased the release rate of naproxen sodium. Influence of EC coating level and Opadry concentration were HPMC content dependent. When HPMC content was 15 % and above, increase of EC coating led to a noticeable decrease in drug release. Increase of Opadry level in the EC coating had the opposite effect on naproxen release. Significant difference in K_0 value was observed.

3.2 Effects of EC coating on release kinetics

Figure 22. Effects of HPMC content in the matrix core and amount of EC coating with 10 % Opadry on naproxen sodium release constant K_0.
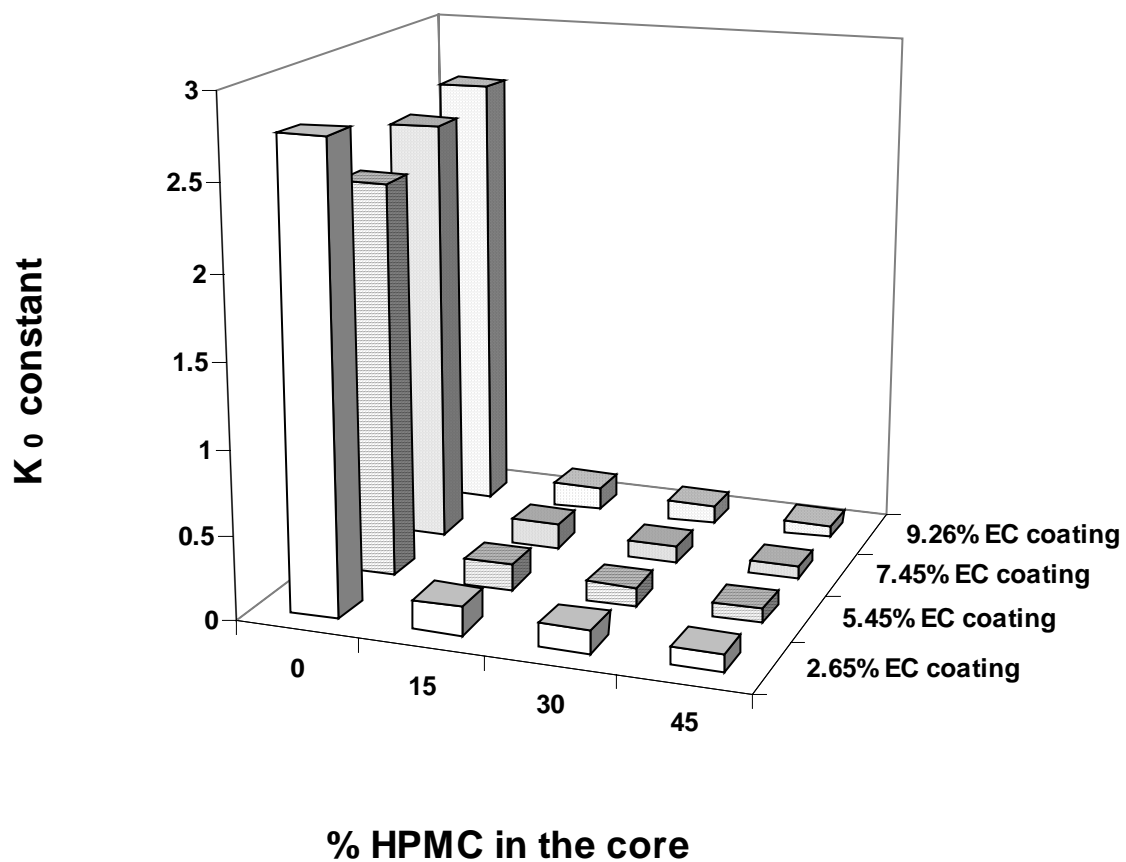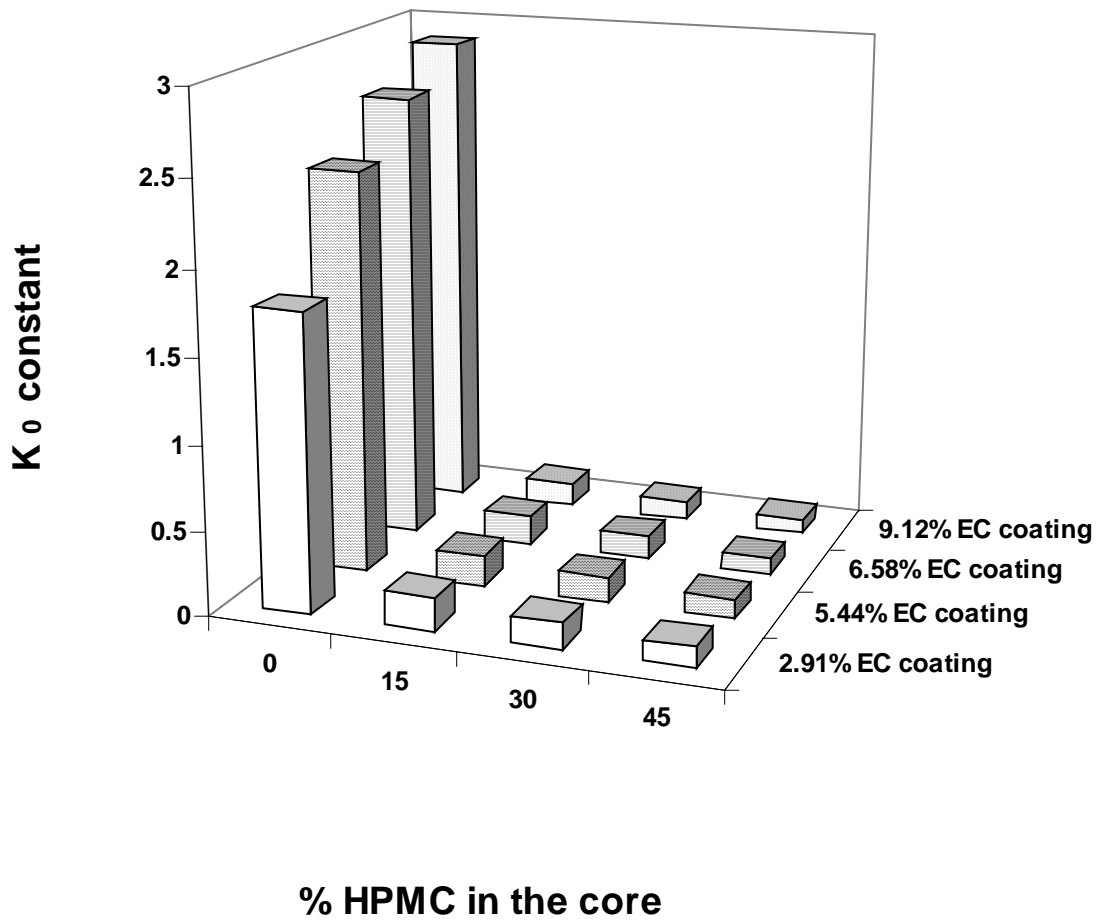
Figure 23.   Effects of HPMC content in the matrix core and amount of EC coating with 20 % Opadry on naproxen sodium release constant K_0.
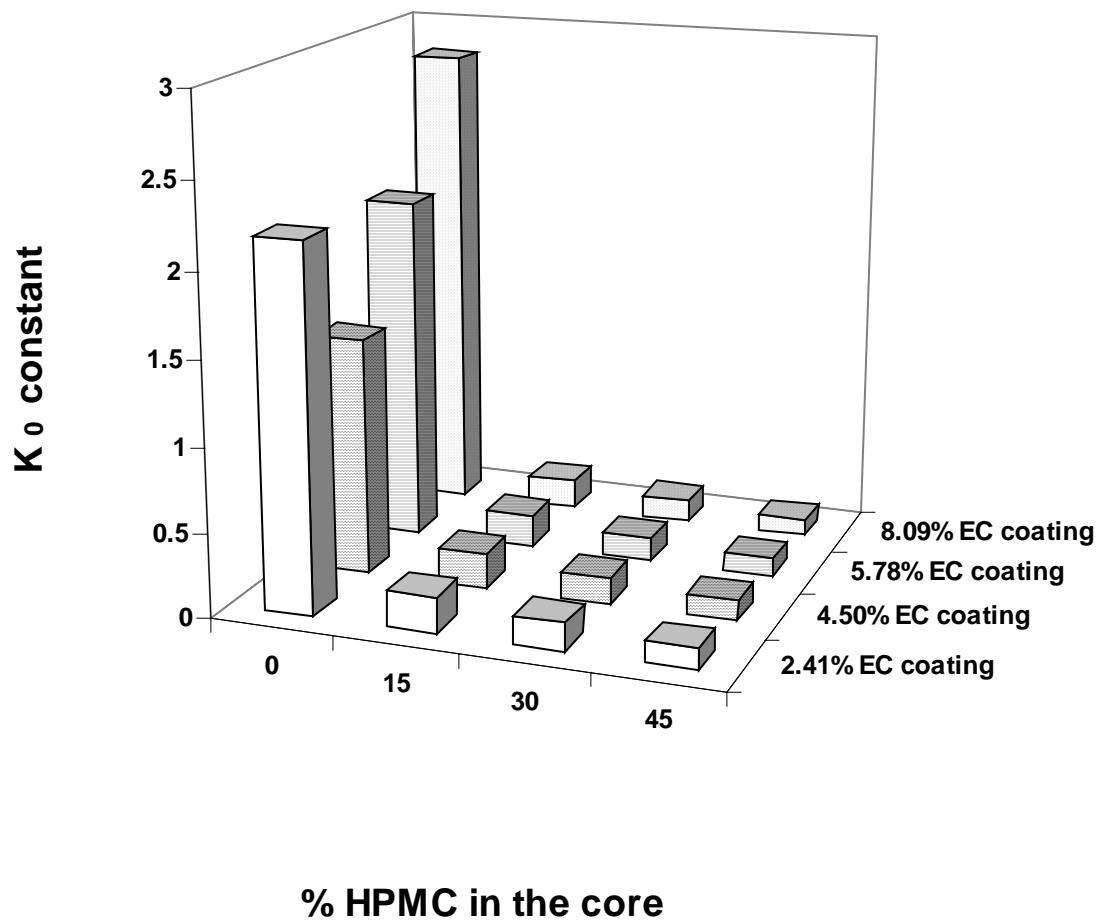
Figure 24.   Effects of HPMC content in the matrix core and amount of EC coating with
30 % Opadry on naproxen sodium release constant K_0.

Release rates of aspirin and naproxen sodium were affected by the HPMC content in the core, EC coating level and amount of Opadry in the EC coating. All the three formulation variables affected the release kinetics of water-soluble naproxen sodium and poorly water-soluble aspirin (Tables 12 - 13).

Increase of EC coat thickness generally changed the release kinetics of aspirin to zero order. Aspirin tablets without EC coating followed Higuchi models for all HPMC concentrations, as indicated by n values ranging from 0.6 - 0.8 (Table 12). However, tablets without HPMC followed zero order kinetics. With 1.78 % EC coating, aspirin tablets with 10 % to 20 % HPMC demonstrated best fit with the zero order model. The n values for the tablets with 10 %, 15 % and 20 % HPMC in the core were 1.1, 0.9 and 1.0 respectively, further indicating conformance to zero release model. When EC coating level was raised to 3.36 %, release characteristics all fitted the zero order model well with n values ranging from 1.2 to 1.5.

The above trends were in agreement with those observed in other studies which used diphenhydramine hydrochloride as a model drug in microcapsules coated with EC (Opota et al., 1999). It was found that the n value of diphenhydramine hydrochloride release increased from 0.70 to 0.97 as EC coating weight increased. This suggested that release kinetics

were originally non-Fickian, but approached Fickian diffusion at higher coating levels, similar to the findings in this study.

The impact of soluble additive in the EC coating on drug release was dependent on the proportion of soluble additive in the coating and thickness of EC coating layer. It was clearly noticed that as the soluble additive level increased in the EC coating, higher EC coating quantity was needed in order to maintain zero order kinetics. When EC coating level was at 1.78 %, aspirin release kinetics generally followed zero order release with *n* values ranging from 0.9 – 1.1, except tablets without HPMC in the core. However, at similar EC coating level, adding 20 % Opadry to the EC coating changed the release kinetics of aspirin tablet from zero to first order. The trend of decreasing *n* value was noticed. The impact of soluble additive diminished when the coating level was increased to 3.79 % and above, with aspirin release kinetics reverting back to zero order. When Opadry concentration was further increased to 30 %, 3.71 % of EC coating level was unable to produce a coating of sufficient integrity to provide constant release kinetics and aspirin release still followed first order kinetics. Only when the level of EC coating increased to 5.78 % and above, the release kinetics reverted back to zero order. An increase in *n* value from below 0.9 to above 1.0 was noted when the release kinetics changed.

As seen for aspirin, the level of coat applied and the incorporation of soluble additive also affected the release kinetics of naproxen sodium. However, the relative extent of the effect was quantitatively dissimilar.

Increased EC coating level could lead to change in the naproxen sodium release kinetics from first order to zero order. It was clearly observed that, when EC coating level was below 3 %, naproxen sodium release kinetics varied due to the differences in Opadry concentration in EC coating and HPMC content in the core. However, when EC coating level was above 8.0 %, naproxen sodium release followed zero order kinetics irrespective of Opadry level and HPMC content.

Effect of Opadry ratio on drug release kinetics was dependent on EC coating thickness and HPMC content. Without Opadry in EC coat, release of naproxen sodium at all coating levels investigated followed the zero order model when HPMC concentration in the core was 15 % and above. Increasing Opadry concentration in EC coat to 10 % changed the release kinetic model. At 2.65 % EC coating level, release of naproxen sodium from matrix tablets changed to first order kinetics. However, increasing EC coating level to 5.45 % and above reverted release kinetics to zero order, irrespective of the HPMC content in the core.

Similarly, when Opadry level was increased to 20 % and 30 %, EC coating level had to be above 5.44 % to maintain the zero order release model.

The above phenomenon was in agreement with the findings of other workers. Studies using a model system based on EC coated beads containing phenylpropanolamine, with aqueous solubility in water of 40 g / 100 ml, demonstrated that drug release followed zero order kinetics (Ozturk et al., 1990). Research using diphenhydramine hydrochloride microgranules coated with aqueous EC dispersion showed an n value increasing from 0.7 to 1.0 as the EC coating level increased from 6 % to 12 %. Release kinetics were non-Fickian first order at lower EC coating level, but approached zero order Fickian diffusion at higher coating levels (Opota et al.,1999).

In the present study, EC coat application actually suppressed drug release in the initial several hours. The degree of suppression was dependent on the coat thickness, soluble additive ratio in the coating formulation, and solubility of drug. When comparing differences in the release curves of systems conforming to Higuchi, first order or zero order models, the biggest differences observed were during the initial one third of the release profile. The Higuchi model showed the greatest non-linearity, followed by first order, and then by zero order. Uncoated matrix tablets exhibited Higuchi release kinetics. Application of EC coating increased

the linearity of the release curve, indicating conversion of release kinetics to first order or zero order. As the EC coating level increased, the release pattern followed first order and eventually zero order kinetics. Increasing the water-soluble additive had the opposite effect. As the ratio of soluble additive to EC polymer increased, the release curve reverted from zero order to first order or Higuchi kinetics.

It was observed that the matrix tablet cores which contained HPMC swelled when they came into contact with the dissolution fluid. At low EC coating load or when EC coat had high soluble additive level, the HPMC swelling strength exceeded the strength of the EC layer, resulting in rupture of the coat in the weakest region at the tablet edge. As the dissolution run continued, the EC layer eventually peeled away from the tablet surface. This observation showed that the coating only remained effective during the initial few hours of the drug release profile, after which drug release was dependant on the properties of the core tablet matrix. At higher coating weight, the greater strength of the thicker coat enabled it to withstand the swelling force of the core and the coat remained intact throughout the dissolution period. In this situation, the applied coat governed the release performance over the entire dissolution period.

Previous investigations showed that two components were possibly contributing to the zero order release mechanism of EC coated pellets. One of these was the osmotic force through aqueous pores, while the other was the diffusion force through the continuous polymer phase and aqueous pores (Ozturk et al, 1990). These contributed to drug release simultaneously. A plot of release rate vs. osmotic pressure revealed an inverse linear relationship with a non-zero intercept. The steep dependency of release rate on osmotic pressure suggested that osmotically driven release is a major component, while the non-zero intercept indicated some contribution from diffusion mechanisms. Drug release rate (dm/dt) at the steady state could be expressed in terms of these two components by the following equation (Ozturk et al, 1990):

$$dm/dt = (AS/h)L_p\sigma\Delta\pi + PAS/h \qquad\qquad (16)$$

where dm/dt is equal to K_0, A is the surface area of the dosage form, h is the thickness of the coating film, S is the drug solubility, L_p is the hydraulic permeability of the coating film, σ is the reflection coefficient, $\Delta\pi$ is the osmotic pressure difference across the coating film, and P is the permeability coefficient of the drug through coating film.

4. Mathematical relationship of drug release constant K_0 with HPMC levels in the EC coated matrix tablets

Drug release from the EC coated naproxen sodium matrix tablets generally fitted best to zero order kinetics. Therefore K_0 values were used for evaluation. When the zero order constant K_0 of different coating formulations at different coating levels was plotted against the HPMC content in the tablet core, a linear relationship ($R^2 > 0.99$) was obtained in most cases (Figures 25-28). The relationship could be expressed as follows:

$$K_0 = - a \ X \ C_{HPMC} \ + \ b \hspace{3cm} (17)$$

where C_{HPMC} refers to the HPMC concentration in the matrix tablet core and a, b are constants. The results of a, b and R^2 value at different EC coating amount and Opadry level are shown in Table 14. From the experimental data, a showed no direct relationship with the EC coating level, as a value for each coating formulation were very similar. However, b values showed a clear relationship with EC coating level applied to the matrix tablets. b values decreased considerably as EC coating quantity increased.

Figure 25. Correlation of K_0 with HPMC content in the naproxen sodium matrix core at different EC coating levels, without Opadry. (■) 2.87 % EC coat (□) 4.50 % EC coat (●) 6.82 % EC coat (○) 8.83 % EC coat

Figure 26. Correlation of K_0 with HPMC content in the naproxen sodium matrix core at different EC coating levels, with 10 % Opadry. (■) 2.65 % EC coat (□) 5.45 % EC coat (●) 6.68 % EC coat (○) 9.26 % EC coat

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Figure 27. Correlation of K_0 with HPMC content in the naproxen sodium matrix core at different EC coating levels, with 20 % Opadry. (■) 2.91 % EC coat (□) 5.44 % EC coat (●) 6.58 % EC coat (○) 9.12 % EC coat
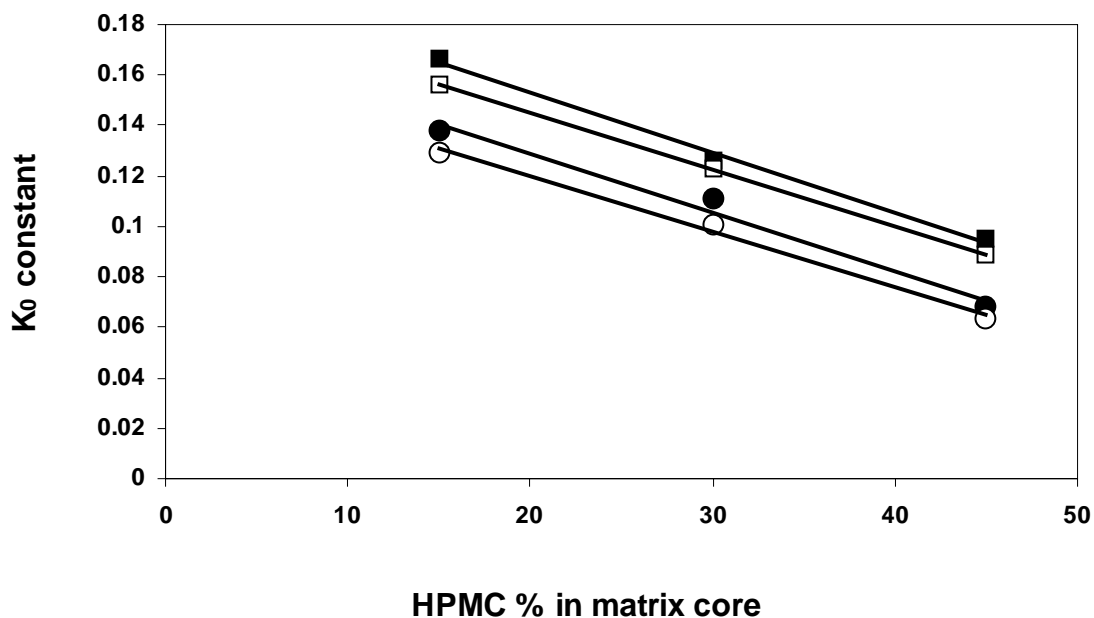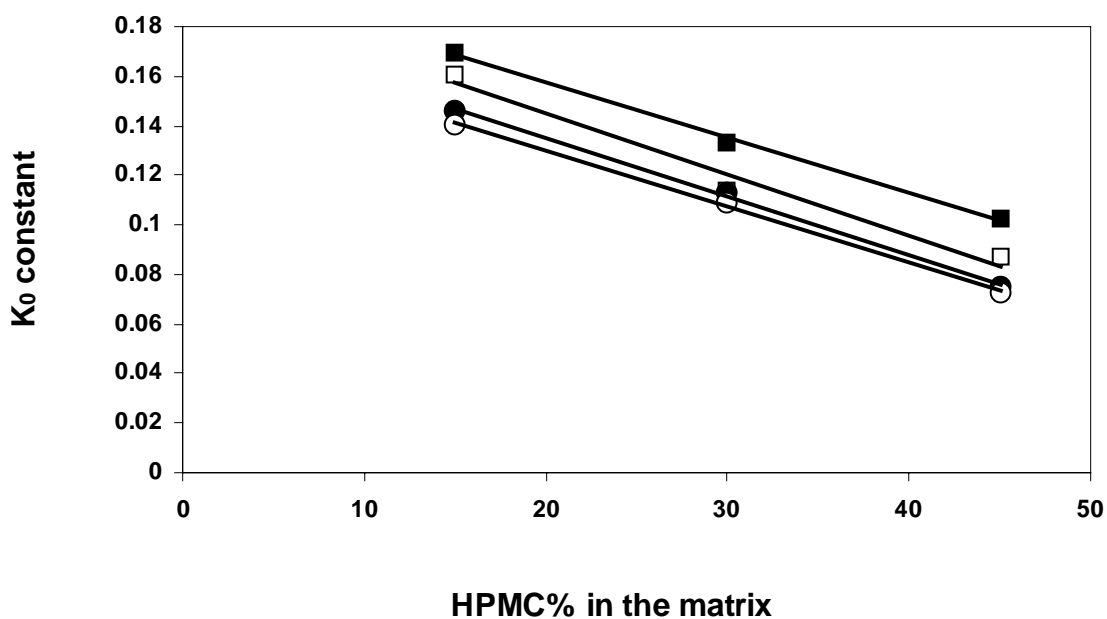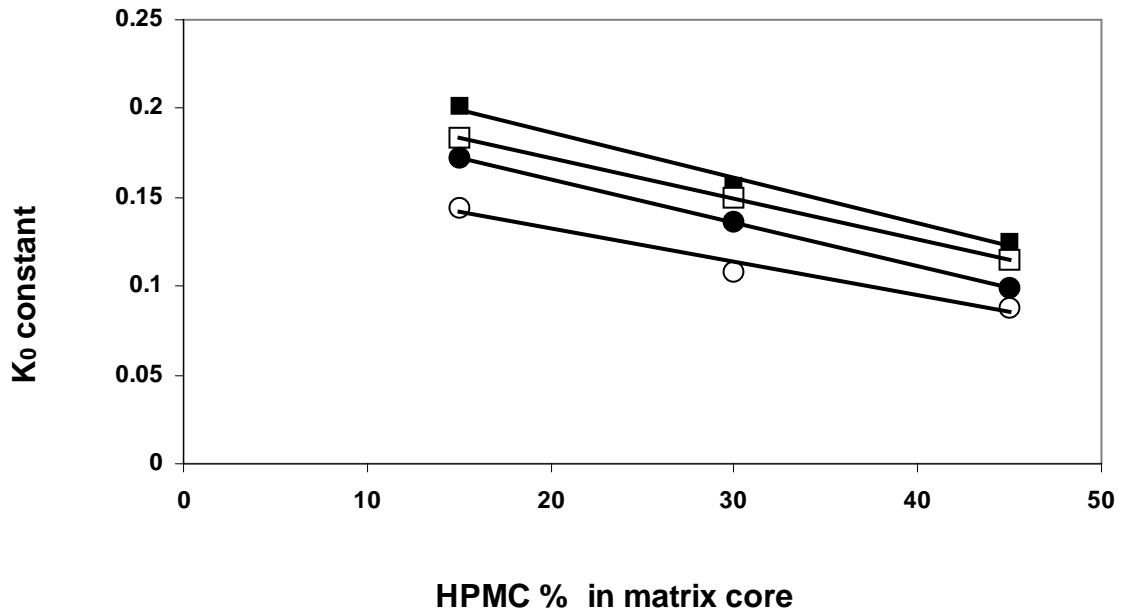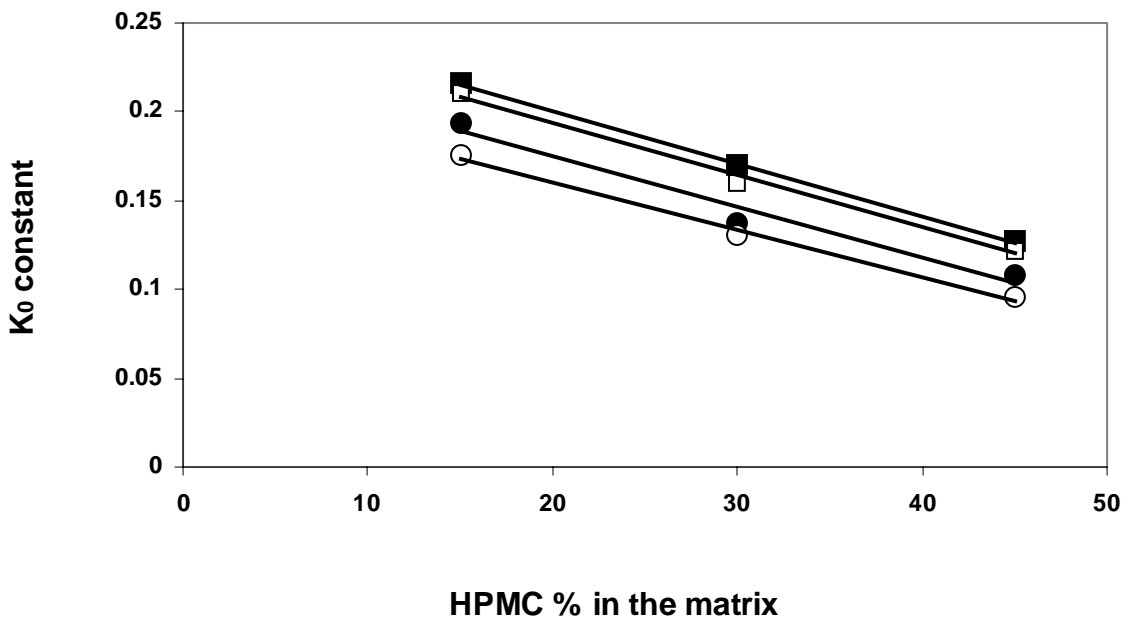

Figure 28. Correlation of K_0 with HPMC content in the naproxen sodium matrix core at different EC coating levels, with 30 % Opadry. (■) 2.41 % EC coat (□) 4.50 % EC coat (●) 5.78 % EC coat (○) 8.09 % EC coat

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Table 14. Relationship of K_0 value of naproxen sodium tablet with HPMC content in the tablet core, at different EC coating and Opadry levels

EC coating level (%)	Opadry level in EC coating (%)	a value	b value	R^2
2.87	0	0.0024	0.2010	0.9939
4.50	0	0.0022	0.1900	0.9998
6.82	0	0.0023	0.1750	0.9822
8.83	0	0.0022	0.1635	0.9930
2.65	10	0.0023	0.2098	0.9993
5.45	10	0.0022	0.1832	0.9882
6.68	10	0.0024	0.1795	0.9854
9.26	10	0.0022	0.1735	0.9999
2.91	20	0.0026	0.2381	0.9901
5.44	20	0.0023	0.2182	0.9998
6.58	20	0.0025	0.2094	1.0000
9.12	20	0.0019	0.1699	0.9686
2.41	30	0.0030	0.2599	0.9999
4.50	30	0.0030	0.2530	0.9937
5.78	30	0.0029	0.2318	0.9700
8.09	30	0.0027	0.2135	0.9949

For a poorly water-soluble drug such as aspirin, a linear relationship was not observed between K_0 and HPMC content in the tablet core. Neither was any linear relationship found with EC coating amount and soluble additive level.

V. Conclusion

In monolithic matrix system, particle size properties of the controlled release polymer, HPMC, had significant impact on drug release performance.

The rate of aspirin released from the matrix tablet generally decreased as the mean particle size of HPMC was reduced. The mean particle size of 113 μm for HPMC particles was identified as a critical criterion for obtaining consistent drug release profile. When mean particle size of HPMC was greater than 113 μm, a markedly higher rate of drug release was observed. In contrast, less significant effects on release rate were observed when using HPMC powder of mean particle size 113 μm or smaller.

Drug release mechanism was affected by HPMC mean particle size and concentration. When HPMC mean particle size was 113 μm or smaller, dissolution profiles gave a better fit with first order kinetics, indicating a combination of both erosion and diffusion as the controlling factors for drug release from matrix tablet. Drug release mechanism changed as HPMC mean particle size was 180 μm and above.

Polymer powders consisting of particles of similar mean particle sizes but of different size distributions were found to influence drug release rate but not the drug release mechanism. Drug release from both the sieved and unsieved polymer powders fitted better to first order release model. However, a difference in K_1 value was observed when HPMC content was below 20 %.

HPMC content was identified to be very important because of its influence on the effects of HPMC particle size and size distribution. Maintaining HPMC content above 20 % was helpful in developing a robust matrix system.

Drug release constant was proportionally related to polymer mean particle size and relative number of polymer particles in the matrix system, as demonstrated by the following equation:

$$K_1 = d/ (N_{polymer} \ X \ P_{polymer})^{1/3} + a$$

where $N_{polymer}$ refers to the relative number of polymer particles in the formula, $P_{polymer}$ is the mean particle size of the polymer powder and d is a constant indicating sensitivity of the matrix system to changes in particle size and polymer quantity. The value, a, is a release retarding

constant. This result can be used to eliminating the negative effects of varied polymer particle properties on matrix performance.

The release performance of water-soluble naproxen sodium and sparingly soluble aspirin from EC coated HPMC matrix tablets was investigated. Drug release rate decreased as HPMC content in the matrix core creased. Higher EC coating level led to lower drug release rate as the membrane permeability was decreased. Increase of Opadry concentration in EC coating increased drug release rate due to increased porosity and diffusion channels. The release of aspirin was more sensitive to EC coating level, while that of naproxen sodium was influenced more significantly by HPMC content in the core.

Application of EC coating to matrix tablets was found to suppress drug release rate during the initial several hours, the magnitude of suppression was dependent on the coating thickness and soluble additive concentration. Release kinetics normally followed the zero order model at higher EC coating levels. At lower EC coating levels, increase of Opadry concentration in the EC coating changed the release kinetics from zero order to first order. This impact diminished when EC coating level was increased.

K_0 obtained from naproxen sodium tablets coated with different EC coating formulations and different coating load had a linear relationship with HPMC content in the core, which was expressed in the following equation. This relationship was not found with aspirin tablets.

$K_0 = - a \ X \ C_{HPMC} \ + \ b$

where C_{HPMC} refers to the HPMC concentration in the matrix tablet core and a, b are constants. The constant, a showed no direct relationship with the EC coating level, as a value for each coating formulation were very similar. However, b values showed a clear relationship with EC coating level applied to the matrix tablets and the b values decreased considerably as EC coating quantity increased.

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