Development of a Sustained Release Dosage Form for an Iron Chelator

by

Dilip Kaul

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DEVELOPMENT OF A SUSTAINED RELEASE DOSAGE FORM FOR AN IRON CHELATOR

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ABSTRACT

Sustained release tablet formulations for a new orally active iron chelator (1,2, dimethyl-3-hydroxy-pyrid-4-one, DMHP or L1) have been developed. Coprecipitates containing DMHP and various kinds of polymers (Eudragit RSPM and Eudragit RLPM, and HPMC-E4M, E10M, and K4M grades) were prepared by the solvent method. The coprecipitates were compressed into tablets for further studies. The dissolution profiles as a function of (i) the type of polymer (ii) polymer content, and (iii) pH were determined. Both Eudragit types (RLPM and RSPM) and all HPMC grades exhibited significant sustained release activity. Above a certain ratio, increase in the polymer concentration did not provide any further decrease in the release rates. All grades of HPMC and both Eudragit RSPM and Eudragit RLPM showed non-Fickian release kinetics and no formulation showed any significant pH dependent release kinetics. Coating the tablets with Aquacoat® provided additional control over the release of drug. All formulations showed either non-Fickian or near zero-order release. In cases where Aquacoat® did not release any DMHP, the use of a channeling agent (PEG 4000) proved partially successful in providing some drug release. The role of HPMC and Eudragits as well as Aquacoat® coatings in the formulation of a sustained release tablet of a water soluble drug is demonstrated.

ACKNOWLEDGMENTS

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INTRODUCTION

1.1. THALASSEMIA

The thalassemia syndromes are a heterogeneous group of inherited disorders manifested in the homozygote by profound anaemia and in the heterozygote by red cell abnormalities of relatively trivial significance. The transfusion-dependent anemias such as thalassemia major, which generally cause iron overload in patients, can lead to multi-system disorders as observed in hemochromatosis and can be fatal in most of the cases. The disease thalassemia can be classified in to two major categories : (a) α-thalassemia which is caused by retarded production of α-chains of globin and (b) ß-thalassemia which occurs due to a decrease in the synthesis of ß-chains by different mechanisms and may affect any of the steps of ß-globin gene expression (transcription, RNA processing, and translation) (1). The hemoglobin production in patients is considerably less than normal but structurally the hemoglobin cells are normal in appearance. A decreased synthetic rate of one type of globin chains results in ineffective erythropoiesis, with markedly enhanced intramedullary loss of developing red cells.

Homozygous ß-thalassemia is a severe disorder, characterized by symptoms such as anemia, jaundice, failure to thrive, hepatosplenomegaly and skeletal changes, which cause the characteristic facial appearance of the disease. If the patients are adequately blood-transfused then these symptoms will not develop and the patients will remain relatively normal especially during the first decade of their life. After the age of 10 to 11 years, both poorly and well transfused, children begin to show signs of liver, heart and endocrine dysfunction which is a consequence of excess iron in the body. The iron overloading, particularly of the myocardium, has serious clinical repercussions and is the major cause of death during the second decade of life (2). In human cells, proteins function as iron carriers, for example, Lactoferrin, Ovotransferrin and transferrin (3-5). Transferrin serves a dual function in the cells, (i) restricting access of microorganisms to iron and (ii) transporting the iron from sites of absorption and heme degradation to those of storage and utilization.

1.1.1. Iron Storage in the Body

In human cells, ferritin is used for iron storage. Ferritin has a molecular weight of approximately 450 kDa and can store up to 4500 atoms of ferric iron as a mineral core within the hollow protein shell (6). Ferritin molecules with 1200-1400 atoms are most efficient in facilitating further rapid accumulation as well as prompt release when the metal is required for metabolic activity.

1.1.2. Treatment of Iron Load

The treatment of transfusional iron overload conditions is quite complex. The only drug that has been approved so far and currently in use is Desferrioxamine mesylate (DF; Desferal), an iron chelator (7-8). Although DF is now well established (9) and its use reduces or prevents the complication of iron overload (10), it has certain disadvantages. DF is not absorbed orally and following intravenous (IV) administration its biological half-life is only 5 to 10 minutes. It is rapidly metabolized and excreted in the urine. Therefore, in clinical practice it is administered as a slow infusion for 6-8 hours (11-12) for at least 5 days a week, for in some cases for several years. This dosage regimen is very taxing and expensive and patient compliance in the long run is low. DF is also known to produce ototoxicity on long term usage (13), cause hypotension, growth retardation, and neurological side effects (14-16).

Hence, there is a great need to develop a new iron chelator that is as effective as DF, less toxic, inexpensive, orally active, and that could remove excess iron from the body.

1.1.3. The Properties of an Ideal Metal Chelating Drug

An ideal chelator for a specific toxic metal ion should have the following characteristics:

(1) high formation constant for the toxic metal ion,

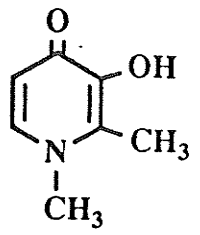
(2) high selectivity for the toxic metal ion amongst all other essential elements present in the biological systems,
(3) ability to penetrate into the biological compartment where the toxic metal ion has been largely deposited or stored,
(4) high stability against enzymatic degradation in the extracellular spaces prior to uptake into target organs, and
(5) low toxicity of drug and drug-metal complex.

1.1.4. New Chelating Agents

Many new chelating agents have been developed (17) and tried in humans including rhodotoluric acid, 2,3-dihydroxybenzoic acid, cholylhydroxamic acid, and isonicotinyl hydrazone (PIH). Most of these chelating agents have been discarded either because of their high toxicity or low activity following oral administration (18).

Recently a new class of orally effective iron chelators, alpha-keto-hydroxypyridones have been synthesized and tested in humans and various animal models. The alpha-ketohydroxypyridones are synthetic compounds that combine features of the hydroxamates and catechols. The most prominent amongst alpha-ketohydroxypyrid-ones is 1,2-dimethyl-3- hydroxypyrid-4-one (DMHP or L1 or CP20). DMHP was shown to promote urinary iron excretion and also that maximum excretion of iron occurs in the first twelve hours after dosing, and the excretion level returns to the base line within 12 to 24 hours (19-22).

1.1.4.1. 1,2-Dimethyl-3-Hydroxypyrid-4-one (DMHP)



1,2-dimethyl-3-hydroxy
pyrid-4-one (DMHP)

DMHP has a LD_{50} of 600-700 mg/kg in rats, and its administration either intraperitoneally or intragastrically to mice for one month at the dose of 200 mg /kg body weight daily produced no apparent toxicity (23). DMHP has not shown any apparent toxicity when given to humans for one year (24). Kontoghiorghes in a recent study has reported that 126 thalassemia patients on DMHP for 15 months, showed no short-term side effects. However, suppression of blood cell production was observed but only at very high DMHP doses. Only one patient developed agranulocytosis and thrombocytopenia (25).

DMHP, although polar in nature, has a relatively low aqueous solubility of 15 mg/ml. To induce adequate iron excretion from the body, the DMHP should be administered in large doses (usually 2 to 3 g per day for a 70 kg patient). A solution formulation at this high dose would require a large volume. A tablet dosage form therefore, is essential and most convenient for administration of large doses of DMHP. Because of the short elimination half-life of DMHP (approximately 1 hour in dogs and rabbits), it is an ideal candidate for the development of a sustained/controlled release dosage form.

Most of the pharmacokinetic of DMHP work has been done on experimental animal models, viz., rabbits and dogs (S. Venkataram and Y. E. Rahman, unpublished data). In dogs, after intravenous administration of DMHP solution, the half-life ($T_{1/2}$) of DMHP has been found to be 60 minutes, the total body clearance (TBC) was 1.2 l/kg. hr and the volume of distribution at steady state (V_d) was 0.8 l/kg. After administration of DMHP tablets, the oral bioavailability was 61.0% and the peak plasma concentration (C_{max}) of 52.4 µg/ml was reached in 1.03 $\pm$ 0.55 hr (T_{max}).

1.2. SUSTAINED RELEASE (SR) DRUG DELIVERY SYSTEMS

Current trends provide new, safer, economical, and more efficient means for well-being of mankind by developing new drug delivery systems. Conventional fast release oral preparations deliver their drug contents all at once for absorption into the body. This leads to high peak drug levels beyond therapeutic and approaching toxic levels. If the drug is excreted at a rapid rate the levels decline below therapeutic level within a few hours, thereby necessitating frequent dosing. This results in widely fluctuating drug levels. This may not only compromise efficacy of the drug and produce toxic side effects but will also result in poor compliance.

The desirability of slow, constant release oral medication was first reported by Lipowski (26) nearly half a century ago. In early 1950, this concept was for the first time applied with the introduction of the Spansule line of products (27-28). During the last 30 years a

substantial number of drug delivery systems, purporting to prolong the action of drugs, have been introduced in a slow but steady stream onto the market. The bulk of research and development effort in this area has been concerned with dosage forms for the oral routes although increasing attention is being paid to the intramuscular, skin, eye, and other routes of drug administration (29-36). Successful fabrication of sustained release products is usually difficult and involves consideration of the physico-chemical properties of the drug, pharmacokinetic parameters of the drug, route of administration, disease states to be treated, and placement of the drug in a dosage form that will provide the desired temporal and spatial delivery pattern for the drug. Major advances in this kind of drug delivery system did not occur for several decades due to the apparent unreliability of some of the products as well as lack of supportive sciences such as polymer, analytical, medical, and biopharmaceutical. It is only within the past few years that the full potential and wide range applicability of the sustained release technology has been realized. In a report presented by Higuchi et al. (37), they stated ' the approach to the design of oral drug delivery is evolving rapidly, both quantitatively and qualitatively, so that the situation is considered to be on the threshold of being revolutionary'. All evidence seems to support this statement because the field of oral sustained /controlled drug release is definitely advancing fast.

Simple definition of sustained release drug systems is any drug or dosage form modification that prolongs/delays the therapeutic activity of the drug. Further, in the absence of suitable clinical

evidence of this sustaining effect one can accept the prolongation of drug levels in the blood.

The oral route of drug administration is preferred route when systemic drug effects are sought since self administration is facilitated, it is usually the lowest in cost, and it is typically the most reliable and safest method of self medication. Thus, when sustained release drug products are being considered, an oral product is usually the goal.

1.2.1. Advantages of Sustained Drug Delivery Systems

Sustained release (SR) dosage forms are invariably more expensive than conventional formulations, and they can be justified only when they offer one or more distinct therapeutic advantages (38). Some of the advantages of SR are given below:

1. achieving rapid onset and then maintaining desired therapeutic drug levels,
2. large dosage intervals,
3. minimal fluctuations in drug levels,
4. less amount of total drug used,
5. reduced inconvenience to the patient, and increased compliance,
6. saving patient caring time,
7. avoiding night time dosing,
8. more uniform pharmacological response, and
9. reduced side effects.

Despite many advantages cited above, SR formulations have certain limitations and disadvantages.

1.2.2. Disadvantages of Sustained Release Drug Delivery Systems

1. possibility of dose dumping,
2. reduced potential for accurate dose adjustment,
3. slow absorption may delay onset of action, however, this can be corrected if a fraction of the drug content is designed for immediate delivery,
4. increased potential for first pass metabolism,
5. possible reduction in systemic availability, and
6. drug release period restricted to residence time in gastrointestinal tract.

1.2.3. Rationale for Sustained Release Design

The selection of a drug candidate for the design of a sustained release system depends largely upon pharmacologic, therapeutic, and pharmaceutical considerations (39). Major criteria for the selection of a drug candidate are:

1. short biological half-life,
2. narrow therapeutic index,
3. efficient GI absorption,
4. small daily dose,

5. no first pass metabolism, and
6. marketing benefits.

Sustained release systems by design, contain multiple doses in a single unit. The size of the dosage unit, therefore, can become the limiting factor. Generally, it is feasible to develop a swallowable dosage unit with less than 800 mg of drug. Prior to developing a sustained release dosage form, one must assess the relationship between the drug levels and therapeutic action.

1.2.4. Design Strategy

For designing an oral sustained release drug delivery system, there are a number of *in-vitro* and *in-vivo* aspects involved during the developing phase. The physico-chemical properties like solubility, pka, stability, compressibility of the drug, type of delivery systems, and selection of appropriate excipients, processability, mechanism of drug release, and evaluation of drug release rate are among the *in-vitro* considerations. Single and multiple dose studies , influence of food and time of dosing, estimation of *in-vivo* drug release, *in-vitro/in-vivo* correlations, inter- and intra-subject variability, and clinical efficacy are among the *in-vivo* considerations.

1.2.5. Graphic Interpretation of the Dissolution Process

The dissolution process can be graphically presented by plotting the cumulative amount of drug dissolved/released F(t) versus time (t),

depending on the algebraic function describing the process as shown in Figure 1.

Figure 1a shows zero-order dissolution according to equation $F(t) = kt$. In fixed time interval, the amount of the drug released into the solution is the same, common example of this kind of release are oral osmotic therapeutic systems.

Figure 1b illustrates the first-order dissolution process described by the equation $F(t) = 1-kt$, conventional tablets generally follow this equation.

Figure 1c shows a plot obtained from the cube root law, described by the equation $F(t) = 1- (1-kt)^3$. This dissolution is observed in dosage forms containing many drug particles of the same size and shape, or their agglomerates, dissolving evenly.

Figure 1d represents the graphic interpretation of the square root equation $F(t) = k\sqrt{t}$, illustrating drug dissolution from a matrix, where it is dissolved in the matrix-forming substance and release is controlled by diffusion.

1.2.6. Types of Sustained Release Dosage Forms

Most of the sustained release products can be designated among the following types:

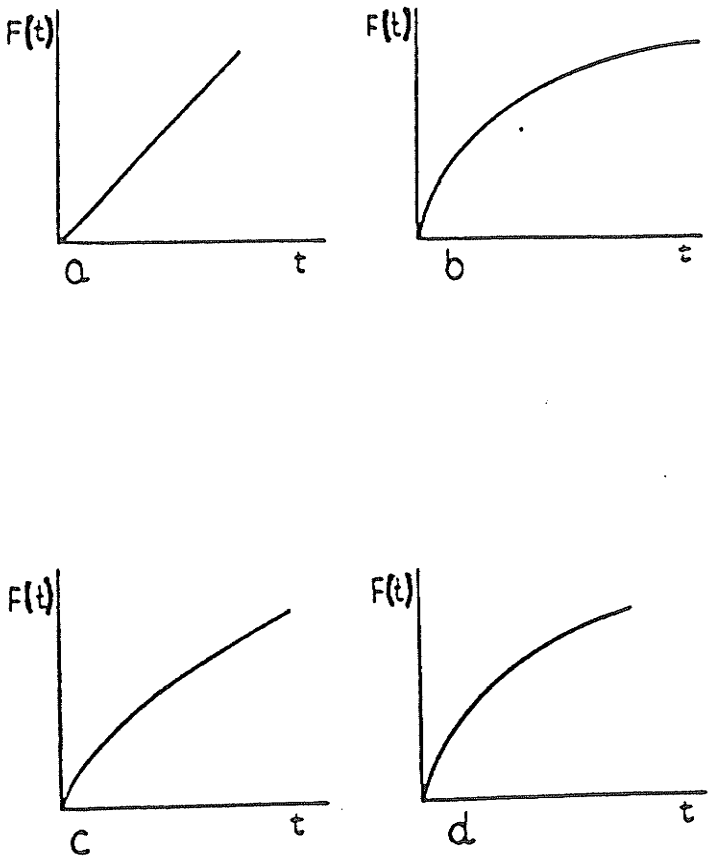


Figure 1. Plots between the cumulative amount of drug released F(t) and time (t) showing various dissolution processes : (a) zero-order process, (b) first-order process, (c) dissolution according to the cube root law, and (d) dissolution according to the square root equation.

1. single unit (matrix tablets, coated tablets, capsules),
2. multiple unit (granules, beads, micro-capsules),
3. inert, insoluble matrix,
4. hydrophilic gel matrix (bioadhesive, erodible and non-erodible), and
5. ion-exchange resins.

The choice between the single unit and multiple units would depend upon the drug and release pattern desired. Multiple units generally exhibit less variability because small pellets (<2 mm) in the presence of food, are retained in the stomach for much shorter time than the large tablets (40). The GI transit time , therefore, would be an important factor to consider in selecting a type of dosage form in relation to the duration of drug release and variable performance. Tablets containing either insoluble wax and polymer materials or hydrophilic polymers are widely utilized in sustained release products.

1.3. DRUG RELEASE RATE AND DOSE CONSIDERATIONS

An ideal type of sustained release product would be one in which the rate of drug delivery is phased to the needs of the condition at hand. Thus, such factors as moment to moment variations in drug needs of the condition could be incorporated into the drug release pattern (41-42). However, one generally lacks the technological sophistication to prepare a product with such a variable release rate and

frequently does not understand the drug needs of the condition sufficiently to incorporate this into the design of the product.

$$\text{Dosage Form} \xrightarrow{k_r} \text{GI tract} \xrightarrow{k_a} \text{Blood} \xrightarrow{k_e} \text{Urine}$$

Scheme 1

$$\text{Dosage Form} \xrightarrow{k_r} \text{Blood} \xrightarrow{k_e} \text{Urine}$$

Scheme 2

The model for oral drugs as shown in scheme 1 is generally used to describe the drug movement in the body, where k_r, k_a, and k_e represent the rate constants for drug release, absorption, and elimination, respectively. For a sustained release dosage form k_r is much smaller than k_a, thus becoming rate limiting in Scheme 1 and reducing the model to that shown in scheme 2. In order to maintain a constant level of drug in some desired target tissue, the question is what release pattern from the dosage form (drug input) is needed to produce such a profile. It can be easily shown that a zero-order release of drug from the dosage form or, conversely, constant availability to the body is the most appropriate release pattern (43). For a drug whose disposition in the body can be described by a

simple, one-compartment model, the rate of drug loss at any point in time can be described as

Rate out= $k_r^o = C_t \quad k_{el} \quad V_d$ ----------> equation (i)

where C_t is the concentration of the drug in the blood/tissue at time t, k_{el} is the total elimination rate constant, and V_d is the apparent volume of distribution for the drug. In Figure 2, the desired concentration of the drug is shown as plateau concentration or maximum in the nonsustained blood drug level profile, which presumably would be the mid point of the therapeutic range. In order to maintain this drug level indefinitely, it is only necessary to put the drug back in at the same rate it is being removed, or

Rate in = Rate out = $k_r^o = C_t \; k_{el} \; V_d$ ---------> equation (ii)

One can envision the simplest sustained drug product as an intravenous drip whereby the rate of drug supply matches that which is lost and is constant (zero-order). For oral and other routes of drug administration to provide drug via a zero-order pattern whose rate constant describing delivery is determined by the terms shown in equations (i) and (ii). To determine the total amount of drug for the dosage form one merely adds the amount of drug needed to achieve the desired blood level quickly (the immediately available portion) to the sustaining portion. The sustaining portion is determined by multiplying the zero-order rate constant for sustained drug delivery k_r^o by the desired sustaining time (h):

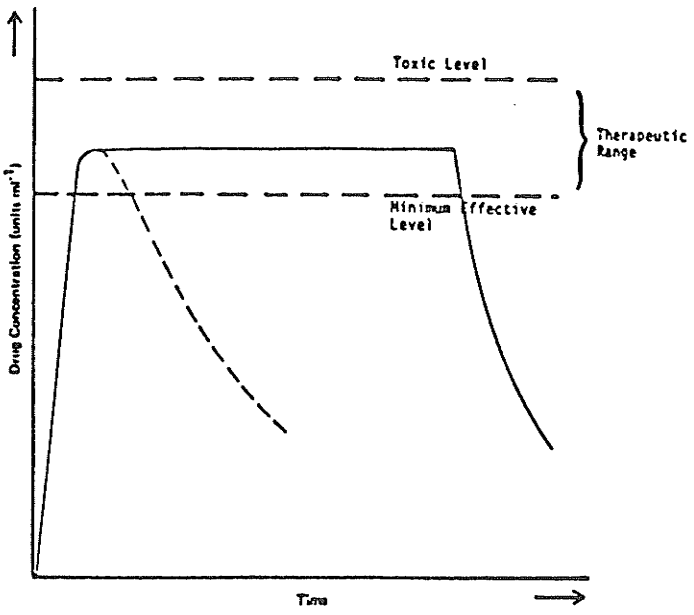


Figure 2. The typical blood or tissue drug level versus time profile : (----) represents an ideal Sustained drug delivery system and (---) represents corresponding level from a nonsustained dosage form.

$W = D_i + k_r^o \; h$ ----------> equation (iii)

where W is the total dose and D_i is the initial dose. If the drug is released from the dosage form by first-order process then following equation describe the total dose (W)

$W = D_i + k_{el} \; C_t \; V_d \; /k_r^1$ ----------> equation (iv)

Where k_r^1 is the first-order drug release rate constant.

1.4. MECHANISM OF SUSTAINED RELEASE DRUG DELIVERY SYSTEMS

For a dosage form to release the drug at a zero-order rate means that the rate of drug release is independent of drug concentration (44):

$dC/dt = k_r^o$ ----------> equation (v)

or in terms of amounts:

$dM/dt = k_r^o$ ----------> equation (vi)

Most of the time it is not possible to prepare a constant release product and a slow first-order release of drug is employed. A slow first-order release will approximate a zero-order release as long as only a fraction of drug release is followed.

There are several mechanisms and dosage form modifications to attain zero-order release rate. They can be classified into three main systems,

(1) Diffusion controlled release systems
(2) Dissolution controlled release systems
(3) Osmotically controlled release systems.

1.4.1. Diffusion Controlled Release Systems

A wide variety of sustained release products are based on diffusion controlled release of the drug. The following discussion will bring into perspective those properties that should be considered while formulating a dosage form based on this approach.

Fick's first law of diffusion states that a drug diffuses in the direction of decreasing concentration across a membrane where J is the flux of the drug in amount/area-time,

$J = - D \frac{dC}{dx}$ ----------> equation (vii)

where D is the diffusion coefficient in area/time, C is the concentration, and x is the distance (Figure 3). Assuming steady state, the above equation on integration yields

$J = -D (C_1 - C_2)/ l$ ----------> equation (viii)

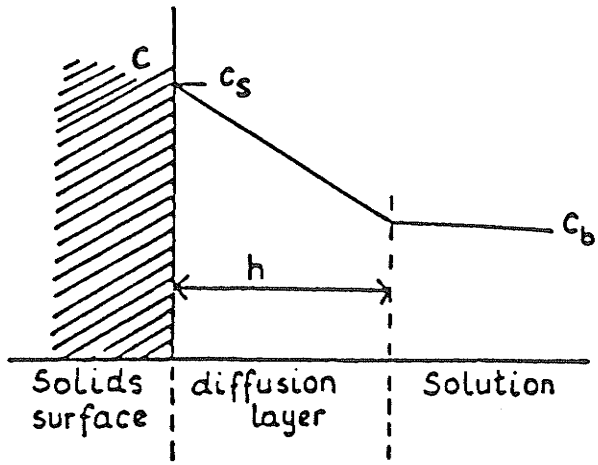


Figure 3. Dissolution process according to Fick's diffusion-layer model.

or when expressed in simple form when a water-insoluble membrane is employed:

$$dM/dt = ADK (C_1 - C_2)/ l \quad \text{----------} > \qquad \text{equation (ix)}$$

where A is the area, K is the partition coefficient of drug into the membrane, l is the diffusional pathlength, and $(C_1 - C_2)$ is the concentration gradient across the membrane. In order to have a constant release rate, the right hand terms of equations (viii) and (ix) must be maintained constant. In other words, the area of diffusion, diffusional pathlength, concentration gradient, partition coefficient, and diffusion coefficient must remain constant. Usually, one or the more of the above parameters will change in oral sustained release dosage forms giving rise to non-zero-order release.

The more common diffusional approaches for sustained drug release are shown in Figure 4. In most cases the drug must partition into a polymeric membrane of some sort and then diffuse through the membrane to reach the biological milieu. When the tablet or micro-capsule contains excess drug, a constant activity of drug will be maintained until the excess has been removed, giving rise to constant drug release. In Figure 4a the polymer is water-insoluble and the important parameter is solubility of drug in the membrane since this gives rise to driving force for diffusion. In Figure 4b either the polymer is partially soluble in water or a mixture of water-soluble and water-insoluble polymers is used. The water-

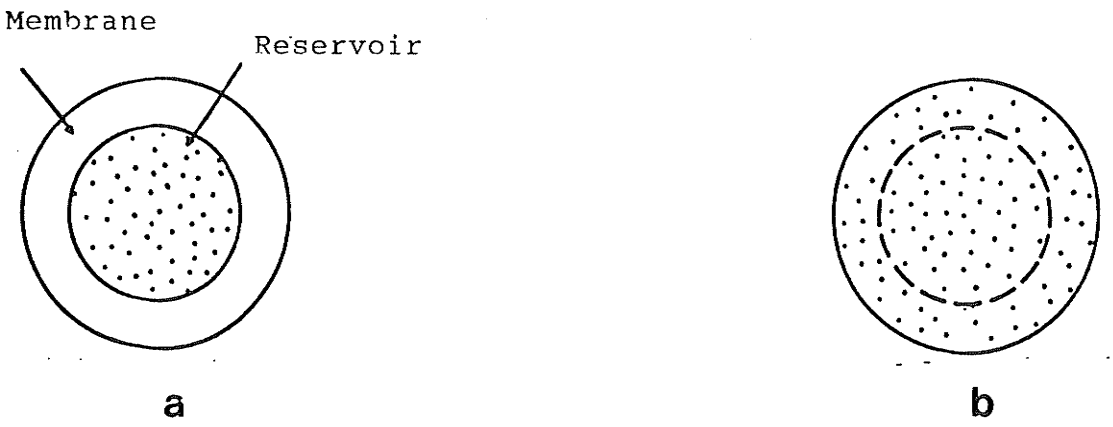


Figure 4. Diffusion control of drug release by (a) a water-insoluble and (b) a partially water-soluble polymers.

soluble polymer then dissolves out of the film yielding small channels through which the drug can diffuse. The small channels would presumably give a constant diffusional pathlength and hence maintain constant conditions as described earlier.

1.4.2. Dissolution Controlled Release System

In this case the drug is embedded in a polymeric material and the dissolution rate of the polymer determines the release rate of the drug. The drug release rate, if governed by erosion or dissolution, can be expressed as

$$dM/dt = A\ dx/dt\ f(c)$$

where dx/dt is the erosion rate, f(c) is the concentration profile in the matrix and A is the area. A constant erosion rate can produce a zero-order release kinetics, provided the drug is dispersed uniformly in the matrix and area is maintained constant (45-46). Often times, swelling of the system causes change in the area and thus produces non-zero-order release.

The common forms of dissolution control release systems are shown in Figure 5. In Figure 5a we have a barrier coat across a microcapsule or nonpareil seed containing drug and the release of the drug is controlled by the dissolution rate and the thickness of the barrier coat. Varying the coating thickness, or layering concentric spheres

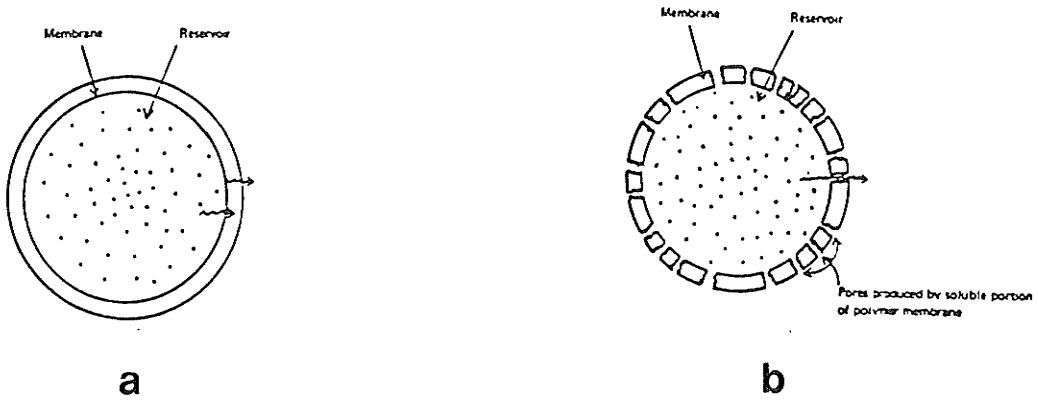


Figure 5. Dissolution control of drug release via (a) thickness and dissolution rate of the membrane barrier coat and (b) polymer core erosion or polymer coating erosion.

of coating material and drug reservoir material, yields different release times producing the repeat action dosage form. Once the polymer has dissolved, all of the drug contained in the capsule is available for dissolution. In Figure 5b the drug is either embedded in a polymer or coated with a water-soluble polymer, which in turn is compressed into a slowly dissolving tablet. The release rate is controlled by the dissolution rate of the polymer or tablet.

1.4.3. Osmotic Controlled Release Systems

In this type of drug delivery systems, osmotic pressure is the driving force that generates constant drug release. As shown in Figure 6, this system is fabricated by applying a semipermeable membrane around a core of an osmotically active drug or a core of an osmotically inactive drug in combination with an osmotically active salt. A delivery orifice is drilled in each system by laser or by a high-speed mechanical drill (47-49). When an osmotically active system is exposed to water or any body fluid, water will flow into the core due to an osmotic pressure difference across the coating membrane.In principle, this delivery system dispenses drug continuously at a zero-order rate until the concentration of the osmotically active salt in the system is below saturation solubility, whereupon a non-zero-order release pattern results (50).

The wall can be made without any orifice. In this case, as the water is imbibed, the system can build up hydrostatic pressure until the wall breaks and the contents are released to the environment (51).

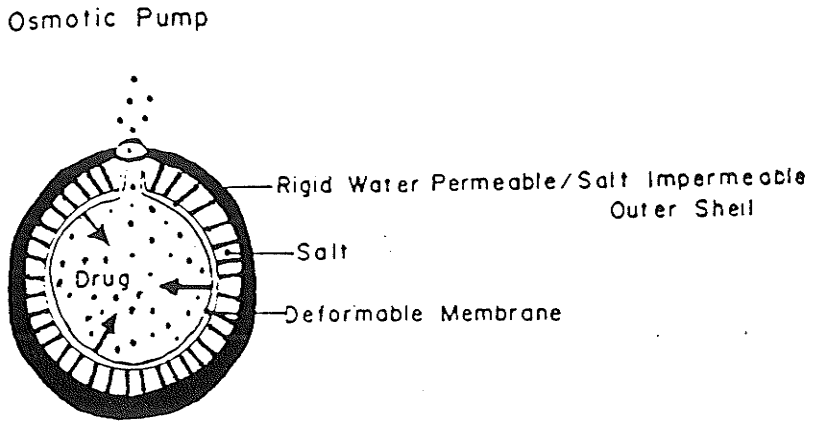


Figure 6. A schematic representation of an osmotic pump device for sustained/controlled drug delivery.

This osmotic bursting device can be employed to control drug release by varying either the thickness or the area of semipermeable membrane.

This system requires only osmotic pressure to be effective, and is essentially independent of the environment. As a consequence, this should be an excellent Sustained/Controlled release system for oral dosage forms, because there are rather harsh inconsistent conditions of pH and mixing in the digestive tract. Thus, the drug delivery rate from an oral osmotic therapeutic system can be precisely predetermined regardless of pH change (52).

1.5. MODES OF POLYMER EROSION AND DRUG RELEASE

There are three types of drug delivery systems associated with biodegradable matrices. They are diffusion-controlled, swelling-controlled, and chemically-controlled systems (Figures 7-8). Most drug delivery devices act by a combination of these three mechanisms. The time frame in which a drug delivery device biodegrades and in which the drug is released often defines the controlling mechanisms. Polymer degradation can take place throughout the drug release process, during only a portion of drug-release time, or only after device exhaustion. Most biodegradable devices are designed to degrade only after the drug they carry is exhausted.

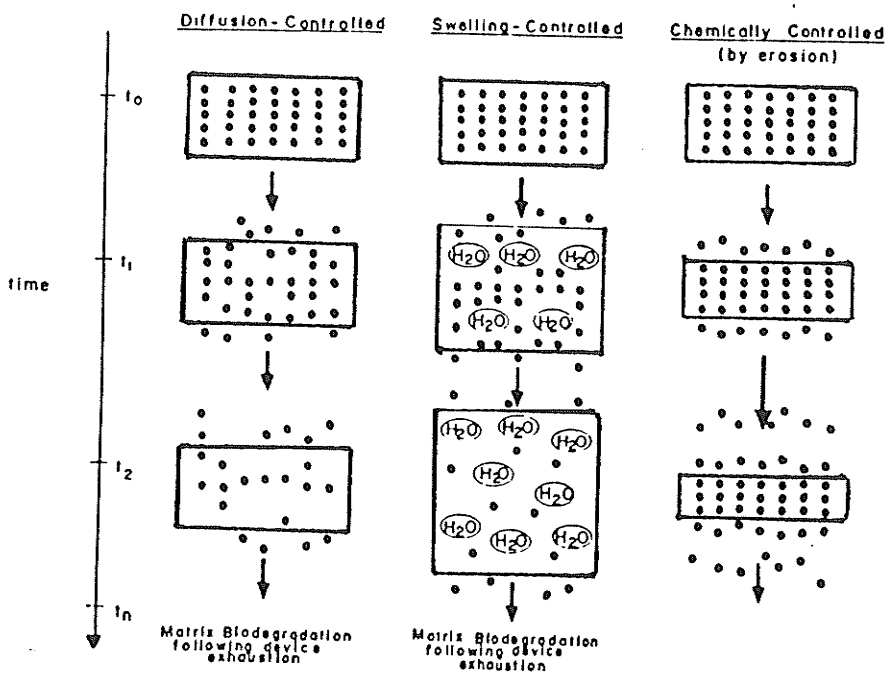


Figure 7. A schematic drawing illustrating the three mechanisms, (i) Diffusion-controlled, (ii) Swelling-controlled, and (iii) Chemically-controlled (by erosion), for sustained/controlled drug release from a polymer matrix.

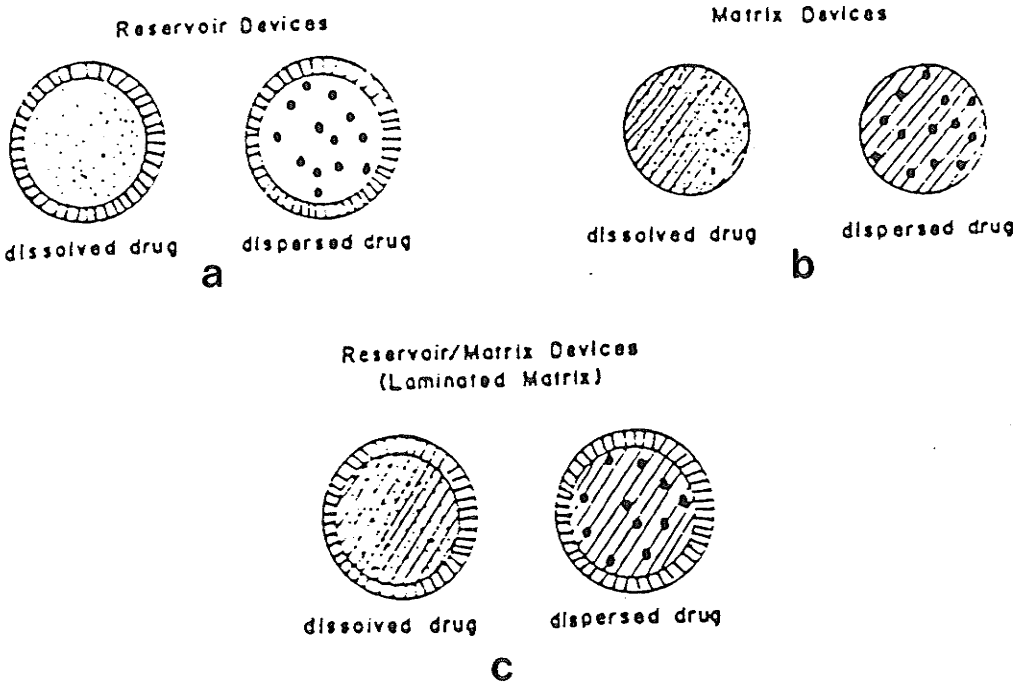


Figure 8. A schematic representation of three types of (a) Reservoir, (b) Matrix, and (c) Reservoir/Matrix (Laminated) polymer based drug delivery devices.

1.5.1. Diffusion-Controlled Systems

Diffusion-controlled nonbiodegradable drug delivery devices have been studied in depth by several researchers (53). The release characteristics for nonbiodegradable systems can be applied in the study of biodegradable systems as long as the matrix remains intact and its permeability remains unchanged until the drug it contains is released.

Two types of diffusion-controlled devices have been used in drug delivery systems. These are reservoir devices and matrix devices (Figure 8). The drug component of either type of device can be dissolved or dispersed within the device. Release of a dispersed drug from a polymer matrix, by diffusion, occurs in four steps.

(a) Dissolution of the drug into the surrounding polymer or pores, (b) molecular diffusion of the drug across or through the polymer barrier along its concentration gradient (c) drug desorption from the polymer, and (d) diffusion into the external medium or tissue. When a drug is dissolved in the delivery matrix and the mechanism for the delivery is diffusional, then the thermodynamic driving force is the concentration gradient (54-55) and release predictions can be made based on Fick's law of diffusion. When the drug is dispersed as particles rather than dissolved, an equation derived from Fick's law can be used to predict release rates (56-57). Diffusional release is dependent on the relative solubilities (or permeabilities) and

diffusivities of the drug in both the membrane and in the surrounding medium.

1.5.1.1. Reservoir Devices

Reservoir systems are hollow devices in which an inner core of dissolved, suspended, or neat drug is surrounded by a polymer membrane. These devices are diffusion controlled and follow the release kinetics given by equation below:

$$M_t = D_{eff} (A C_s t/h)$$

The effective diffusivity D_{eff} for a nonporous polymer is the drug diffusion coefficient in the membrane, while in a porous membrane D_{eff} contains a correction factor for membrane porosity and tortuosity. The amount of drug released as a function of time t depends on this D_{eff}, the membrane area A, the drug solubility C_s, and the membrane thickness h. Since the drug concentration within the device is much higher than that on the outside, the driving force for diffusion across the membrane is constant with the time.

1.5.1.2. Matrix (Monolithic) Devices

In general, the term matrix device implies a drug delivery system in which drug is dispersed, either molecularly or as solid drug particles, within a polymer network. Within the context at least four different types of devices can be envisioned. These include :

(i) dissolved matrix devices wherein the drug is dissolved within a crosslinked polymer at or below the saturation solubility of drug in the polymer; (ii) dispersed matrix devices in which drug is dispersed as discrete solid particles within a polymer such that the concentration of the drug far exceeds its saturation solubility in the polymer; (iii) porous matrix devices which are analogous to dispersed devices except that the initial drug load is sufficient to produce contiguous channels throughout the polymer network; and (iv) surface treated devices which have a core which is analogous to types (i) to (iii) and a surface layer which is of much lower permeability to the drug than is the core.

The major advantages of matrix devices are the ease of manufacture and the fact that drug will not 'dump' upon rupture (58). The major disadvantage is that the drug release rate will decrease with time. It is possible to minimize this variation, but this will occur at the expense of ease of manufacture.

A matrix (or monolithic) device is easy to formulate, gives a higher initial release rate than a reservoir device, and can be made to release at a nearly constant rate. The rate of release of drugs suspended in an inert matrix has been described by Higuchi (59-60).

The amount of total drug released from a planar system having a homogeneous matrix (Figure 9a) into a bathing medium acting essentially as a perfect sink would be determined by the relationship

a b

Figure 9. Two methods of drug release from (a) homogeneous matrix and (b) granular matrix with connecting capillaries.

$$Q = \sqrt{Dt(2A-Cs)\,Cs}$$

where Q is the amount of drug released after time t per unit exposed area, D is the diffusivity of the drug in the homogeneous matrix media, A is the total amount of drug present in the matrix per unit volume, and C_s is the solubility of the drug in the matrix substance.

For the leaching type release mechanism occuring through diffusion movement utilizing intergranular openings (Figure 9b), the above relation must be modified for the effective volume and diffusional pathlength where diffusion can occur. It can be readily be seen for this system that

$$Q = \sqrt{DE(2A-EC_s)C_s t/T}$$

where Q is the amount of drug released after time t per unit exposed area, D is the diffusivity of the drug in the permeating fluid, T is the tortuosity factor of the capillary system, A is the total amount of drug present in the matrix per unit volume , C_s is the solubility of the drug in the permeating fluid, and E is the porosity of the matrix. For the purpose of data treatment, equations above are conveniently reduced to :

$$Q = k\sqrt{t}$$

Therefore, a plot of amount of drug released versus the square root of time should be linear if the release of the drug from the matrix is

diffusion controlled. If the release of the drug is diffusion controlled, then by the Higuchi model, one may control the release of the drug from a homogeneous matrix by varying the following parameters:

(i) initial concentration of drug in the matrix, (ii) porosity, (iii) tortuosity, (iv) polymer system making up the matrix, and (v) solubility of the drug.

1.5.2. Swelling-Controlled Systems and Hydrogels

Drug release from a hydrophilic matrix occurs as the swelling front develops and moves slowly through the device. The drug is released as the polymer chains relax. As with the diffusion-controlled devices, drug release generally precedes matrix biodegradation. Hopfenberg (61) first described this process for a dye leaching out of a polystyrene matrix into hexane. Higuchi suggested release with respect to time from a porous hydrophobic matrix was due to water ingress as a function of tortuosity, porosity, drug diffusion coefficient, and solubility. Diffusion is usually Fickian under equilibrium conditions. However, during the swelling process a state of equilibrium may not exist and diffusion may be non-Fickian (62).

During the last two decades, polymers which swell in an aqueous medium have often been used for the preparation of controlled-release dosage forms. Swellable polymers that are water-insoluble are commonly called hydrogels and water-soluble types are called

hydrophilic polymers. In the swelling controlled-release systems, the release of the solute (e.g., drug) is controlled by one or more of the following processes : transport of the solvent into the polymer matrix, swelling of the associated polymer, diffusion of the solute through the swollen polymer, erosion of the swollen polymer, etc. Synthetic polymers which are relatively well known for this purpose are poly (hydroxyalkyl-methacrylate), poly (vinyl alcohol), ethylene vinyl alcohol, and their copolymers, poly (ethylene oxide), and cellulose ethers such as hydroxypropylcellulose (HPC), Methylcellulose (MC), Sodium carboxymethylcellulose (NaCMC), and hydroxypropylmethylcellulose (HPMC).

Over the past few decades, hydrophilic matrices are becoming extremely popular in controlling the release of soluble drugs from solid dosage forms . Hydrophilic matrix consists of a mixture of one or more active ingredient(s) with one or more gel forming agent(s). The mixture is usually compressed into tablets. Various types of polymers used as hydrophilic matrices are reviewed (63). Among the various hydrophilic polymers, water-swellable cellulose ethers namely : MC, NaCMC, HPC, and HPMC listed in various pharmacopoeiae are frequently encountered in pharmaceutical literature as matrices for drug delivery systems. Ease of compression, their ability to accommodate large percentage of drug and negligible influence of the processing variables on release rates are some of the other reasons for their popularity. Various cellulose ethers which are available commercially and can be used to control the release of active agent have been thoroughly reviewed (64-65).

The first report on the use of compressed cellulose matrices for oral controlled release dosage form was appeared in 1962 (66). Later, from time to time various formulation factors influencing the release of drugs from compressed hydrophilic matrices, viz : viscosity of the polymer (67-69), ratio of the polymer to the drug (70-71), mixture of the polymers (72-74), compression pressure (75-77), thickness of the tablet, tablet shape and added diluents (78), particle size of the drug, surface area of the tablet (79), molecular size of the drug (80) , and solubility of the drug (81) were studied by several workers. In an attempt to understand the mechanism of release of drug from the hydrophilic matrices, several mathematical models have been proposed (82-89). Hydrogels are water-insoluble network polymers which are glassy in the dehydrated state. In the presence of water, hydrogels absorb a significant amount of water (10 to 98% of their volume) to form elastic gels (90-91). Although hydrogels are of either natural or synthetic origin, it is the covalently cross-linked synthetic hydrogels that have been gaining increasing popularity in various biomedical applications, ranging from soft contact lenses to drug delivery systems (92-95).

In addition to hydrogel's inertness and good biocompatibility, their ability to release entrapped drug in aqueous medium and the ease of regulating such drug release by controlling water swelling and crosslinking density make hydrogels particularly suitable as drug carriers in the controlled release of pharmaceuticals.

Depending on the intended route of administration, drug-loaded hydrogel delivery systems are prepared into different geometries such as disks, granules, microcapsules, and beads. Owing to their stability and dosing requirements, these drug-loaded hydrogel delivery systems are stored and administered either in the swollen, rubbery state for ophthalmic and implant applications or in the dry glassy state for oral delivery use. In the latter area, the most popular delivery system has been granules or beads where the drug is uniformly dissolved or dispersed in the hydrogel matrix, because of its lower cost and relative ease of fabrication. The release of water-soluble drugs from such dehydrated hydrogel matrices involves the simultaneous absorption of water and desorption of drug via a swelling-controlled diffusion mechanism. Such swelling-controlled diffusion generally does not follow a Fickian diffusion mechanism. The existence of some molecular relaxation process in addition to diffusion is believed to be responsible for the observed non-Fickian behavior (96). Thus, hydrogels offer a unique combination of release mechanisms not readily available in other types of delivery systems.

1.5.3. Chemically-Controlled (Erosion-Controlled) Systems

These kind of systems can be broadly classified into three main categories:

(i) Enteric Coating

(ii) Matrix with Covalently attached Drug

(iii) Devices with entrapped drug

1.5.3.1. Enteric Coating

Enteric coatings were originally designed for oral dosage forms. These coatings are resistant to gastric fluid acid (pH 1-3) but disintegrate in the alkaline environment (pH 6.3-8) of the intestinal tract (97). Enteric coatings are generally comprised of polymer films that are pH sensitive. The pH sensitive enteric coatings are usually made up of linear polymers having ionizable carboxylate groups. Shellac, cellulose acetate phthalate (CAP) and synthetics such as methylacrylic acid-acrylic ester copolymers are examples of commonly used enteric coating materials.

Heller (98) demonstrated the ability of partially esterified copolymer of methyl vinyl ether and maleic anhydride to undergo surface erosion and exhibit zero-order release kinetics. Drug release was affected by exploiting the pH sensitivity of the polymer (99).

Besides oral route, there are other routes such as intravaginal, intrauterine, rectal, ocular, and topical where devices containing dissolving linear polymers have been used. Poly (vinyl alcohol), a dissolving hydrogel, has been used in the ocular delivery of pilocarpine over short period of time (100).

1.5.3.2. Matrix with Covalently Attached Drug

Kim (101) and Ringsdorf (102) have reviewed devices in which a drug is covalently bound to a polymer matrix. Applications of pendant chain systems have generally centered around short delivery times (hours) where the use of such devices can localize delivery reducing systemic toxicity and increasing therapeutic efficacy (103-106). In these devices the drug is usually bound as a pendant group, e.g., poly (amino acids) with steroid pendant groups (107). These drug containing polymers act as a drug delivery system as they biodegrade.

1.5.3.3. Devices with Entrapped Drug

Chemically controlled drug delivery has involved devices containing entrapped drug. These devices use hydrophobic polymers that are hydrolytically labile. Such a device ideally degrades in a heterogeneous fashion with no bulk or homogeneous erosion. As the surface of such a device erodes, the entrapped drug is released.

1.6. KINETICS OF SWELLING AND DRUG RELEASE FROM DRY HYDROGELS

In many applications, especially oral delivery, drug-loaded hydrogels are usually stored in a dry, glassy state before usage due to stability and dosing requirement. The release of water-soluble

drugs from initially dry hydrogel matrices generally involves the simultaneous absorption of water and desorption of drug via a swelling-controlled mechanism. Thus, as water penetrates a glassy hydrogel matrix containing dissolved or dispersed drug, the polymer swells and its glass transition temperature is lowered. In most cases, a sharp penetrating front separating the glassy phase from the rubbery phase, in addition to a volume swelling, is also observed (108-118).

In terms of drug distribution, this solvent front also separates the undissolved core from the partially extracted region, with the dissolved drug diffusing through this swollen rubbery region into the external releasing medium. Depending on the relative magnitude of the rate of polymer relaxation at the penetrating solvent front and the rate of diffusion of the dissolved drug, the release behavior during the initial stage of the solvent penetration may range from Fickian to non-Fickian (anomalous), including the so-called Case II diffusion. Typically, for a polymer slab, Fickian diffusion is characterized by a square-root-of-time dependence in both the amount diffused and the penetrating diffusion front position. On the other hand, Case II transport, which is completely governed by the rate of polymer relaxation (119), exhibit a linear-time dependence in both the amount diffused and the penetrating front position. In most cases, the intermediate situation, which is often termed non-Fickian or anomalous diffusion, will exist whenever the rates of Fickian diffusion and polymer relaxation are comparable.

When the fractional drug release from an initially dry hydrogel sheet is plotted as a function of the square root of time, linearity in the plot is observed only after periods of time. This illustrates the non-Fickian and time-dependent nature of the initial swelling period (120). Once the hydrogel matrix is hydrated, the drug release becomes Fickian, giving rise to linearity. Phenomenologically, it is possible to express the fraction released, 'M_t/M_∞' as a power function of time 't', for at least the short time period,

$$M_t / M_\infty = k\, t^n$$

where k is a constant characteristic of the system and n is an exponent characteristic of the mode of transport. For n = 0.5, the solvent diffusion or drug release follows the Fickian diffusion mechanism. For n > 0.5, non-Fickian or anomalous diffusion behavior is generally observed (121). The special case of n =1 gives rise to a Casell transport mechanism, which is of particular interest because of the drug release from such devices having constant geometry will be zero order. Other parameters such as Deborah number (122), which measures the relative importance of relaxation to diffusion, and the swelling interface number , which compares the relative mobilities of the penetrating solvent and the drug in the presence of polymer relaxation, are valuable in the conceptual realization of various diffusion mechanisms.

1.7. SUSTAINED RELEASE DRUG DELIVERY BY LATEX FILM COATING

The word latex is used to refer to aqueous colloidal dispersions of synthetic polymers as prepared by emulsion polymerization (123). An aqueous polymer dispersion or latex consists of submicron polymer particles suspended in water. When compared with organic polymer solutions, latices have the advantage of high polymer content at low viscosity. Latex polymer films offer a very useful new tool to transform water-insoluble polymers into water-based coating materials. Finely divided submicron dispersions of such polymers as ethylcellulose (EC), cellulose acetate phthlate (CAP), and methylmethacrylate copolymers have been prepared by emulsification technique for film application to solid dosage forms.

Pseudolatices, such as Aquacoat® and Aquateric® polymer dispersions, can be prepared from any existing thermoplastic water-insoluble polymer. Aquacoat® aqueous polymeric dispersions are high solids colloidal dispersion for pharmaceutical film coating. Aquacoat® is a 30% solids polymer dispersion of submicron ethyl-cellulose spheres. Size distribution is narrow and viscosity is typically below 150 cps. For pharmaceutical use, EC, CAP, and other cellulosics are preferred, as they have a history of regulatory approval and utility in sustained/controlled release dosage forms.

Upon drying above the minimum film formation temperature, aqueous latices are converted into dry polymer films. The film

formation (Figure 10) occurs in three stages : (1) evaporation of water and concentration of latex particles, (2) deformation and coalescence of the latex particles, and (3) further fusion by interdiffusion of the polymeric molecules of adjacent latex particles. Aquacoat® gives film properties superior to those of polymer solutions, while completely eliminating organic solvents. Aquacoat® being an aqueous vehicle can deliver high polymer solid to the tablet surface. Because of the low viscosity of the dispersion liquid, the time required for coating of the tablets are considerably less. Aquacoat® improves the pharmaceutical elegance of the coated tablet by improving the clarity, stability as well as by giving a thinner film.

1.7.1. Latex Film Drug Transport

In vitro dissolution results suggest that drug release through a latex film occurs by constant diffusion through the film independent of concentration as long as a concentration gradient in the coated tablet or nonpareil seed is maintained. The latex film deposited on the tablet surface regulates drug release as a linear function with time. The important variables which greatly affect the release rate profiles through a latex film, are dissociation constant, solubility, and the pH of the dissolution medium. The surface area available for drug diffusion is also a critical variable where the mechanism of drug release is diffusion controlled by a thin film membrane and the kinetics are zero-order and Fickian.

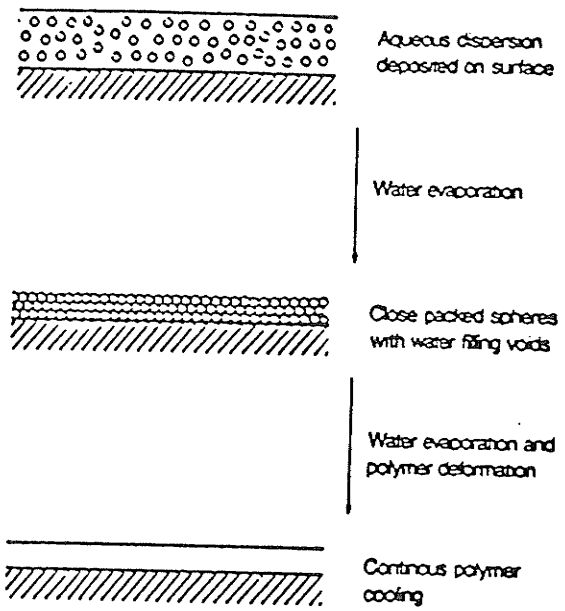


Figure 10. A schematic representation of mechanism of latex film formation.

1.8. PURPOSE OF THE STUDY

The main objectives of the project were to:

(i) To formulate a sustained release tablet dosage form for 1,2, dimethyl-3-hydroxy-pyrid-4-one, an orally active iron chelator. Initial experiments showed that DMHP has a very short biological half-life, hence qualifying as an ideal candidate for such a dosage form.

(ii) To study the kinetics of DMHP release from the various sustained release tablets prepared.

(iii) Establish pH-dependence of release rates.

(iv) To evaluate the possibility of obtaining dual control over the release rates by incorporating both matrix and coating features into a formula.

The above objectives were achieved by the following approaches:

(i) DMHP was synthesized according to a published method.

(ii) Coprecipitates of DMHP with various grades of Eudragit or Hydroxypropyl methyl cellulose (HPMC) were prepared and compressed to yield sustained release matrix tablets.

(iii) The dissolution of DMHP was studied as a function of the polymer concentration in the SR tablet.

(iv) The dissolution of DMHP from these tablets was measured as a function of pH in pH 2.0 and pH 7.4 buffers at 37^0C.

(v) To obtain dual control over the release rate, the tablets containing the various SR matrix tablets were coated with ethylcellulose (Aquacoat®) pseudolatex dispersions.

(vi) The effect of channeling agents in the coating on DMHP release from the tablets was also studied.

(vii) Common mathematical models were used to explain the kinetics of drug release.

Chapter II

EXPERIMENTAL

2.1. Chemicals and Equipment

2.1.1. Chemicals

1. 3-Hydroxy-2-methyl-4-pyrone (Maltol): Sigma Chemical Co., St. Louis, MO, USA ; Aldrich Chemical Co.Inc., Milwaukee, WI, USA.
2. Microcrystalline Cellulose PH101 (Avicel): FMC Corporation, Philadelphia, PA, USA.
3. Eudragit RLPM and Eudragit RSPM: Rohm Pharma, GMBH, Darmstadt, Germany.
4. Hydroxypropylmethylcellulose (HPMC) E4M, E10M, and K4M Premium CR Grades: A gift from The Dow Chemical Co., Midland, Michigan, USA.
5. Methylamine (40% aqueous solution): Fisher Scientific Co., Fair Lawn, N.J., USA.
6. Dibutyl Sebacate (UNIFLEX DBS): Union Camp Co., Jacksonville, Florida, USA.
7. Aquacoat® : FMC Corporation, Newark, DE, USA.
8. Potassium Chloride: Mallinckrodt Inc., Paris, Kentucky, USA.

9. Potassium Phosphate Monobasic: Mallinckrodt Inc., Paris, Kentucky, USA.

10. Disodium Phosphate: BDH Ltd., Poole, England.

11. Sodium Hydroxide: Fisher Scientific Co., Fair Lawn, N. J., USA.

12. Activated Charcoal: The British Drug House, Toronto, Ontario, Canada.

13. Carbowax® PEG 4000: Fisher Scientific Co., Fair Lawn, N. J., USA.

14. Talc Powder: Allen and Hanburys, Toronto, Ontario, Canada.

15. Lactose: Allen and Hanburys, Toronto, Ontario, Canada.

16. Polyvinyl Pyrrolidone (PVP): BDH Chemicals, Toronto, Ontario, Canada.

17. Tartrazine Powder (FD &C Yellow#5): BDH Chemicals, Toronto, Ontario, Canada.

18. Fast Green F.C.F. (FD &C Green#3): Stuart Brothers, Winnipeg, Manitoba, Canada.

19. Corn Starch: Best Foods Canada Inc., Etobicoke, Ontario, Canada.

2.1.2. Solvents

1. Ethanol: Fisher Scientific Co., Fair Lawn, N. J., USA.

2. Methanol: Mallinckrodt Canada Inc., Pointe-Claire, Quebec, Canada.

3. Hydrochloric Acid: Baxter Corporation, Toronto, Ontario, Canada.

2.1.3. Equipment

1. UV-Spectrophotometer: Shimadzu model UV-160, Shimadzu Corp., Kyoto, Japan.
2. Tablet Compression Machine: Model F-3, Manesty Machines, Liverpool, England.
3. Six-Unit Dissolution Apparatus: Vander Kamp 600, Van-Kel Ind., N. J., USA.
4. Friabilator: Erweka Friabilator TA 3-R, Erweka Apparatebau, GMBH, Frankfurt, Germany.
5. Coating Spray Gun: Crown Spra-tool #8011 Powder Pak, Crown Industrial Products Co., Hebron, IL, USA.
6. Hardness Tester: Erweka Hardness Tester TB24, Erweka Apparatebau, GMBH, Frankfurt, Germany.
7. Fluidized Bed Drier: Aeromatic Ltd., Muttenz, Basle, Switzerland.
8. Centrifuge: DYNAC Centrifuge, Clay Adams, Parsippany, N. J., USA.
9. Timer: Kodak Timer, Eastman Kodak Co., Rochester, N. Y., USA.
10. Micro Balance: Micro Gram-ATIC Balance, E. Mettler, Zurich, Switzerland.
11. Hot Air Oven: Labline, Inc., Chicago, Illinois, USA.
12. Variable Transformer: The Superior Electric Co., Bristol, Connecticut, USA; STACO Energy Products Co., Dayton, Ohio, USA.
13. pH Meter: Fisher Accumet® pH Meter, Model 610, Fisher Scientific Co., Fair Lawn, N. J., USA.
14. Micropipette: Micropipette Calibra 822, Socorex, ISBA S. A., Renens, Switzerland; Medical Laboratory Automation, Inc., Pleasantville, N.Y., USA.

15. V-Blender: The Patterson-Kelley Co., Inc., East Stroudsburg, PA, USA.

16. Propeller Type Stirrer: Precision Scientific Co., Chicago, IL, USA.

17. Vortex Mixer: Vortex JR. Mixer, Scientific Industries, Inc., Springfield, MA, USA.

18. Adjustable Stirrer: Fisher Stedi-Speed Adjustable Stirrer, Fisher Scientific Co., Fair Lawn, N. J., USA.

19. Moisture Balance: Cenco Moisture Balance, Central Scientific Co., Chicago, Illinois, USA.

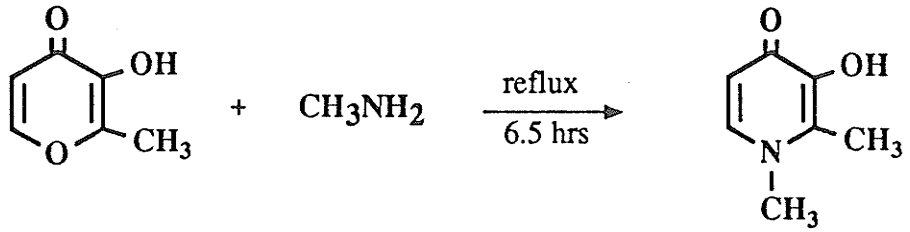
20. Weighing Balances: Mettler PE 360, Mettler AE 160, and Mettler PJ 400, E. Mettler, Zurich, Switzerland.

21. Rotavapor: Buchi Laboratoriums-Technik AG, Switzerland.

22. Hot Plate with Stirrer: Corning Hot Plate Stirrer PC-351, Corning Glass Works, Corning, N.Y., USA.

2.2. METHODOLOGY

2.2.1. Synthesis of 1,2-dimethyl-3-hydroxypyrid-4-one (DMHP)



Maltol — Methyl amine (40%) — 1,2-dimethyl-3-hydroxy pyrid-4-one (DMHP)

DMHP was synthesized according to the method published by Kontoghiorghes and Sheppard (22). Ten grams of 3-hydroxy-2-methyl-4-pyrone (Maltol) was dissolved in 200 ml of distilled water and refluxed with 3 equivalents of aqueous methylamine (40%) for 6.5 hrs. The resultant solution was allowed to cool to room temperature and an appropriate amount of decolorizing charcoal was added to the solution and allowed to stand for 30 min. It was then filtered on a buchner funnel while the solution was still warm. The dark brown filtrate obtained was evaporated at 70^{o}C under vacuum in a rotary evaporator to obtain a dark brown solid. Repeated (2 to 3 times) crystallizations were carried out in hot water and then finally recrystallized from a mixture of water and ethanol (1:1 by volume) to yield colorless crystals which were dried to constant weight in a hot air oven at 105^{o}C. The product yield ranged between 45-50%. Proton NMR and mass spectra of the compound agreed with the published values for DMHP.

2.2.2. Ultra-Violet (UV) Analysis of DMHP

For quantitation, fifty milligrams of DMHP were dissolved in 100 ml of KCl-HCl acid buffer (pH 2.0), henceforth referred to as acid buffer, and 10 ml of this solution were diluted to 100 ml with acid buffer. Further dilutions were made with acid buffer to obtain concentrations ranging from 1µg to 25 µg/ml. The absorbance of the solutions was measured at λ_{max}=276 nm and a calibration curve was constructed. A regression equation for the straight line was computed. The calibration curve was verified using solutions of DMHP of known concentration and was found to agree well with the value calculated from the regression equation.

Similar procedure was applied to obtain a calibration curve in phosphate buffer at pH 7.4 at λ_{max}=278 nm. This calibration curve was also agreed well with the value calculated from the regression equation.

2.2.3. General Procedure for the Preparation of Coprecipitates

All coprecipitates were prepared by the 'solvent method'. The required amount of DMHP and excipient (Eudragit RSPM ,Eudragit RLPM, MCC, HPMC-E4M, HPMC-E10M, and HPMC-K4M) were weighed out and dissolved in ethanol (95% v/v) and transferred into a jacketed beaker. The solvent was evaporated to dryness with constant stirring at controlled moderate temperatures (45-50^{0}C by

circulating hot water through the jacket), to obtain a granular solid residue. Each batch of the prepared coprecipitate was tested for DMHP content uniformity by dissolving a weighed amount of the co-precipitate in either acid or phosphate buffer and measuring the drug content spectrophotometrically at 276 nm and 278 nm respectively.

2.2.4. Dosage Forms

Two main types of oral dosage forms were selected for the study, namely (i) uncoated and (ii) coated tablets. In case of uncoated tablet formulations (Table 1), the dissolution studies were carried out in two different dissolution mediums, (i) in acid buffer at pH 2.0 and (ii) in phosphate buffer at pH 7.4. Whereas in coated tablets (Table 2) the dissolution study was done in acid buffer (pH 2.0) for the first 120 minutes and then the dissolution medium was made alkaline (pH 8.0) by careful addition of concentrated (5N) Sodium Hydroxide solution. Various formulations with different compositions along with corresponding formula numbers are shown in Tables 1-2. The terms DMHP, MCC, Eud. RSPM, Eud. RLPM, HPMC-E4M, HPMC-E10M, HPMC-K4M, and PEG 4000 correspond to Dimethylhydroxypyridone, Microcrystalline cellulose, Eudragit RSPM, Eudragit RLPM, Hydroxypropylmethylcellulose-E4M, Hydroxypropyl-methylcellulose-E10M, Hydroxypropylmethylcellulose-K4M, and Polyethylene glycol respectively.

Table 1. List of Uncoated Tablet Formulations Used for Dissolution Studies in either Acid Buffer or Phosphate Buffer.

Formula #	Composition	Formula #	Composition
1	PURE DMHP	14	DMHP:HPMC E4M (1:0.5)
2	DMHP:MCC (1:0.5)	15	DMHP:HPMC E4M (1: 1)
3	DMHP:MCC (1: 1)	16	DMHP:HPMC E4M (1: 2)
4	DMHP:MCC (1: 2)	17	DMHP:HPMC E4M (1: 4)
5	DMHP:MCC (1: 4)		
6	DMHP:EUD. RSPM (1:0.5)	18	DMHP:HPMC E10M (1:0.5)
7	DMHP:EUD. RSPM (1: 1)	19	DMHP:HPMC E10M (1: 1)
8	DMHP:EUD. RSPM (1: 2)	20	DMHP:HPMC E10M (1: 2)
9	DMHP:EUD. RSPM (1: 4)	21	DMHP:HPMC E10M (1: 4)
10	DMHP:EUD. RLPM (1:0.5)	22	DMHP:HPMC K4M (1:0.5)
11	DMHP:EUD. RLPM (1: 1)	23	DMHP:HPMC K4M (1: 1)
12	DMHP:EUD. RLPM (1: 2)	24	DMHP:HPMC K4M (1: 2)
13	DMHP:EUD. RLPM (1: 4)	25	DMHP:HPMC K4M (1: 4)

Table 2. List of Coated Formulations Used for Dissolution Studies in acid Buffer (0-120min) and Phosphate Buffer (120-480 min).

Formula #	Composition	Formula #	Composition
1	PURE DMHP	22	DMHP:HPMC K4M (1:0.5)
2	DMHP:MCC (1:0.5)	23	DMHP:HPMC K4M (1: 1)
3	DMHP:MCC (1: 1)	24	DMHP:HPMC K4M (1: 2)
4	DMHP:MCC (1: 2)	25	DMHP:HPMC K4M (1: 4)
5	DMHP:MCC (1: 4)		
6	DMHP:EUD. RSPM (1:0.5)	26	DMHP:HPMC K4M (1: 1) 2% PEG 4000
7	DMHP:EUD. RSPM (1: 1)	27	DMHP:HPMC K4M (1: 2) 2% PEG 4000
8	DMHP:EUD. RSPM (1: 2)	28	DMHP:HPMC K4M (1: 4) 2% PEG 4000
9	DMHP:EUD. RSPM (1: 4)		
10	DMHP:EUD. RLPM (1:0.5)	29	DMHP:HPMC E10M (1: 1) 2% PEG 4000
11	DMHP:EUD. RLPM (1: 1)	30	DMHP:HPMC E10M (1: 2) 2% PEG 4000
12	DMHP:EUD. RLPM (1: 2)	31	DMHP:HPMC E10M (1: 4) 2% PEG 4000
13	DMHP:EUD. RLPM (1: 4)		
14	DMHP:HPMC E4M (1:0.5)	32	DMHP:EUD. RSPM (1: 1) 2% PEG 4000
15	DMHP:HPMC E4M (1: 1)	33	DMHP:EUD. RSPM (1: 2) 2% PEG 4000
16	DMHP:HPMC E4M (1: 2)	34	DMHP:EUD. RSPM (1: 4) 2% PEG 4000
17	DMHP:HPMC E4M (1: 4)		
18	DMHP:HPMC E10M (1:0.5)	35	DMHP:HPMC K4M (1: 1) 10% PEG 4000
19	DMHP:HPMC E10M (1: 1)	36	DMHP:HPMC K4M (1: 2) 10% PEG 4000
20	DMHP:HPMC E10M (1: 2)	37	DMHP:HPMC K4M (1: 4) 10% PEG 4000
21	DMHP:HPMC E10M (1: 4)		
22	DMHP:HPMC K4M (1:0.5)	38	DMHP:HPMC E10M (1: 1) 10% PEG 4000
23	DMHP:HPMC K4M (1: 1)	39	DMHP:HPMC E10M (1: 2) 10% PEG 4000
24	DMHP:HPMC K4M (1: 2)	40	DMHP:HPMC E10M (1: 4) 10% PEG 4000
25	DMHP:HPMC K4M (1: 4)		
		41	DMHP:EUD. RSPM (1: 1) 10% PEG 4000
		42	DMHP:EUD. RSPM (1: 2) 10% PEG 4000
		43	DMHP:EUD. RSPM (1: 4) 10% PEG 4000

2.2.5. Preparation of Tablets

In the beginning of the study, two kinds of tablets were prepared to identify any differences in their behavior. In the first method, DMHP and the selected excipient were blended in a V-blender for 10 minutes and the resultant physical mixture was compressed. In the second method (which was eventually adopted for the rest of the study), the coprecipitate which was obtained by the above mentioned procedure was used for making tablets. Tablets were pressed on a single punch tableting machine by manual rotation of the fly wheel using 100 mg of physical mixture or coprecipitate. Constant compression pressure was maintained for all tablets. A 7/32" diameter flat punch-die set was used for all tablets. All other settings of the tablet machine were kept constant throughout the study.

2.2.6. Tablet Hardness and Friability Test

All properties of tablets were evaluated within 24 hrs after compaction. The mean crushing strength (n=5) was determined using a hardness tester. For the determination of friability, 5 tablets were dedusted with a soft brush to remove all adhering particles and accurately weighed. The tablets were placed in a friabilator rotated for 4 minutes (or 100 revolutions). The tablets were dedusted to remove any adhering particles and reweighed. From the difference of the two weights, the friability of the tablets was calculated and expressed as percent loss in weight.

2.2.7. Content Uniformity Test

The test was done for all formulations. A tablet was dissolved in 1000 ml of acid buffer or phosphate buffer . Samples of 5 ml each were withdrawn and diluted up to 100 ml. The concentration of DMHP in the last solution was measured spectrophotometrically at 276 and 278 nm for acid and phosphate buffers, respectively. Standard calibration curves previously plotted were used for the determination of the amount of DMHP in the tablets.

2.2.8. Preparation of Dissolution Media

2.2.8.1. KCl-HCl Buffer Solution (pH 2.0)

The acidic dissolution medium was prepared by dissolving 14.91 g of potassium chloride (KCl) in one liter of deionized distilled water, to which 236 ml of 0.2N HCl were added. The volume of the solution was made up to 4 liters with water and the pH of the resultant solution was measured on a pH meter calibrated with a standard buffer solution of pH 4.00.

2.2.8.2. Phosphate Buffer Solution (pH 7.4)

9.07 g of monopotassium phosphate (KH_2PO_4) and 47.48 g of Disodium phosphate ($Na_2H_2PO_4 . 2H_2O$) were separately dissolved in 1 and 4 liters of deionized water respectively. 788 ml of monopotassium phosphate solution was mixed intimately with

3212 ml of Disodium phosphate and stirred for some time and the pH was observed on a pH meter.

2.2.9. Preparation of the Coating Dispersion

Aquacoat® polymeric dispersion (30% solids, mainly ethyl cellulose) was first shaken vigorously for a few minutes and then 100 g of it was accurately weighed and mixed with 7.2 g of Dibutyl sebacate (DBS). The mixture was stirred for one hour with the help of a propeller type mixer at a moderate speed so as to minimize excessive shearing of the ethyl cellulose dispersion. This concentrated dispersion was used for tablet coating. Appropriate amounts of PEG 4000 were added into the coating dispersion to yield 2% and 10% PEG 4000. This coating dispersion was used to study the possible role of PEG 4000 as a channeling agent.

2.2.10. Dissolution Testing

The in-vitro release kinetics of DMHP from the various tablets prepared were investigated using the standard USP Dissolution Method II, the paddle method. A six-unit dissolution apparatus was utilized with paddles rotating at 50 rpm. One tablet each was placed in 900 ml of acid or phosphate buffer previously degassed and equilibrated to 37.0 $\pm$ 0.3^{o} C, for the course of the study. Three ml samples were withdrawn at 5, 10, 15, 30, 60, 90, 120 minutes and then every hour upto 5 hours. The volume of the dissolution medium was kept constant by adding 3 ml of fresh degassed buffer each time

a sample was withdrawn. Each sample was immediately centrifuged to remove any undissolved particles and 1 ml of clear supernatant was withdrawn and diluted up to 10 ml with appropriate buffer solutions. The absorbance of the solution was determined at 276 nm for the acid buffer and 278 nm for the phosphate buffer. Drug concentration of each sample was calculated from a standard calibration curve. Each dissolution study was done in triplicate, the mean ± s.d. are plotted in all the diagrams. However, the error bars in most cases fell within the size of the symbols used in plotting.

2.2.11. Tablet Coating

2.2.11.1. Coating Conditions

Parameter	Condition
Pan size	16" Stainless Steel
Inlet air temperature	60-70^{o} C
Outlet air temperature	35-40^{o} C
Spray nozzle diameter	1 mm
Spray on	10 seconds
Spray rate	100 mg/min
Total coating time	50-60 min
Average coat weight	5%

Spray gun to tablet bed distance	10 inches
Spray gun	Crown Spra-tool with non-flammable propellent

2.2.11.2. Coating Procedure

About 100 g of placebo tablets distinctly colored for identification were placed in a coating pan along with 5 to 10 colorless tablets made from coprecipitate of DMHP and excipients. The coating pan was rotated at 12-14 rev/min for 5 minutes. Each DMHP tablet was withdrawn from the coating pan, dedusted and reweighed for any change in the tablet weight due to attrition. Most of the time, no change in the tablet weight was observed. DMHP tablets were placed back into the coating pan and the coating procedure was started by spraying the coating dispersion for 10 seconds and maintaining all the conditions described above. Coating dispersions were freshly prepared. During the coating operation, the coating dispersion was kept under constant stirring using a magnetic stirrer. The coated tablets were weighed periodically to monitor any change in weight. The coated tablets were dried in the hot air oven at $60^{o}C$. The coating weight was determined by calculating the difference in the weight before and after coating. Dissolution studies were carried out within 48 hours of coating according to the procedure previously described.

Chapter III

RESULTS AND DISCUSSION

3.1. GENERAL OBSERVATIONS

Initially, the release of DMHP from tablets made from physical mixtures of DMHP and polymers in different ratios [eg., HPMC-E4M, E10M, and K4M, Eudragit RSPM and Eudragit RLPM, and MCC in 1:0.5, 1:1, 1:2, and 1:4 (DMHP:Excipient)] were compared with those made from coprecipitates of DMHP and polymers. No significant difference in DMHP release pattern was observed between the tablet made from physical mixtures and coprecipitates. However, the granular solid material obtained by coprecipitation technique was free flowing and hence more suitable for tablet compression than the physical mixtures. Because of this advantage, coprecipitation was preferred over physical mixtures. All ratios cited are on a weight by weight basis and they represent Drug:Excipient.

3.2. TABLET HARDNESS, FRIABILITY, AND CONTENT UNIFORMITY

The hardness test showed that all the tablets studied were within a predetermined range of 7 $\pm$1 kg. All batches of tablets passed the

friability test, typically the values were less than 1% loss in weight. The content uniformity test showed good agreement between the experimental and theoretical values.

3.3. ANALYSIS OF DMHP

A linear calibration curve which obeyed Beers law over the concentration range of 1 to 25 μg/ml was obtained for DMHP in both acid buffer at pH 2.0 and phosphate buffer at pH 7.4 (Figure 11 a-b). Regression analyses of the experimental points for DMHP in acid buffer yielded a slope = 0.0547, intercept = 0.0011, and correlation coefficient, r = 1.0, and in phosphate buffer gave a slope = 0.090, intercept = 0.004, and correlation coefficient, r = 1.0.

3.4. DISSOLUTION OF DMHP FROM UNCOATED TABLETS

Dissolution studies of uncoated tablets were performed in two different dissolution mediums namely acid buffer at pH 2.0 and phosphate buffer pH 7.4.

3.4.1. Dissolution Study of Uncoated Tablets in Acid Buffer (pH 2.0)

The dissolution profiles of DMHP from various tablet formulations are shown in Figures 12a through 17a. In all diagrams, the dissolution profile of DMHP from tablets containing no excipient (only

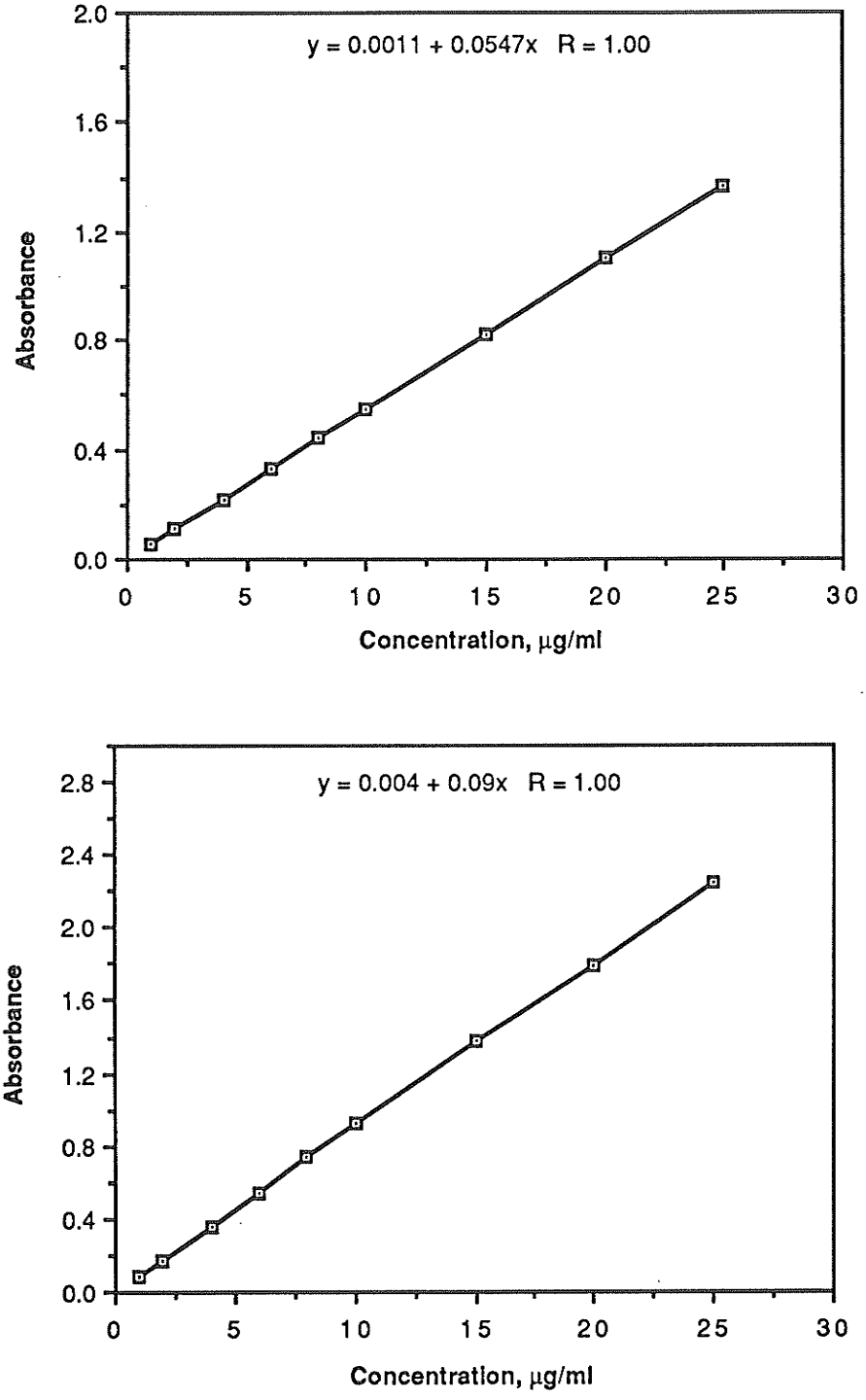
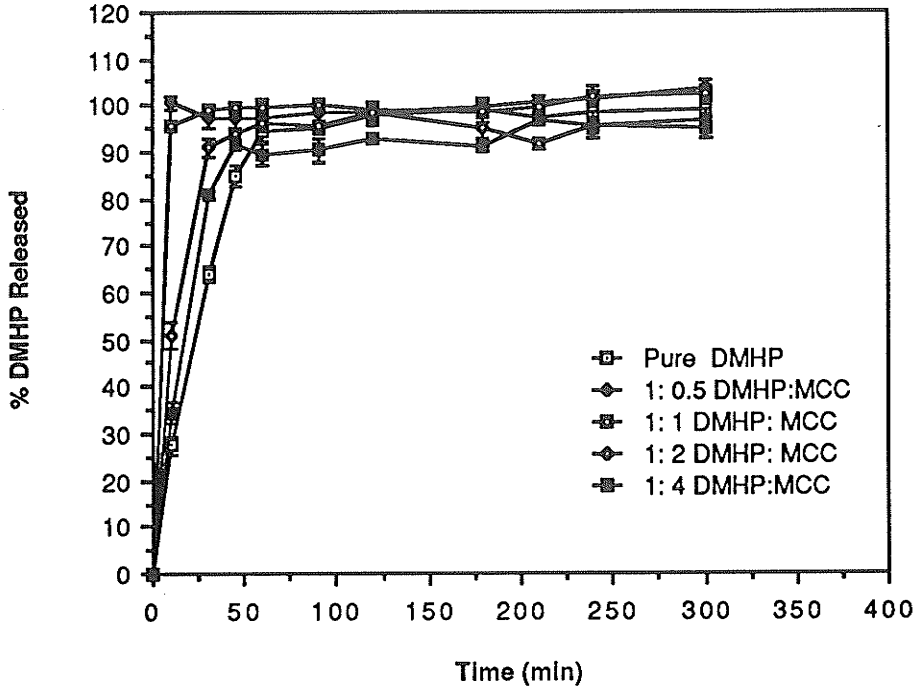


Figure 11. Beers Plots for the quantitation of DMHP in (a) acid buffer at pH 2.0 and (b) phosphate buffer at pH 7.4.

DMHP) is shown as the control. The release patterns from different kinds of polymeric formulations are described separately. Statistical analysis of the data was done with the help of Duncan's multiple range test for variables at a probability level of 0.05. Three time points (10 min, 60 min, and 300 min) were selected for all comparisons in order to represent early, intermediary, and final dissolution rate profiles.

3.4.1.1. MCC Formulations (Formula # 2-5)

In Figure 12a, the results of the dissolution profiles of DMHP from tablets containing DMHP only (Formula #1) and those containing various ratios of MCC (Formula # 2-5) are compared. It is obvious from the diagram that MCC containing formulations released DMHP almost instantaneously whereas in pure DMHP tablets, the release was fast but unlike MCC. This clearly demonstrates that MCC is an agent useful as an excipient only for rapid drug release. In the beginning of the study, the release pattern of DMHP from all the formulations were significantly different (Table 3) but as time progressed the patterns became similar and gave no significantly different release rates with a few exceptions (Tables 4 and 5). The MCC formulations were significantly different in comparison to those formulations where polymers such as Eudragits and HPMC were employed as discussed in later sections. Because of the presence of MCC, all the tablets burst into tiny fragments very soon after their placement in the dissolution medium and dissolved within a short period of time releasing nearly 100% of the DMHP within an hour.



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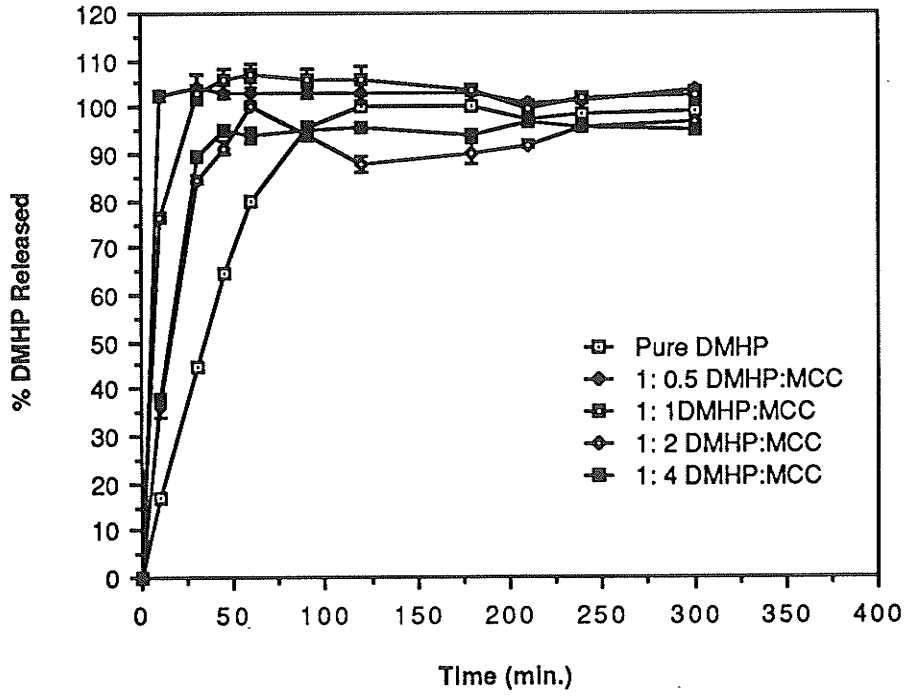


b

Figure 12. Dissolution profiles of DMHP from DMHP:MCC tablet formulations as percentage of DMHP released vs time in (a) acid buffer and (b) phosphate buffer.

Table 3. Duncan's Multiple Range Test of Uncoated Tablets in Acid Buffer (pH 2.0) at 10 minutes.

F = Formula ^{e} and N = Number of Samples

ALPHA=0.05 DF=50 MSE=1.19107

MEANS WITH THE SAME LETTER ARE NOT SIGNIFICANTLY DIFFERENT.

DUNCAN GROUPING	MEAN	N	F
A	98.8000	3	2
B	95.8000	3	3
C	51.3333	3	4
D	33.9667	3	5
E	29.8667	3	1
F	20.0000	3	10
F			
G F	19.3333	3	13
G			
G	17.8333	3	6
H	16.0333	3	17
H			
I H	14.5333	3	12
I			
I J	13.8667	3	11
I J			
I J	13.0000	3	8
J			
J	12.5667	3	7
K	9.8667	3	9
L	8.0333	3	16
L			
M L	7.6667	3	15
M L			
M L N	7.3667	3	14
M L N			
M L N	6.8667	3	19
M L N			
M L N	6.6000	3	22
M L N			
M L N	6.5333	3	24
M L N			
M L N	6.4333	3	18
M L N			
M L N	6.1000	3	23
M N			
M N	5.9000	3	25
M N			
M N	5.7000	3	21
N			
N	5.4667	3	20

Table 4. Duncan's Multiple Range Test of Uncoated Tablets in Acid Buffer (pH 2.0) at 60 minutes.

F = Formula # and N = Number of Samples

ALPHA=0.05 DF=50 MSE=1.50867

MEANS WITH THE SAME LETTER ARE NOT SIGNIFICANTLY DIFFERENT.

DUNCAN GROUPING	MEAN	N	F
A	99.633	3	3
A A	98.600	3	4
A A	98.133	3	2
B	94.933	3	1
C	91.633	3	5
D	70.600	3	10
E	45.833	3	12
F	43.700	3	6
F F	42.367	3	11
F F	42.133	3	13
G	33.467	3	8
G G	32.033	3	7
H H	31.133	3	9
I	28.267	3	17
J	26.133	3	16
K	24.033	3	18
K K	23.533	3	21
K K	23.500	3	14
K K	22.367	3	15
L L	21.233	3	20
L M	21.167	3	22
L M	21.033	3	19
L M	20.433	3	23
M M	19.200	3	24
N N	17.367	3	25

Table 5. Duncan's Multiple Range Test of Uncoated Tablets in Acid Buffer (pH 2.0) at 300 minutees.

F = Formula # and N = Number of Samples

ALPHA=0.05 DF=50 MSE=2.112

MEANS WITH THE SAME LETTER ARE NOT SIGNIFICANTLY DIFFERENT.

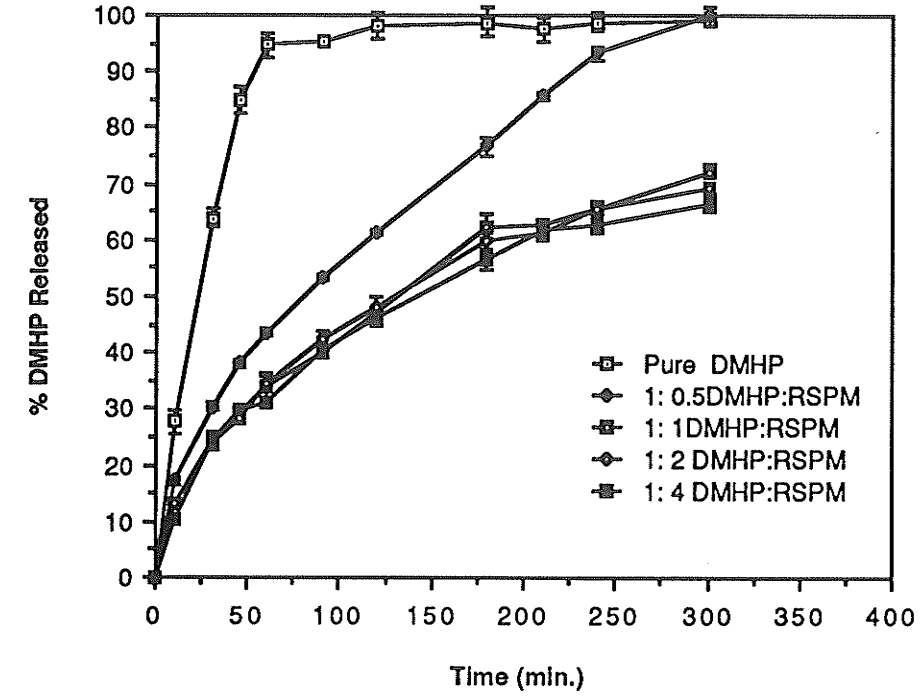
DUNCAN GROUPING	MEAN	N	F
A	101.833	3	2
A A			
A	101.567	3	3
A A			
A	100.867	3	6
A A			
A	100.833	3	10
A A			
A	100.700	3	1
A A			
B A	99.400	3	4
B B			
B	97.600	3	5
C	94.867	3	11
D	86.600	3	12
E	81.967	3	13
F	73.633	3	17
F F			
F	73.600	3	7
F F			
G F	72.967	3	18
G F			
G F	72.700	3	14
G F			
G F	71.533	3	21
G			
G	70.567	3	8
H	67.833	3	15
H H			
H	67.767	3	9
H H			
H	67.133	3	19
H H			
H	66.767	3	16
H H			
H	65.800	3	23
I	62.267	3	22
I I			
I	62.033	3	24
I I			
I	61.667	3	20
J	47.433	3	25

This effect is not surprising since the capillary action of MCC has been well documented (31).

3.4.1.2. Eudragit RSPM and Eudragit RLPM Formulations (Formula# 6-13)

Tablets made from DMHP:Eud. RSPM (Formula # 6-9) coprecipitates showed marked decrease in release as compared to the release from pure DMHP and DMHP:MCC tablets (Figure 13). Incorporation of a relatively small amount of Eud. RSPM (1:0.5) drastically decreased the dissolution of DMHP. By the end of the run (300 min), this formulation released all the DMHP contained in the tablet. But formulations containing higher amounts of Eud. RSPM (1:1, 1:2, and 1:4) released only about 74.0%, 71.0%, and 68.0% of DMHP respectively at the end of 300 min (Table 5). With the exception of Formula # 6 at 300 minutes, all the ratios of Eud. RSPM and at all time points tested were significantly different from the control tablets (Tables 3-5).

Although Eud. RLPM formulations (Formula # 10-13) followed the general trend of Eud. RSPM, the release rates for all ratios (except 1:0.5) were slightly higher as shown in Figure 14a. Increase in Eud. RLPM (1:1) suppressed the dissolution of DMHP only slightly. At all time points and at all ratios, Eud. RSPM gave a lower percent release than the corresponding Eud. RLPM system. In the beginning of the study, the release behavior of all the formulations were quite similar but at the end of the study the release pattern became



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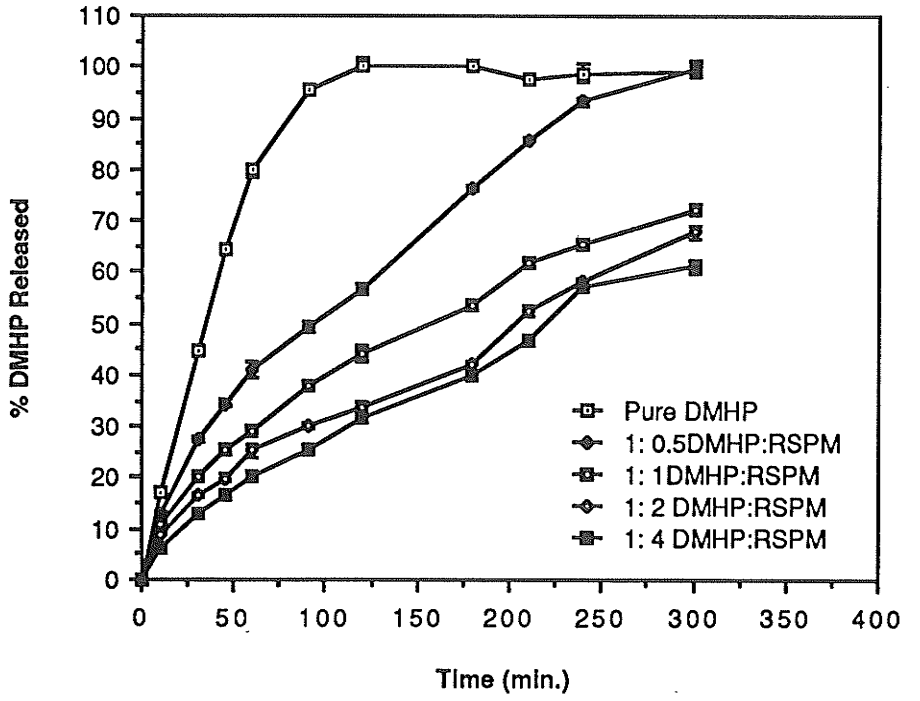

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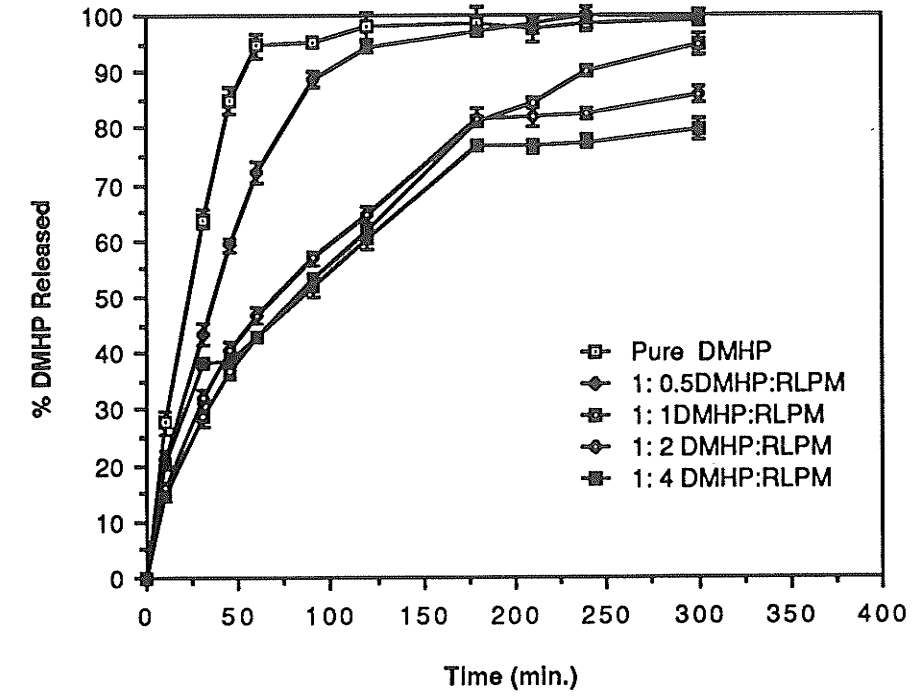
Figure 13. Dissolution profiles of DMHP from DMHP: Eud. RSPM tablet formulations as % DMHP released vs time in (a) acid buffer and (b) phosphate buffer.



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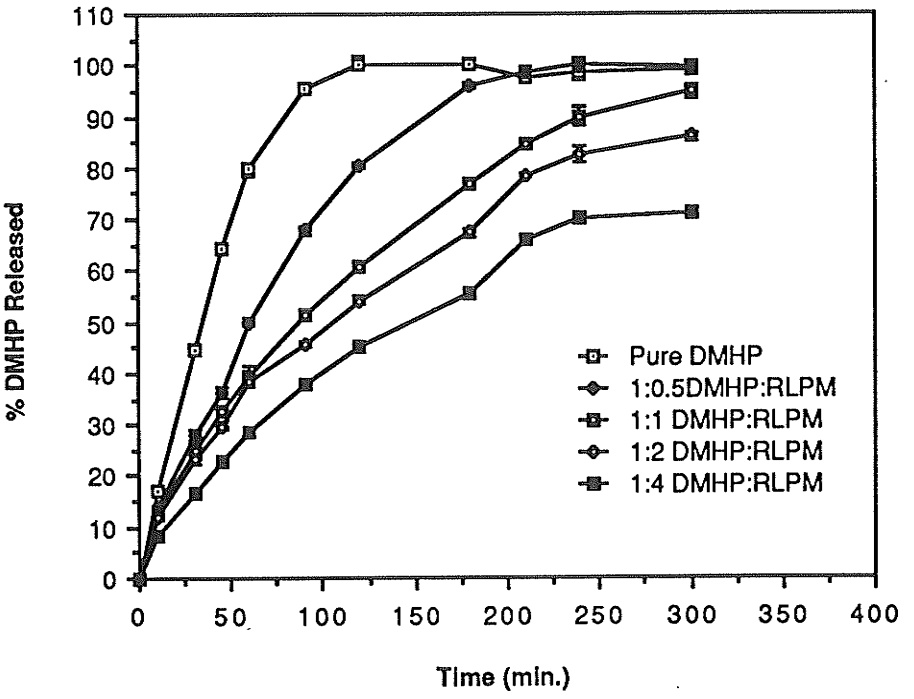

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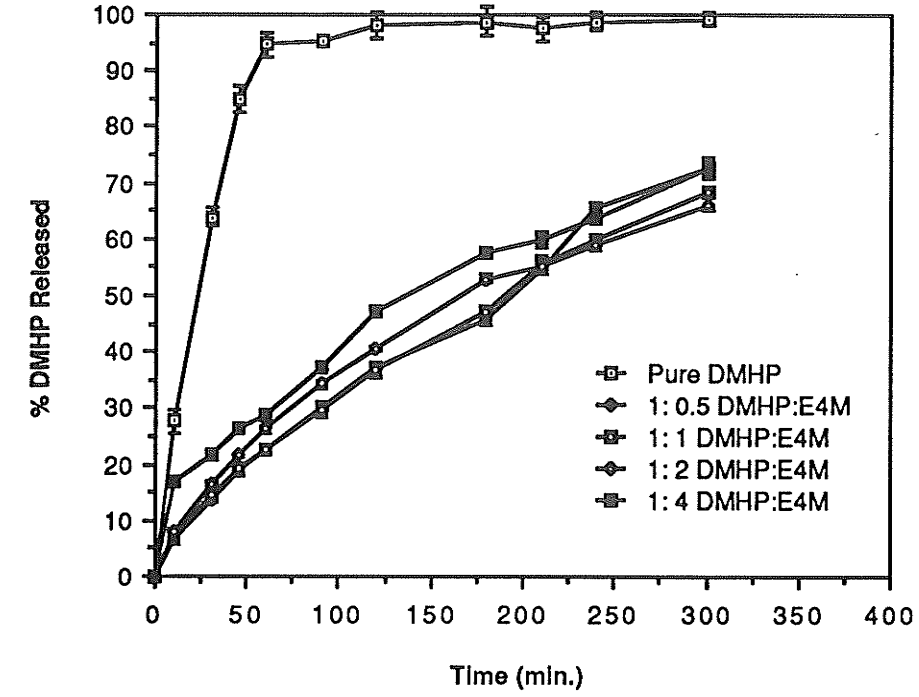
Figure 14. Dissolution profiles of DMHP from DMHP: Eud. RLPM tablet formulations as % DMHP released vs time in (a) acid buffer and (b) phosphate buffer.

significantly different for all the ratios studied. This indicates that Eud. RLPM is not as good as Eud. RSPM for sustained/controlled release of a water soluble drug such as DMHP. These results are as expected since Eud. RLPM is freely permeable whereas Eud. RSPM is slightly permeable to water.

3.4.1.3. HPMC- E4M, E10M, and K4M Formulations (Formula # 14-25)

A drastic reduction in DMHP dissolution was observed for all grades of HPMC and at all ratios studied ranging from 1:0.5 to 1:4. In Figures 15a to 17a the results of DMHP release from tablets containing various grades of HPMC are summarized. In all cases a plot of percent released versus time seemed linear after an initial burst effect, although not very prominent. The slopes of these lines were nearly the same irrespective of HPMC grade as shown in Figure 15a (HPMC-E4M, Formula # 14-17), Figure 16a (HPMC-E10M, Formula # 18-21), and Figure 17a (HPMC- K4M, Formula # 22-25).

In general, the dissolution profiles of all grades, at all ratios and at all time points were significantly different from that of control. However, comparison between the various ratios revealed very variable results. At 10 min., after the start, increasing the weight ratio of a given grade of HPMC did not hinder the dissolution of DMHP any further, i.e., no statistically significant difference could be seen between tablets containing low and high HPMC content. But at later time points, this effect became variable ranging from being signifi-



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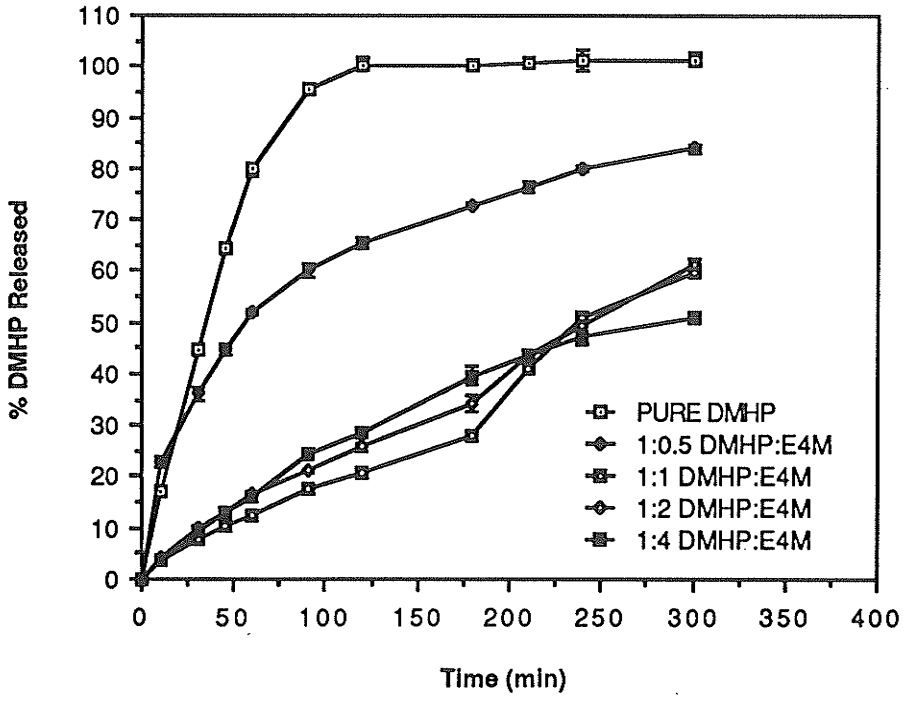

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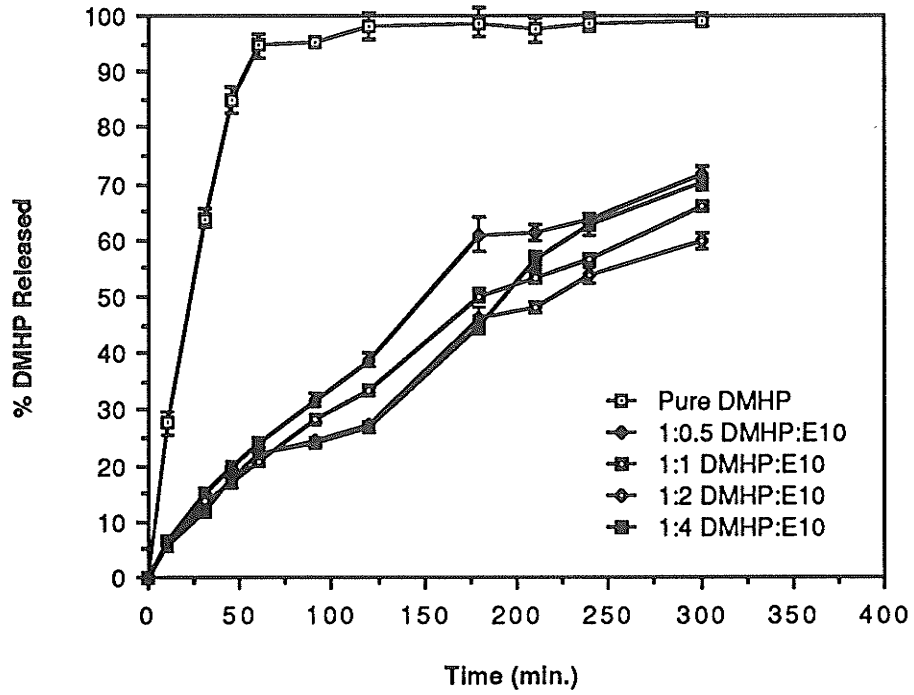
Figure 15. Dissolution profiles of DMHP from DMHP: HPMC-E4M tablet formulations as % DMHP released vs time in (a) acid buffer and (b) phosphate buffer.



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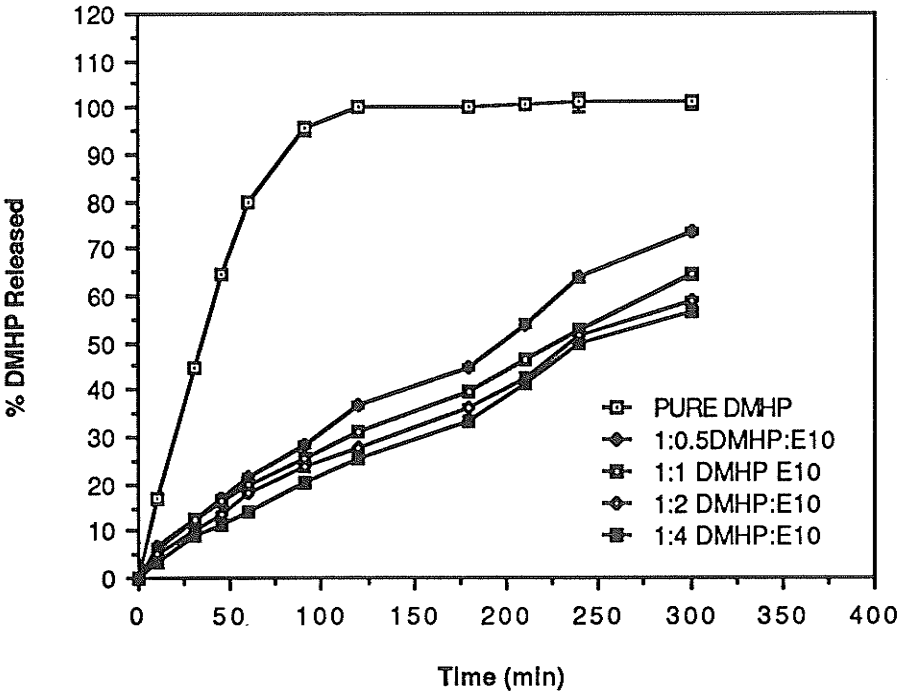

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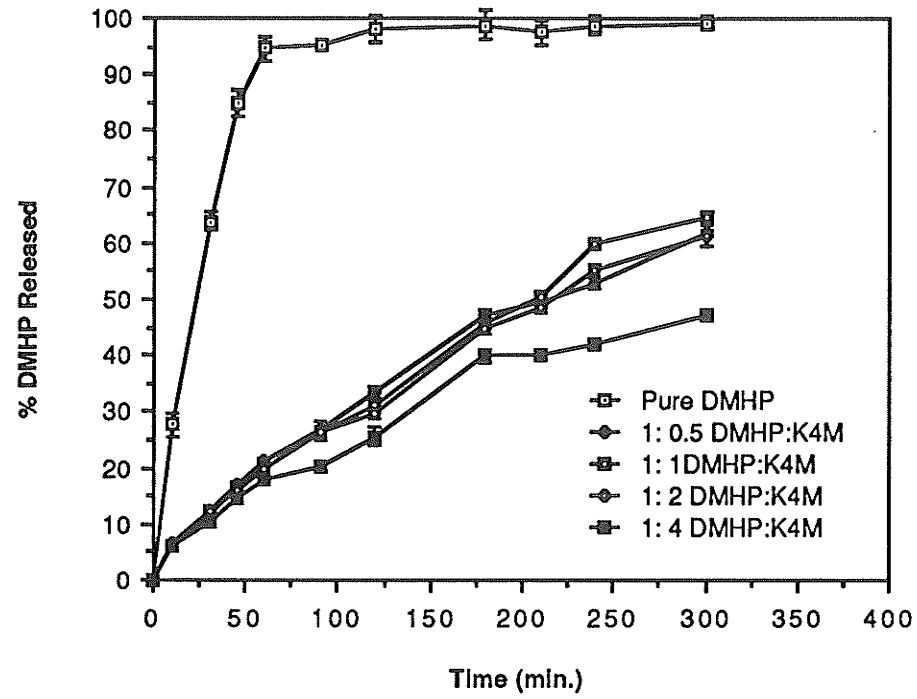
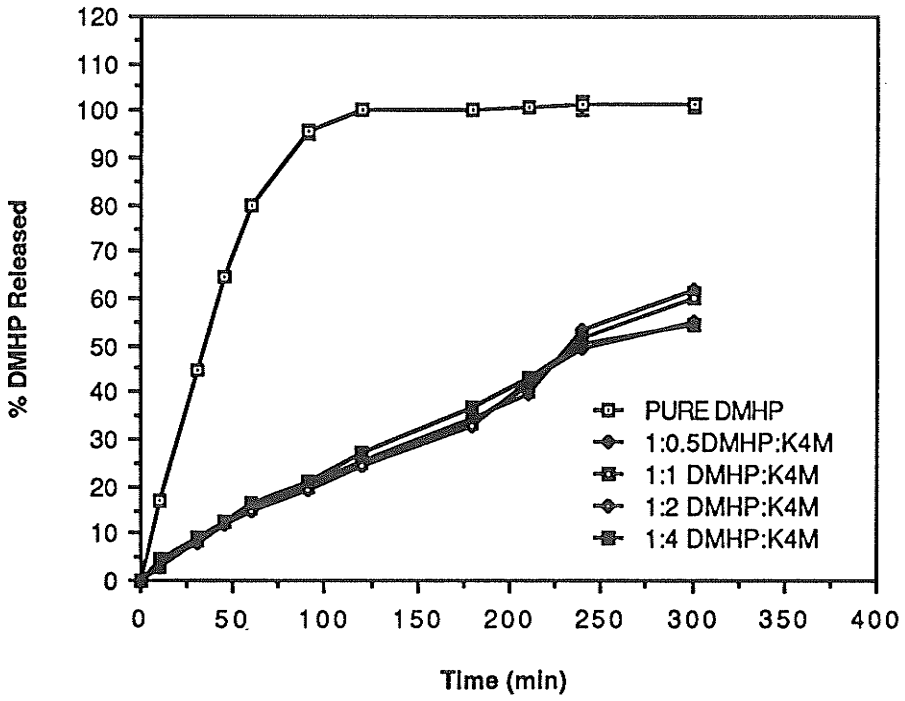
Figure 16. Dissolution profiles of DMHP from DMHP: HPMC-E10M tablet formulations as % DMHP released vs time in (a) acid buffer and (b) phosphate buffer.



a



b

Figure 17. Dissolution profiles of DMHP from DMHP:HPMC-K4M tablet formulations as % DMHP released vs time in (a) acid buffer and (b) phosphate buffer.

cant at some ratios to not significant at others as shown in Tables 3-5. Further experiments are needed to explain these results. The formulations behaved very similar to each other towards the end of the dissolution study. The main factor that results in controlled DMHP release from HPMC containing tablets is the rate of formation of a protective gel layer on the tablet exterior. Once the gel layer is formed, it controls further water penetration into the tablet core. As the outer gel layer fully hydrates and dissolves, a new layer must replace it and be tight and strong enough to retard diffusion to continue sustaining uniform drug release. HPMC-K4M has the fastest relative rate of hydration and hence begins to control DMHP release sooner than the other grades although not statistically significant at 0.05 level. The utility of HPMC polymers in controlling the rate of release of DMHP from tablet formulations is amply demonstrated.

3.4.2. Dissolution Study of Uncoated Tablets in Phosphate Buffer (pH 7.4)

Figures 12b to 17b represents the dissolution profiles of DMHP release from formulations containing different kinds of excipients. The dissolution profile of DMHP from tablets containing no excipient (only DMHP) is shown as control. The effect of MCC and other polymers on the release of DMHP from various formulations are given below.

3.4.2.1. MCC Formulations (Formula # 2-5)

The dissolution of DMHP in phosphate buffer from tablets containing MCC is shown in Figure 12b. In the initial stages of study, the release of drug from MCC formulations was faster than pure DMHP formulation. Regardless of the MCC content, all tablets released nearly 100% of DMHP within 45 minutes. Again, similar to the dissolution profiles in acid buffer, the disintegration of tablets in the first 10 minutes of the test seemed to contribute to different amounts dissolved.

3.4.2.2. Eudragit RSPM and Eudragit RLPM Formulations (Formula # 6-13)

The difference in the dissolution profiles of tablets containing Eud. RSPM and Eud. RLPM at various ratios were more discernible in phosphate buffer than seen in acid buffer (Figures 13b and 14b). The decrease in dissolution was more pronounced as the polymer concentration in the tablet increased.

The dissolution of DMHP from tablets containing Eud. RSPM was significantly different from the control at all ratios and all time points tested. Furthermore, there was a perfect negative rank order correlation, in that as the polymer content was increased the dissolution rate decreased at all time points. This release behavior was maintained till the end of the study. The release of DMHP in 300

minutes was about 100.0%, 79.9%, 68.0%, and 62.0% respectively for DMHP:Eud. RSPM formulations (Formula # 6-9).

Again, for the same reasons as explained before, Eud. RLPM formulations (Formula # 10-13) were less effective in controlling the release rates of DMHP than the corresponding Eud. RSPM formulations. The release profiles of drug from Eud. RLPM formulations were similar to those obtained in acid buffer. By the end of the dissolution study, Eud. RLPM formulations in low to high ratios released about 101.0%, 92.0%, 90.0%, and 72.0% of drug respectively (Tables 6-8). The rank order correlation in this case was not as perfect as Eud. RSPM formulations.

3.4.2.3. HPMC- E4M, E10M, and K4M Formulations (Formula # 14-25)

Figures 15b through 17b represent the DMHP release profiles from tablets containing various grades of HPMC. HPMC-E4M in relatively small amount (1:0.5) decreased DMHP release significantly as compared to the control (Figure 15b). Further increase in HPMC-E4M concentration brought about a large drop in the dissolution of DMHP and this effect seemed to plateau with even higher concentrations of the polymer. However percentage dissolved at all ratios were significantly different from each other and the control at all time points (Tables 6-8).

Table 6. Duncan's Multiple Range Test of Uncoated Tablets in Phosphate Buffer (pH 7.4) at 10 minutes.

F = Formula # and N = Number of Samples

ALPHA=0.05 DF=50 MSE=1.19107

MEANS WITH THE SAME LETTER ARE NOT SIGNIFICANTLY DIFFERENT.

DUNCAN GROUPING	MEAN	N	F
A	98.8000	3	2
B	95.8000	3	3
C	51.3333	3	4
D	33.9667	3	5
E	29.8667	3	1
F	20.0000	3	10
F			
G F	19.3333	3	13
G			
G	17.8333	3	6
H	16.0333	3	17
H			
I H	14.5333	3	12
I			
I J	13.8667	3	11
I J			
I J	13.0000	3	8
J			
J	12.5667	3	7
K	9.8667	3	9
L	8.0333	3	16
L			
M L	7.6667	3	15
M L			
M L N	7.3667	3	14
M L N			
M L N	6.8667	3	19
M L N			
M L N	6.6000	3	22
M L N			
M L N	6.5333	3	24
M L N			
M L N	6.4333	3	18
M L N			
M L N	6.1000	3	23
M N			
M N	5.9000	3	25
M N			
M N	5.7000	3	21
N			
N	5.4667	3	20

Table 7. Duncan's Multiple Range Test of Uncoated Tablets in Phosphate Buffer (pH 7.4) at 60 minutes.

F = Formula # and N = Number of Samples

ALPHA=0.05 DF=50 MSE=1.23173

MEANS WITH THE SAME LETTER ARE NOT SIGNIFICANTLY DIFFERENT.

DUNCAN GROUPING	MEAN	N	F
A	104.0333	3	3
B	100.3333	3	2
C	94.2333	3	5
D	90.6000	3	4
E	78.4667	3	1
F	51.1667	3	14
F			
F	50.6000	3	10
G	41.8667	3	6
G			
G	41.7000	3	11
H	38.3000	3	12
I	30.1667	3	7
I			
I	28.8000	3	13
J	25.7667	3	8
K	22.1000	3	18
K			
K	21.3000	3	9
K			
K	20.5667	3	19
L	17.9000	3	20
L			
M L	16.9333	3	16
M L			
M L N	16.2333	3	25
M N			
M N	15.9000	3	23
M N			
M N	15.7667	3	17
N			
O N	14.7667	3	21
O N			
O N	14.6333	3	22
O			
O	13.7333	3	24
O			
O	12.8333	3	15

Table 8. Duncan's Multiple Range Test of Uncoated Tablets in Phosphate Buffer (pH 7.4) at 300 minutes.

F = Formula # and N = Number of Samples

ALPHA=0.05 DF=50 MSE=0.894533

MEANS WITH THE SAME LETTER ARE NOT SIGNIFICANTLY DIFFERENT.

DUNCAN GROUPING	MEAN	N	F
A	102.4667	3	1
A			
A	102.0333	3	3
A			
A	101.3333	3	10
A			
A	100.8667	3	2
B	98.7000	3	4
C	96.4333	3	5
C			
C	95.9000	3	6
D	91.9000	3	11
D			
D	90.4667	3	12
E	84.4333	3	14
F	79.4667	3	7
G	73.7000	3	18
H	71.5333	3	13
I	68.0333	3	8
J	65.4000	3	22
J			
J	64.6667	3	19
K	62.4667	3	9
K			
K	61.5000	3	16
L	59.6333	3	15
L			
L	59.1000	3	23
L			
L	58.8000	3	20
M	56.6667	3	21
N	54.8333	3	24
N			
N	54.5000	3	25
O	51.2333	3	17

HPMC- E10M formulations also behaved (Figure 16b) in a predictable way, i.e., increase in polymer concentration effectively reduced the release of drug from the formulations. By the end of dissolution study, HPMC-E10M formulations in 1:0.5, 1:1, 1:2, and 1:4 concentrations released 74.0%, 65.0%, 59.0%, and 57.0% of drug respectively. However, statistical significance between the formulations varied at different time points from being significantly different to not different (Tables 6-8).

DMHP release from HPMC-K4M was the slowest throughout the dissolution study amongst all polymers studied (Figure 17b). Even here, although all the ratios were different from the control, statistical significance between the various ratios varied from being significantly different to not different (Tables 6-8). This again is in agreement with the theory that HPMC-K4M being the fastest in hydrating should be the slowest in releasing contained drug.

We can conclude that HPMC polymers in general are better in controlling the dissolution release rate of the drug from the various formulations studied when compared to Eud. RSPM and Eud. RLPM polymers. Amongst HPMC hydrogels, the effectiveness can be ranked as HPMC K4M>HPMC E10M>HPMC E4M. This demonstrates the effectiveness of these hydrogels as sustained release formulation materials even at low concentrations. An additional advantage that has to be noted here is the ability of these coprecipitates to be directly compressed into tablets with good hardness and friability.

3.5. DISSOLUTION OF DMHP FROM COATED TABLETS

This section of the study was done to achieve a zero-order release rate of DMHP by the application of a pseudolatex coating to tablets already containing a rate controlling substance in the matrix, i.e., the ideal of "dual control" on release rates is proposed. Four time points (10 min, 60 min, 300 min, and 480 min) were chosen for comparisons in case of coated tablets and these time points represented an initial, intermediary, pre final, and final dissolution rate profiles.

In case of tablets coated to produce a 5% increase in core weight a further reduction in DMHP release rate was observed as compared to the corresponding uncoated tablet. Coating of the tablets also yielded DMHP release without any kind of burst effect which was observed in some cases of uncoated tablets. The dissolution studies of coated tablets were performed for 480 minutes. The release patterns of the drug from different kinds of formulations are described under separate headings.

3.5.1. MCC Formulations (Formula # 2-5)

In the beginning of the study, pure DMHP as well as all MCC containing formulations released very small quantity of drug (Figure 18). They all showed release patterns not significantly different from each other and the control with the exception of

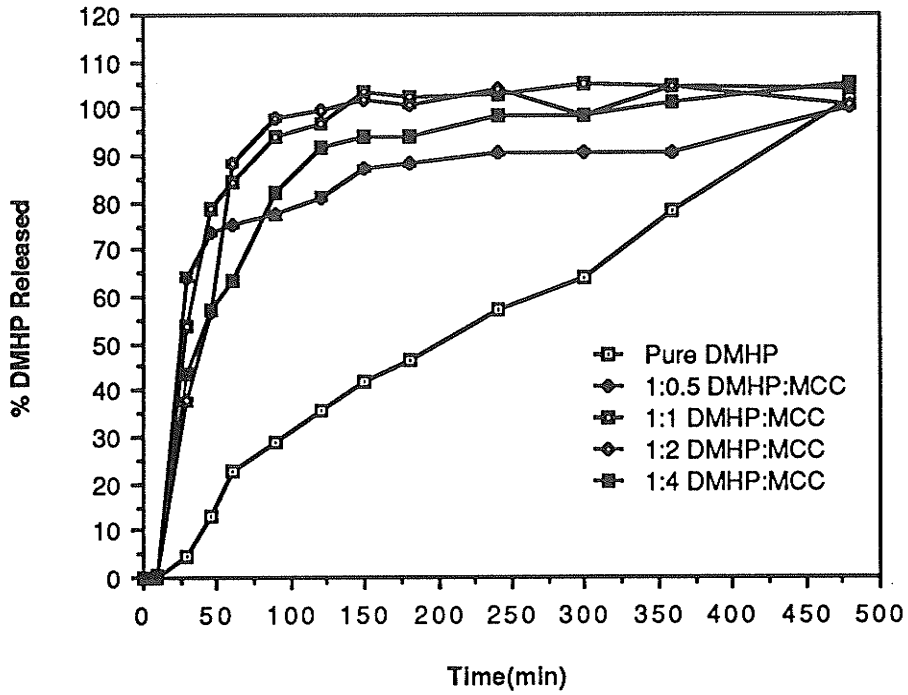


Figure 18. Dissolution profiles of DMHP from DMHP: MCC coated tablet formulations as % DMHP released vs time in acid buffer at pH 2.0 (0-120 min) and in alkaline medium at pH 8.0 (120-480 min).

Formula #2 (Table 9). Pure DMHP tablets continued to show reduced release rate (23.0%) at the end of 60 min. whereas all the MCC formulations gave comparatively high release rates (65.0%-90.0%). Again they were all statistically different from each other and the control (Table 10). Pure DMHP tablets released all of its content (99.3%) only by the end of the study but MCC formulations released 100% of the drug at different times. The release patterns of all these formulations was not significantly different (Table 12) .

3.5.2. Eudragit RSPM and Eudragit RLPM Formulations (Formula # 6-13)

In the beginning of the study, all Eud. RSPM formulations (except 1:0.5) failed to release any DMHP and their release behaviors were similar to each other (Figure19 and Table 9). As time progressed, there was not much difference in the release pattern except 1:0.5 formulation which showed some release and was significantly different from other formulations. By the end of the study, formulations in 1:0.5, 1:1, 1:2, and 1:4 ratios released only about 25.0%, 12.0%, 6.4%, and 6.8% of drug respectively.

Eudragit RLPM formulations (Formula # 10-13) as expected, gave significantly higher dissolution rate as compared to Eud. RSPM as shown in Figure 20. By the end of the study, the Eud. RLPM tablets released 72.0%, 64.0%, 57.0%, and 60.0% for ratios (1:0.5. 1:1, 1:2, and 1:4) respectively. The presence of both Eudragit in the matrix and a rate limiting latex coating therefore provides a means of

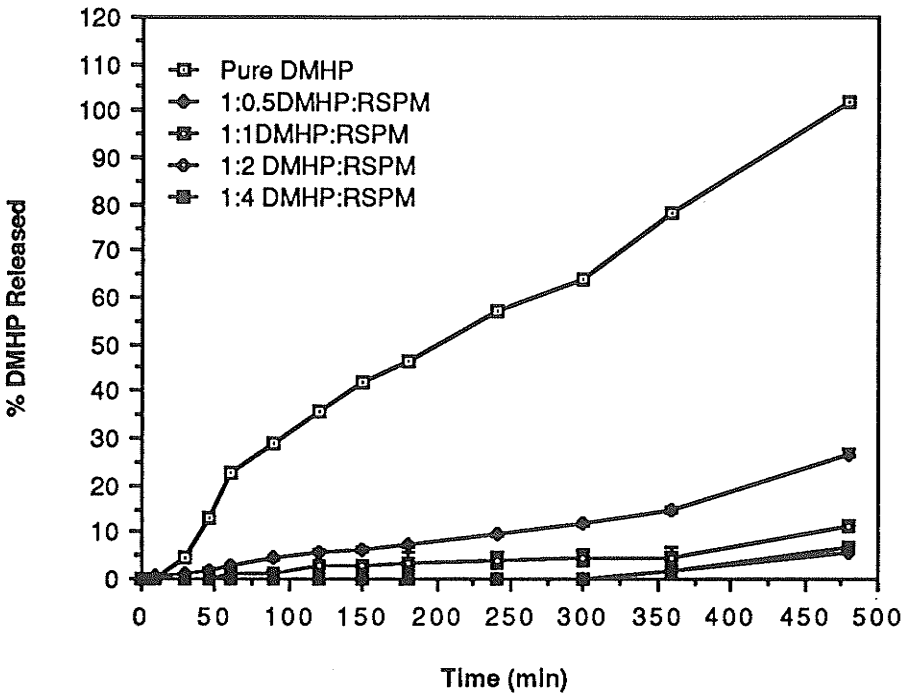


Figure 19. Dissolution profiles of DMHP from DMHP:Eud. RSPM coated tablet formulations as % DMHP released vs time in acid buffer at pH 2.0 (0-120 min) and in alkaline medium at pH 8.0 (120-480 min).

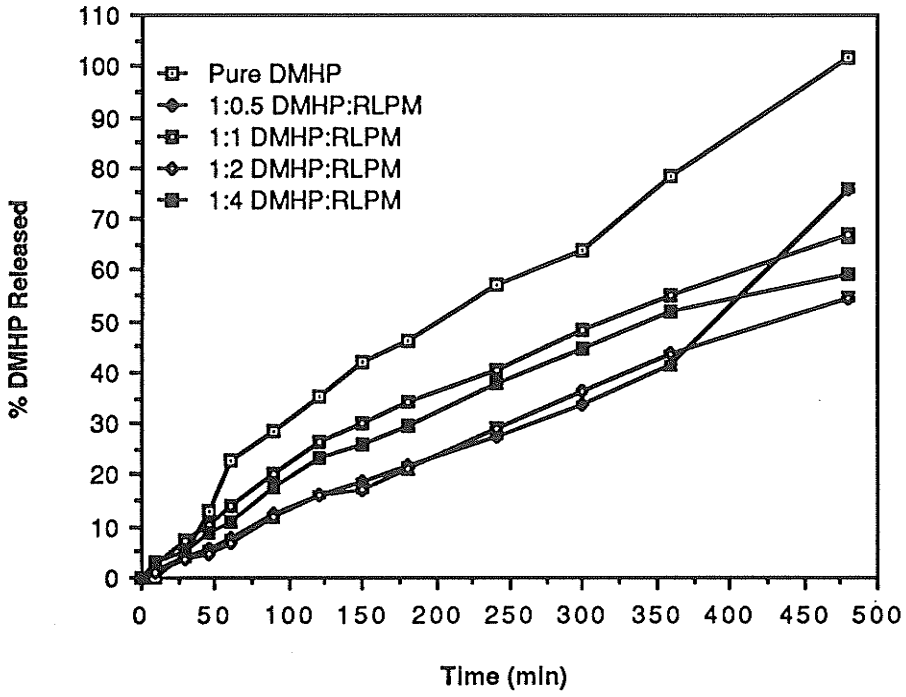


Figure 20. Dissolution profiles of DMHP from DMHP: Eud. RLPM coated tablet formulations as % DMHP released vs time in acid buffer at pH 2.0 (0-120 min) and in alkaline medium at pH 8.0 (120-480 min).

Table 9. Duncan's Multiple Range Test of Coated Tablets in Acid Buffer (0-120 min.) and Phosphate Buffer (120-480 min.) at 10 minutes.

F = Formule # and N = Number of Samples

ALPHA=0.05 DF=86 MSE=0.141008

MEANS WITH THE SAME LETTER ARE NOT SIGNIFICANTLY DIFFERENT.

DUNCAN GROUPING	MEAN	N	F
A	5.8667	3	18
A			
B A	5.3667	3	39
B			
B C	4.9667	3	15
B C			
B C	4.9333	3	14
B C			
B C	4.8000	3	16
C			
C	4.3333	3	17
D	3.2333	3	35
D			
D	3.2000	3	38
D			
D	3.2000	3	13
D			
E D	3.0000	3	36
E D			
E D F	2.8667	3	37
E F			
E G F	2.4667	3	11
G F			
H G F	2.2667	3	40
H G			
H G	2.1667	3	22
H G			
H G	2.1000	3	23
H			
H I	1.7667	3	30
H I			
H I	1.6667	3	24
H I			
H I J	1.6333	3	19
I J			
K I J	1.3667	3	10
K I J			
K L I J	1.1333	3	12
K L I J			
K L I J	1.1333	3	20
K L I J			
K L I J	1.1000	3	2
K L I J			
M K L I J	1.0667	3	27
M K L I J			
M K L I J	1.0667	3	26
M K L I J			
M K L I J	1.0667	3	29
M K L J			
M K L N J	0.9333	3	41
M K L N			
M K L N O	0.7000	3	21
M L N O			
M L N O	0.6333	3	4
M L N O			
M L N O	0.4667	3	3
M L N O			
M L N O	0.4667	3	1
M N O			
M N O	0.3667	3	6
N O			
N O	0.2667	3	5
O			
O	0.0000	3	32
O			
O	0.0000	3	25
O			
O	0.0000	3	28
O			
O	0.0000	3	33
O			
O	0.0000	3	31
O			
O	0.0000	3	7
O			
O	0.0000	3	8
O			
O	0.0000	3	9
O			
O	0.0000	3	34
O			
O	0.0000	3	42
O			
O	0.0000	3	43

Table 10. Duncan's Multiple Range Test of Coated Tablets in Acid Buffer (0-120 min.) and Phosphate Buffer (120-480 min.) at 60 minutes.

F = Formula # and N = Number of Samples

ALPHA=0.05 DF=88 MSE=1.26047

MEANS WITH THE SAME LETTER ARE NOT SIGNIFICANTLY DIFFERENT.

DUNCAN GROUPING	MEAN	N	F
A	90.1667	3	4
B	85.5333	3	3
C	77.9333	3	2
D	65.1000	3	5
E	23.4333	3	1
E	22.2333	3	40
F	21.1000	3	15
F	20.5000	3	14
G	20.1667	3	22
G	19.8333	3	17
G	19.5333	3	16
G	19.2667	3	37
H	18.4333	3	39
H	18.3667	3	18
H	17.2333	3	38
H	16.5000	3	23
I	13.7667	3	11
I	13.2000	3	35
I	12.7667	3	36
J	10.7000	3	29
J	10.3333	3	13
K	9.8667	3	30
K	9.5333	3	26
K	9.0667	3	27
K	7.9333	3	19
K	7.9000	3	24
K	7.8667	3	10
K	7.0667	3	12
L	6.8333	3	31
L	6.7667	3	28
L	5.7000	3	20
L	4.9333	3	21
L	4.1667	3	25
L	3.9667	3	41
L	2.9333	3	6
L	2.6000	3	42
M	0.3000	3	7
M	0.0000	3	32
M	0.0000	3	33
M	0.0000	3	9
M	0.0000	3	34
M	0.0000	3	8
M	0.0000	3	43

Table 11. Duncan's Multiple Range Test of Coated Tablets in Acid Buffer (0-120 min.) and Phosphate Buffer (120-480 min.) at 300 minutes.

F = Formula # and N = Number of Samples

ALPHA=0.05 DF=86 MSE=4.00721

MEANS WITH THE SAME LETTER ARE NOT SIGNIFICANTLY DIFFERENT.

DUNCAN GROUPING	MEAN	N	F
A	103.200	3	3
A A	100.000	3	4
A A A	99.967	3	5
B	90.900	3	2
C	67.667	3	23
C C	65.667	3	1
D	62.233	3	40
D D	61.600	3	22
D D	60.900	3	39
E	56.533	3	37
E E	56.067	3	35
F E E	54.100	3	14
F E E G	53.667	3	15
F E G G	53.533	3	16
F E G G	53.367	3	36
F G	51.533	3	38
H G G	50.333	3	29
H G G	50.100	3	18
I H	47.967	3	11
I J	46.433	3	26
I J	45.767	3	28
I J K	45.367	3	17
J K K	44.300	3	24
J K K	43.500	3	13
L K K	42.000	3	27
M L	39.833	3	31
M L	39.133	3	19
M L	38.600	3	30
M N	36.700	3	12
O N	33.967	3	20
O N	33.800	3	10
O N	33.633	3	21
O	30.467	3	25
P	11.867	3	6
P	11.233	3	41
Q	7.500	3	42
R	2.833	3	7
R	2.833	3	43
R	0.000	3	32
R	0.000	3	33
R	0.000	3	34
R	0.000	3	8
R	0.000	3	9

Table 12. Duncan's Multiple Range Test of Coated Tablets in Acid Buffer (0-120 min.) and Phosphate Buffer (120-480 min.) at 480 minutes.

ALPHA=0.05 DF=86 MSE=8.49977

MEANS WITH THE SAME LETTER ARE NOT SIGNIFICANTLY DIFFERENT.

DUNCAN GROUPING	MEAN	N	F
A	102.933	3	5
A	102.367	3	3
A	102.033	3	4
A	101.433	3	2
A	100.267	3	22
A	99.267	3	1
B	94.367	3	23
C	77.600	3	39
C	77.533	3	35
C	76.033	3	26
C E	75.033	3	40
C E	73.467	3	28
C E	72.767	3	36
C E	72.467	3	37
C E H	72.267	3	38
C E H	72.233	3	14
C E H	72.067	3	10
C E H	71.733	3	29
C E H	70.100	3	27
C E H	68.933	3	18
C E H	67.333	3	15
C E H	66.767	3	16
C E H	66.633	3	24
C E H K	64.300	3	31
C E H K	63.800	3	11
C E H K	59.600	3	13
C E H K M	58.133	3	19
C E H K M	57.333	3	30
C E H K M	56.700	3	12
C E H K M	55.967	3	17
C E H K M	55.400	3	20
C E H K M	53.133	3	21
N	47.267	3	25
O	24.533	3	6
P	17.667	3	41
Q	11.767	3	7
Q R	11.200	3	42
Q R S	8.767	3	33
R S T	6.867	3	9
R S T	6.400	3	8
R S T	6.300	3	32
S T	4.833	3	43
T	2.867	3	34

obtaining dual control over the release rates of a water soluble drug. It is also interesting to not that some of the release patterns were very close to zero-order release. Further work is needed to understand the mechanisms involved here.

3.5.3. HPMC-E4M, E10M, and K4M Formulations (Formula # 14-25)

The release of DMHP from coated tablets containing various grades of HPMC in the matrix are shown in Figures 21, 22, and 23 (E4M, E10M, and K4M respectively). All tablets regardless of the HPMC-E4M content released DMHP in a pattern very similar to that of control tablets. However, they deviated from the control profile after about 150 minutes. By 300 minutes some of the formulations showed significantly different release patterns (Table12).

The effect of HPMC-E10M was more prominent than HPMC-E4M in terms of delaying DMHP release (Figure 22). At concentrations 1:1 and above HPMC-E10M provided excellent control, in fact the release resembled a zero-order profile. All the formulations were significantly different from the control tablets.

The behavior of HPMC-K4M on the other hand was concentration dependent. At relatively low concentrations (1:0.5 and 1:1) the release was almost superimposable to that of control formulation (Figure 23). But substantial reduction in release was obtained when the HPMC-K4M content in the matrix was increased to 1:2 and then 1:4.

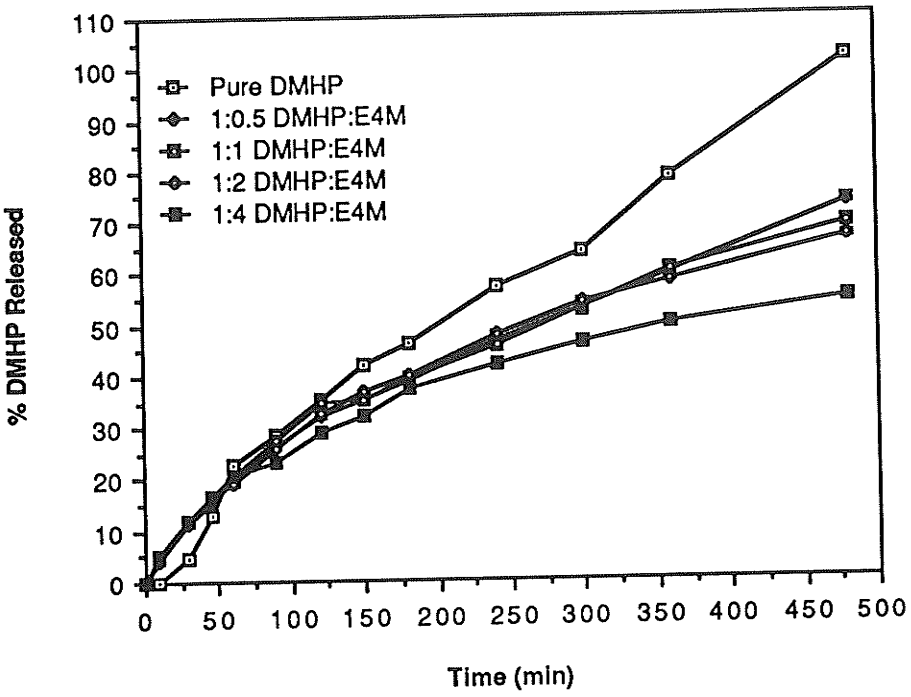


Figure 21. Dissolution profiles of DMHP from DMHP: HPMC-E4M coated tablet formulations as % DMHP released vs time in acid buffer at pH 2.0 (0-120 min) and in alkaline medium at pH 8.0 (120-480 min).

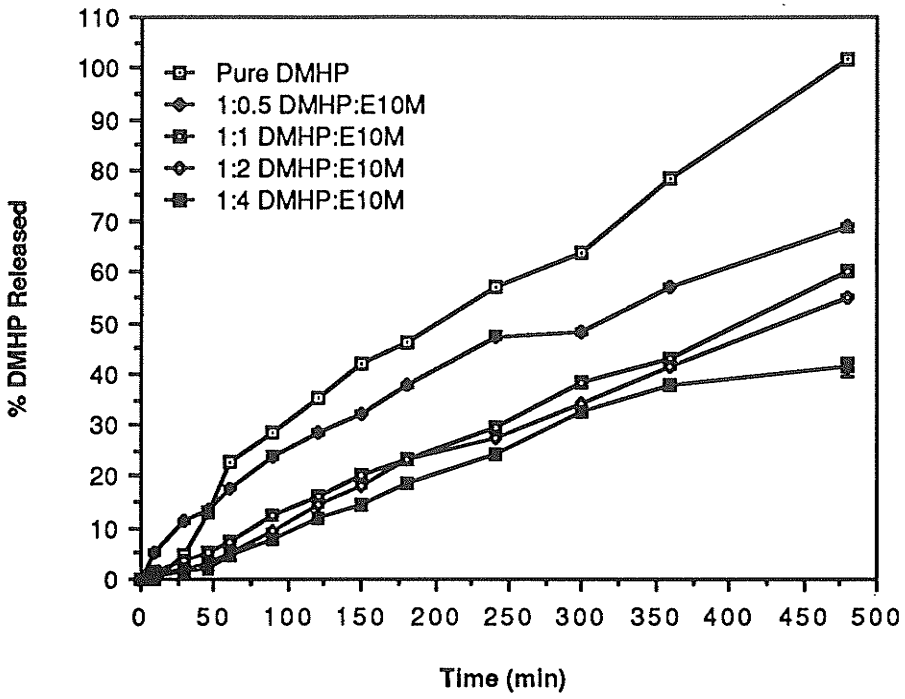


Figure 22. Dissolution profiles of DMHP from DMHP: HPMC-E10M coated tablet formulations as % DMHP released vs time in acid buffer at pH 2.0 (0-120 min) and in alkaline medium at pH 8.0 (120-480 min).

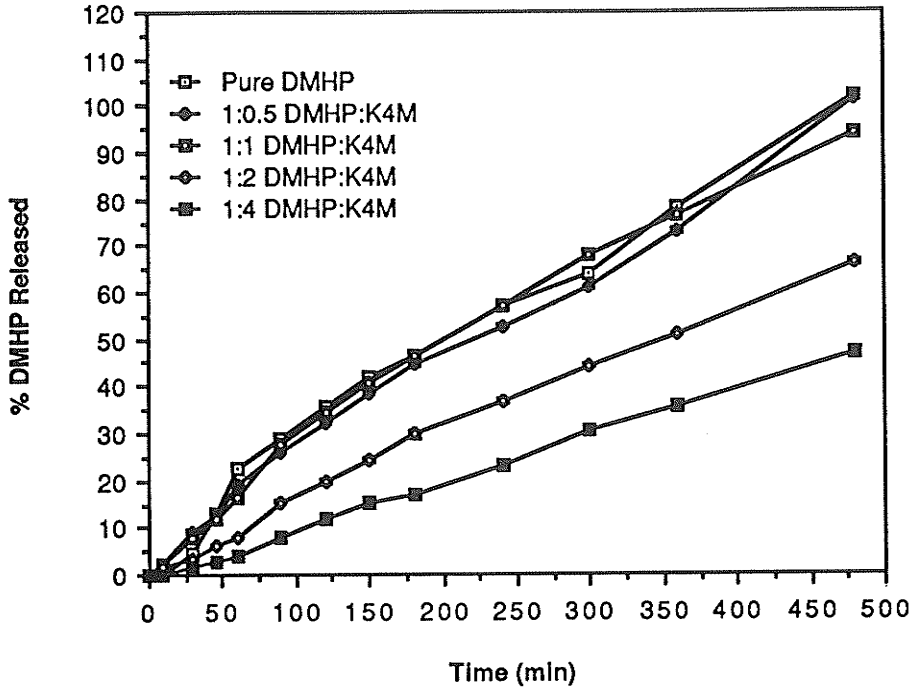


Figure 23. Dissolution profiles of DMHP from DMHP: HPMC-K4M coated tablet formulations as % DMHP released vs time in acid buffer at pH 2.0 (0-120 min) and in alkaline medium at pH 8.0 (120-480 min).

Regardless of whether the tablets were coated or not, no polymer-containing tablet released 100% of DMHP by the end of the dissolution experiment. Film coating with a pseudolatex material showed obvious advantages in prolonging the release particularly when the matrix contained Eudragit or HPMC instead of MCC.

Even in coated tablets, the change in pH from 2.0 (from 0 to 120 min of the study) to pH 7.4 (from 120 min to the end of the dissolution run) did not have any profound impact on the release profiles.

3.6. EFFECT OF CHANNELING AGENT ON RELEASE RATES

An attempt was made to modify the release rate of DMHP from coated tablets by incorporating 2% and 10% PEG 4000 as a channeling agent in the coating. PEG 4000 was added to a coating solution consisting of Aquacoat® and 24% DBS. Selected representative formulations were taken up for this study. DMHP:HPMC-K4M, DMHP:HPMC-E10M, and DMHP:Eud. RSPM in the ratios of 1:1, 1:2, and 1:4 were coated (5% increase in core weight) with 2% and 10% PEG 4000 coating dispersion.

3.6.1. Comparison of Eudragit RSPM Tablets: Uncoated, Coated, and Coated with 2% PEG 4000 and 10% PEG 4000

The results from all formulations containing RSPM are tabulated in Table 13 for comparison. These include Formula # 7, 8, and 9 uncoated and coated tablets (containing DMHP:RSPM 1:1, 1:2, and 1:4

respectively), #32, 33, and 34 coated with Aquacoat® containing 2% PEG 4000 and #41,42, and 43 coated with Aquacoat® containing 10% PEG 4000. At 10 min, the coated tablets did not release any DMHP as compared to about 99% to 12.6% from uncoated tablets. Incorporation of 2% PEG 4000 in the coat as a channeling agent did not release any DMHP. Further increase in PEG 4000 concentration in the coat to 10% gave only a slight release in Formula #41, which contained the smallest amount of RSPM in the matrix (1:1) as compared to the others. By 300 min into the dissolution run, the uncoated tablets released 67.8% to 73.6% DMHP and again, the coating proved impermeable to the dissolution medium since negligible release was observed from Formula # 7 (2.8%) and no release at all from Formulae # 8 and 9 (Figure 24). Incorporation of 2% PEG 4000 did not alter this situation and further increase in PEG 4000 to 10% only released a maximum of 11.2% DMHP (Formula# 41).

Hence we can conclude from these results that applying a latex film coat to RSPM containing tablets although provides an additional means of control could be detrimental to drug release. Channeling agents at low concentrations (2% and 10%) do not significantly alter the dissolution profiles. However, the effect of lower coating level and higher concentrations of PEG 4000 or other agents remain to be studied.

Table 13. Comparison of DMHP Release from Eud. RSPM Tablets : Uncoated and Various Coated Tablets.

Formulation	Uncoated Tab	Coated Tab (Aquacot)	Coated Tab (Aquacoat + 2% PEG 4000)	Coated Tab (Aquacoat+ 10% PEG 4000)
For 10 min. time point				
DMHP:Eud. RSPM (1:1)	12.6	0.0	0.0	0.0
DMHP:Eud.RSPM (1:2)	13.0	0.0	0.0	0.0
DMHP:Eud. RSPM (1:4)	9.9	0.0	0.0	0.0
For 300 min. time point				
DMHP:Eud. RSPM (1:1)	73.6	2.8	0.0	11.2
DMHP:Eud. RSPM (1:2)	70.6	0.0	0.0	7.5
DMHP:Eud. RSPM (1:4)	67.8	0.0	0.0	2.8

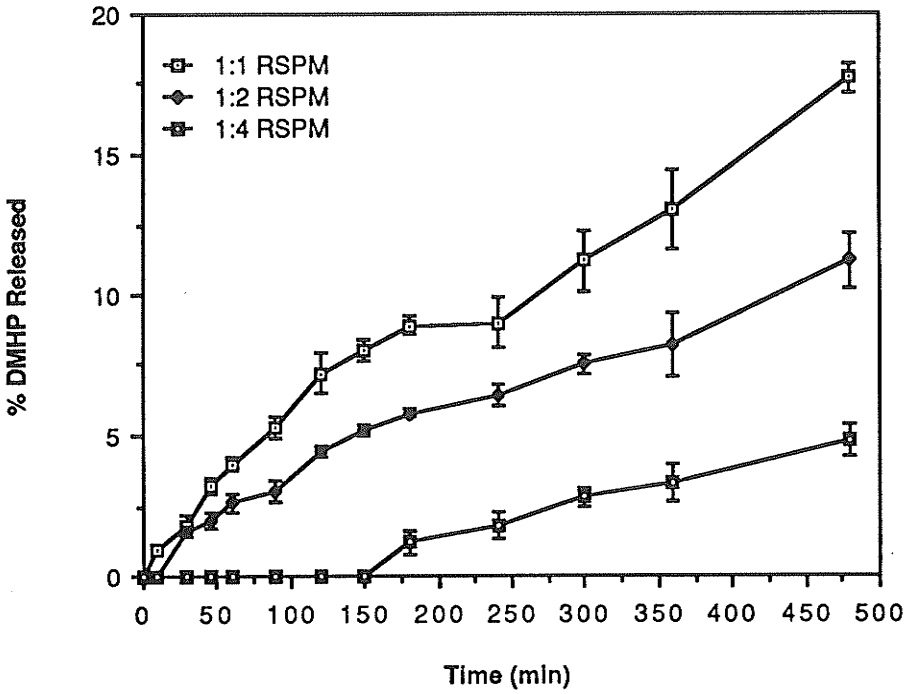


Figure 24. Dissolution profiles of DMHP from DMHP: Eud. RSPM coated tablet formulations containing 10% PEG 4000 as percentage DMHP released vs time in acid buffer at pH 2.0 (0-120 min) and in alkaline medium at pH 8.0 (120-480 min).

3.6.2. Comparison of HPMC-E10M and HPMC-K4M Tablets: Uncoated, Coated, and Coated with 2% PEG 4000 and 10% PEG 4000

These results are presented in Table 14. Unlike RSPM, tablets containing HPMC-E10M showed a better possibility of obtaining dual control over the release of DMHP by aqueous film coating. The uncoated tablets 5.5%, 5.7%, and 6.9% (1:1, 1:2, and 1:4 respectively) by the end of 10 min. The values dropped from 0.7 to 1.6 by the application of the film coat. Incorporation of PEG 4000 at 2% did not improve the release from coated tablets, PEG 4000 at 10% showed marginal increase in DMHP release (Figure 25).

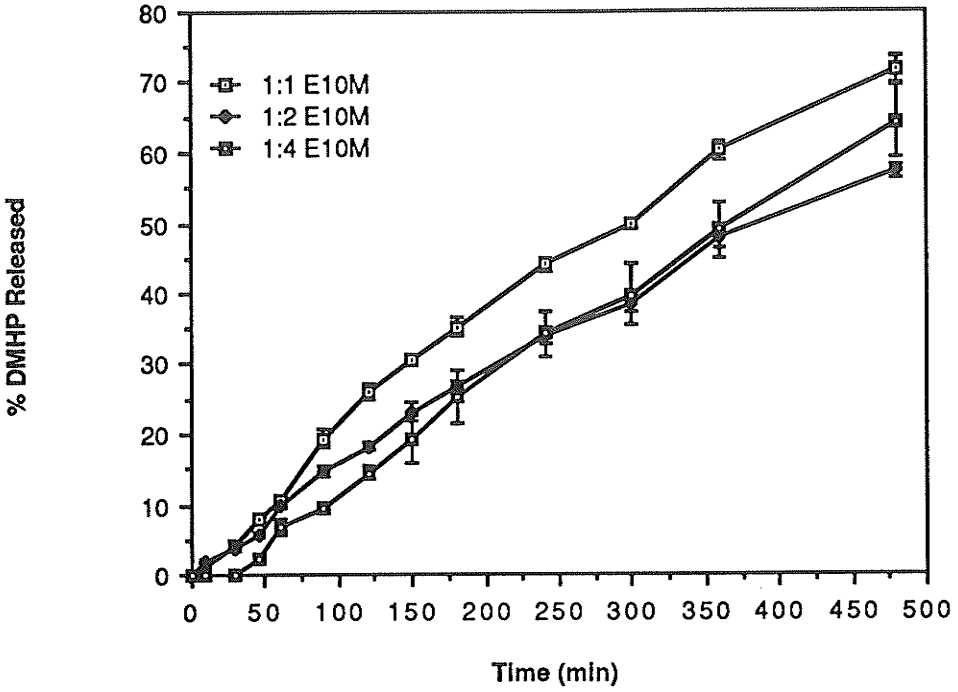
The situation at 300 min. was different. The release profiles followed a very predictable pattern in the sense, application of the film coat decreased DMHP release as compared to uncoated tablets. Addition of 2% PEG 4000 in the coating increased DMHP release as compared to coated tablets containing no PEG 4000 in the coating. Further increase in PEG 4000 to 10% gave a corresponding increase in DMHP release as compared to 2% PEG 4000. The same phenomenon were true for HPMC-K4M formulations with a few exceptions as shown in Table 15 and Figure 26.

Table 14. Comparison of DMHP Release from HPMC-E10M Tablets : Uncoated and Various Coated Tablets.

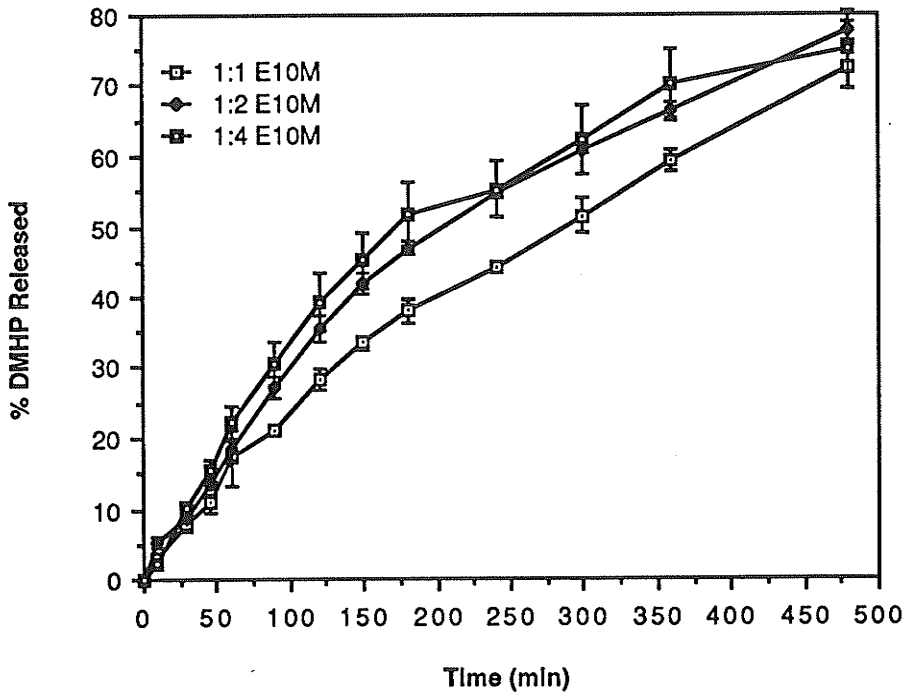
Formulation	Uncoated Tab	Coated Tab (Aquacoat)	Coated Tab (Aquacoat + 2% PEG 4000)	Coated Tab (Aquacoat + 10% PEG 4000)
For 10 min. time point				
DMHP:HPMC-E10M (1:1)	6.9	1.6	1.1	3.2
DMHP:HPMC-E10M (1:2)	5.5	1.1	1.8	5.4
DMHP:HPMC-E10M (1:4)	5.7	0.7	0.0	2.3
For 300 min. time point				
DMHP:HPMC-E10M (1:1)	67.1	39.1	50.3	51.5
DMHP:HPMC-E10M (1:2)	61.7	34.0	38.6	60.9
DMHP:HPMC-E10M (1:4)	71.5	33.6	39.8	62.2

Table 15. Comparison of DMHP Release from HPMC-K4M Tablets : Uncoated and Various Coated Tablets.

Formulation	Uncoated Tab	Coated Tab (Aquacoat)	Coated Tab (Aquacoat + 2% PEG 4000)	Coated Tab (Aquacoat + 10% PEG 4000)
For 10 min. time point				
DMHP:HPMC-K4M (1:1)	6.1	2.1	1.1	3.2
DMHP:HPMC-K4M (1:2)	6.5	1.6	1.1	3.0
DMHP:HPMC-K4M (1:4)	5.9	0.0	0.0	2.9
For 300 min. time point				
DMHP:HPMC-K4M (1:1)	65.8	67.7	46.4	56.1
DMHP:HPMC-K4M (1:2)	62.0	44.3	42.0	53.4
DMHP:HPMC-K4M (1:4)	47.4	30.5	45.8	56.5



a



b

Figure 25. Dissolution profiles of DMHP from DMHP:HPMC-E10M coated tablets, the coating containing (a) Aquacoat® + 2% PEG 4000 and (b) Aquacoat® + 10% PEG 4000 as % DMHP released vs time in acid buffer at pH 2.0 (0-120 min) and in alkaline medium at pH 8.0 (120-480 min).

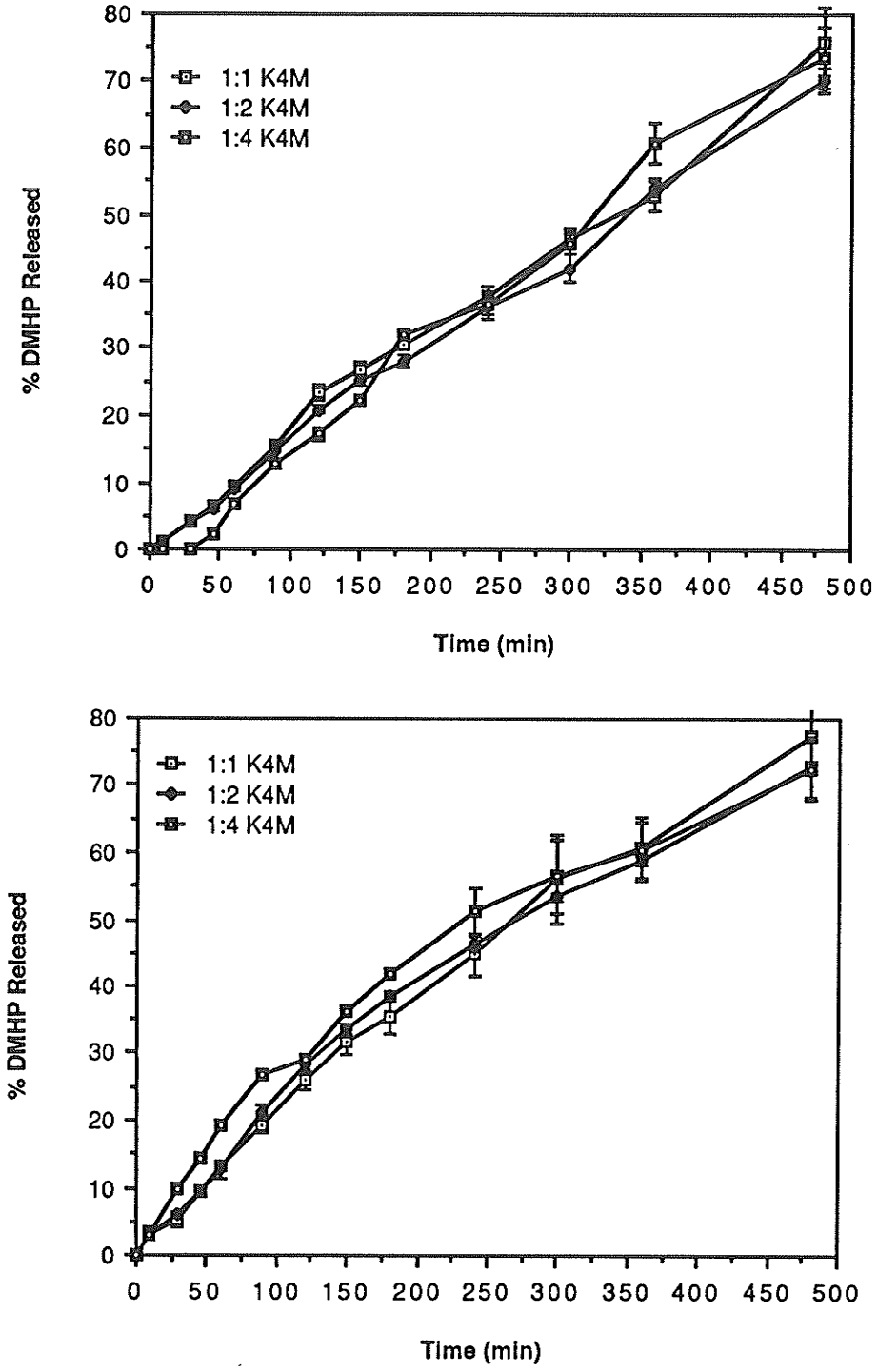


Figure 26. Dissolution profiles of DMHP from DMHP:HPMC-K4M coated tablets, the coating containing (a) Aquacoat® + 2% PEG 4000 and (b) Aquacoat® + 10% PEG 4000 as % DMHP released vs time in acid buffer at pH 2.0 (0-120 min) and in alkaline medium at pH 8.0 (120-480 min).

3.7. KINETICS OF DRUG RELEASE

3.7.1. Uncoated Tablets

The dissolution data were analyzed according to the Higuchi equation which predicts a linear relationship between the amount released versus square root of time for diffusion controlled mechanism of release . However, only certain segments of this graph may exhibit linearity depending on whether diffusion alone or diffusion and relaxation mechanism predominate. In addition, Higuchi plot requires the line to pass through the origin. All polymers at all ratios used in this study showed excellent linearity (∂^2=0.94 or better in most cases) between the percent drug released versus square root of time. However, all compositions exhibited a positive or a negative intercept indicating a burst effect or a lag time before linearity is reached. The intercepts were typically smaller for Eudragit RSPM and Eudragit RLPM as compared to HPMC. The release rate constants (k) are summarized in Table 16-17 and show a general trend in that, increasing the polymer concentration in the coprecipitate results in a decrease in the release rate constant. This is easily understood by measuring T_{25} and T_{50}, the times taken for 25% and 50% of the drug content to be released respectively. In acid buffer, pure DMHP tablets, T_{25} and T_{50} were found to be 14 and 34 minutes respectively. Addition of microcrystalline cellulose at various ratios, as expected, produced much smaller T_{25} values and had slightly variable effect on T_{50} values. This can be attributed to the fact that these tablets readily disintegrated to yield secondary

Table 16. Dissolution Kinetic Parameters K and n, and the Times Taken for 25% and 50% DMHP Dissolution in Acid Buffer from Tablets Made from Various Formulations

Formulation	'n'	'k' ($min^{-1/2}$)	T_{25} (min)	T_{50} (min)
Pure DMHP	*	*	14.0	34.0
DMHP:MCC				
1:0.5	*	*	2.5	10.0
1: 1	*	*	3.0	22.0
1: 2	*	*	5.0	43.0
1: 4	*	*	6.0	37.0
DMHP: EUD.RSPM				
1:0.5	0.5261	5.9153	21.0	75.0
1: 1	0.5081	4.2823	30.0	119.0
1: 2	0.5005	4.1720	30.0	126.0
1: 4	0.5354	4.0466	32.0	134.0
DMHP:EUD. RLPM				
1:0.5	0.4507	6.0699	13.0	35.0
1: 1	0.5509	5.8398	24.0	75.0
1: 2	0.4991	5.3121	21.0	66.0
1: 4	0.4139	4.7423	26.0	80.0
DMHP:HPMC E4M				
1:0.5	0.6919	4.3274	66.0	228.0
1: 1	0.6718	4.1159	66.0	260.0
1: 2	0.6213	4.0358	56.0	228.0
1: 4	0.4608	4.1577	48.0	265.0
DMHP: HPMC E10M				
1:0.5	0.7062	4.5643	68.0	148.0
1: 1	0.6758	4.0207	98.0	177.0
1: 2	0.6794	3.6646	96.0	190.0
1: 4	0.7260	3.2274	104.0	214.0
DMHP:HPMC K4M				
1:0.5	0.6672	3.9993	81.0	204.0
1: 1	0.7200	3.9743	84.0	210.0
1: 2	0.6977	3.7371	84.0	214.0
1: 4	0.6354	2.9297	118.0	330.0

* 'K' and 'n' for these formulations cannot be determined since these tablets disintegrated soon after exposure to the dissolution medium.

Table 17. Dissolution Kinetic Parameters K and n, and the Times Taken for 25% and 50% DMHP Dissolution in Phosphate Buffer from Tablets Made from Various Formulations

Formulation	'n'	'k' ($min^{-1/2}$)	T_{25} (min)	T_{50} (min)
Pure DMHP	*	*	16.0	35.0
DMHP:MCC				
1:0.5	*	*	5.0	11.0
1: 1	*	*	5.0	19.0
1: 2	*	*	7.0	45.0
1: 4	*	*	7.0	36.0
DMHP:EUD. RSPM				
1:0.5	0.5852	6.0593	25.0	76.0
1: 1	0.5801	4.2954	44.0	152.0
1: 2	0.5785	3.8222	59.0	200.0
1: 4	0.6783	3.6723	77.0	215.0
DMHP:EUD. RLPM				
1:0.5	0.6189	6.6946	25.0	59.0
1: 1	0.5898	5.9227	31.0	81.0
1: 2	0.5952	5.3693	34.0	97.0
1: 4	0.6383	4.5926	50.0	134.0
DMHP:HPMC E4M				
1:0.5	0.3803	4.7262	14.0	56.0
1: 1	0.8007	3.4286	151.0	238.0
1: 2	0.7762	3.4898	115.0	244.0
1: 4	0.8356	3.2948	92.0	282.0
DMHP: HPMC E10M				
1:0.5	0.7034	4.3316	73.0	196.0
1: 1	0.6831	3.6714	86.0	225.0
1: 2	0.7275	3.4542	100.0	231.0
1: 4	0.7823	3.3835	116.0	238.0
DMHP: HPMC K4M				
1:0.5	0.8036	3.5675	118.0	238.0
1: 1	0.7858	3.4784	120.0	240.0
1: 2	0.7863	3.3327	120.0	270.0
1: 4	0.8394	3.4135	120.0	270.0

* 'K' and 'n' for these formulations cannot be determined since these tablets disintegrated soon after exposure to the dissolution medium.

particles of varying surface area. Incorporation of the drug in a polymer matrix showed a profound increase in the T_{25} and T_{50} values indicating their importance and effectiveness in providing sustained release of a water soluble drug such as DMHP. The longest T_{25} and T_{50} were observed with HPMC-K4M (118.0 and 330.0 minutes respectively) at a DMHP:HPMC-K4M ratio of 1:4. In most cases as the polymer concentration was increased the T_{25} and T_{50} values increased correspondingly. But an anomalous behavior was seen with HPMC-E4M which showed a slight decrease in T_{25} as its concentration in the coprecipitate was increased and this cannot be readily explained.

The above mentioned general trend in case of acid buffer dissolution studies is also true for DMHP release in phosphate buffer. The longest T_{25} and T_{50} were observed with HPMC-K4M and HPMC-E4M respectively.

The release of DMHP was also studied according to the following equation :

$$M_t/M_\infty = K't^n$$

Where the fraction of the drug released is proportional to a matrix constant (K') which is dependent on the drug's diffusion coefficient in the matrix. The constant n depends on the polymer swelling characteristics and relaxation rate at the swelling front. The value n indicates the mechanism of release ranging from Fickian (n= 0.45

to 0.5) to non-Fickian or anomalous release (n=0.5 to 0.89) to zero-order release (n=1). Hydrophilic polymers that show a fast transition from the dry glassy state to a swollen rubbery state may approach n=1, which in practical is difficult to obtain. As shown in Tables 16 and 17, the value of n for all the systems studied ranged from 0.45 to 0.73. Typically the Eudragit polymers showed values closer to Fickian behavior than HPMC. This is perhaps due to the fact that Eudragit acrylic resins do not swell as much as HPMC hydrogels and in the latter case this swelling is also associated with a transition from the dry glassy state to a rubbery state upon hydration.

3.7.2. Coated Tablets

The same kind of treatment was applied to the dissolution data as in the case of uncoated tablets. Most of the time, the coated tablets showed a lag time effect than a burst effect because of initial slow release of DMHP and those tablets which showed burst effect, the effect was minimal. The release rate constant K obtained from Higuchi's Plot are presented in Tables 18-19. Eudragit RSPM and RLPM defy the general rule that as the polymer concentration in the tablets increases, the release rate constant decreases. However, HPMC in general followed this rule throughout with some exceptions, eg., DMHP:HPMC-K4M (1:1) which gave unusually high dissolution release rate constant (Table 18). Incorporation of 2% and 10% PEG 4000 in the coating also followed this pattern except in case of10% PEG 4000 coating dispersion for DMHP:HPMC-K4M (1:2)

Table 18. Dissolution Kinetic Parameters K and n, and the Times Taken for 25% and 50% DMHP Dissolution from Coated Tablets Made from Various Formulations (0-120 min: Acid Buffer and 120-480 min: Alkaline Medium at pH 8.0)

Formulation	'n'	'k' ($min^{-1/2}$)	T_{25} (min)	T_{50} (min)
PURE DMHP	0.9489	5.2590	73.0	203.0
DMHP:MCC				
1:0.5	*	*	16.0	25.0
1: 1	*	*	18.0	28.0
1: 2	*	*	23.0	39.0
1: 4	*	*	22.0	37.0
DMHP:EUD. RSPM				
1:0.5	**	**	475.0	**
1: 1	**	**	**	**
1: 2	**	**	**	**
1: 4	**	**	**	**
DMHP:EUD. RLPM				
1:0.5	0.9797	3.3671	216.0	390.0
1: 1	0.8394	3.4942	114.0	313.0
1: 2	1.0226	2.9298	210.0	427.0
1: 4	0.8348	3.2408	147.0	338.0
DMHP: HPMC E4M				
1:0.5	0.7039	3.6047	77.0	275.0
1: 1	0.6607	3.4240	78.0	275.0
1: 2	0.6610	3.3849	80.0	268.0
1: 4	0.6101	2.7186	100.0	360.0
DMHP: HPMC E10M				
1:0.5	0.6702	3.4252	97.0	312.0
1: 1	0.9683	3.0846	196.0	450.0
1: 2	1.0970	2.9464	204.0	425.0
1: 4	1.1922	2.4743	245.0	478.0
DMHP:HPMC K4M				
1:0.5	0.9344	4.9969	88.0	221.0
1: 1	0.9678	5.0602	82.0	202.0
1: 2	1.0111	3.5622	156.0	353.0
1: 4	1.2182	2.5639	254.0	490.0

* 'K' and 'n' for these formulations cannot be determined since these tablets disintegrated soon after exposure to the dissolution medium.

** 'K' , 'n', T_{25} and T_{50} for these formulations cannot be determined since these tablets hardly released any amount of DMHP till the end of the dissolution study.

Table 19. Dissolution Kinetic Parameters K and n, and the Times Taken for 25% amd 50% DMHP Dissolution from Coated Tablets Made from Various Formulations Containing 2% and 10% of PEG 4000 (0-120 min: Acid Buffer and 120-480 min: Alkaline Medium at pH 8.0)

Formulation	'n'	'k' ($min^{-1/2}$)	T_{25} (min)	T_{50} (min)
(A) DMHP:HPMC K4M				
(i) For 2% PEG 4000 Coating				
1: 1	1.0738	3.8661	136.0	327.0
1: 2	1.0594	3.2651	150.0	333.0
1: 4	1.3225	3.6324	156.0	310.0
(ii) For 10% PEG 4000 Coating				
1: 1	0.8783	3.7305	114.0	266.0
1: 2	0.8735	3.5930	104.0	274.0
1: 4	0.8022	3.5733	81.0	230.0
(B) DMHP: HPMC E10M				
(i) For 2% PEG 4000 Coating				
1: 1	1.0813	3.5815	115.0	300.0
1: 2	0.9367	2.7973	168.0	367.0
1: 4	1.2975	3.1110	178.0	388.0
(ii) For 10% PEG 4000 Coating				
1: 1	0.8097	3.4733	105.0	280.0
1: 2	0.7494	3.8948	81.0	202.0
1: 4	0.8687	3.9334	72.0	169.0
DMHP: EUD. RSPM				
(i) For 10% PEG 4000 Coating				
1: 1	0.7502	0.7844	**	**
1: 2	0.6924	0.5140	**	**
1: 4	1.4416	0.2174	**	**

** 'T_{25}' and 'T_{50}' for these formulations cannot be determined since these tablets hardly released any amount of DMHP by the end of the dissolution study.

which showed slightly higher (though not significant) dissolution release rate constant as compared to DMHP:HPMC-K4M (1:4) (Table 19).

In general, the coated tablets gave very high T_{25} and T_{50} values in comparison to uncoated tablets either in acid or phosphate buffer. Only exception to this rule was DMHP:MCC coated tablets which showed no significant difference at all time points. Like uncoated tablets, MCC containing tablets disintegrated faster and hence resulted in low T_{25} and T_{50} values. Eudragit RSPM coated tablets showed particularly very slow release and this can be readily observed from the tables (at 480 min for 1:0.5, 1:1, 1:2, and 1:4 the percentage release were 26.7%, 11.1%, 5.8%, and 6.8% respectively). In terms of T_{25} and T_{50} values, Eudragit RSPM gave the lowest values.

DMHP:Eud. RLPM (1:2) had 210 and 427 minutes T_{25} and T_{50} values respectively. Among all the HPMC grades, both K4M and E10M gave very close T_{25} and T_{50} values (254.0 and 490.0 min for HPMC-K4M and 245.0 and 478.0 min for HPMC-E10M) and it proves the effectiveness of coating in sustaining the release of the drug for longer times and which on comparison with uncoated tablet data is significantly high.

The effect of incorporation of 2% and 10% PEG 4000 as a channeling agent in the coating was also studied. The extent of DMHP released from these coated tablets were not significantly different from

plain coated tablets though the T_{25} and T_{50} values were certainly lower than the plain coated tablets. The effect of 10% PEG 4000 was more pronounced than 2% PEG 4000 and it was more obvious in HPMC K4M formulations than HPMC E10M.

The 'n' values of different coated formulation are given in Tables 18 & 19. We can observe from the tables that all the coated tablets showed either non-Fickian or near zero-order release. HPMC-K4M formulations at all concentrations showed 'n' values closer to 1 than any other formulations studied. HPMC-E10M also gave good results except at 1:0.5 ratio where the value of 'n' was 0.6702. HPMC-E4M was not very effective in controlling the rate of the drug in comparison to other HPMC formulations. Eud. RLPM also gave good release rates whereas Eud. RSPM formulations gave very slow release.

Chapter IV

CONCLUSIONS

The results from these studies show that all grades of HPMC and Eudragit acrylic resins that were tested, performed well as matrices for sustained release tablets even when present in small proportions, for example, Drug: HPMC/ Eudragit of 1:0.5. Eudragit RSPM was better than Eudragit RLPM at all concentrations in the tablets in decreasing the release rate of the drug. Neither HPMC nor Eudragits showed marked pH dependent release kinetics. All release profiles in case of uncoated tablets were found to be non-Fickian, Eudragits approaching Fickian behavior. Coating these matrices with Aquacoat® to obtain dual-control over release rates gave good sustained release tablets and release behavior in some formulations was close to zero-order release. Incorporation of 2% and 10% PEG 4000 as a channeling agent in the coating induced the release of DMHP from the coated formulations but it was more obvious in 10% PEG 4000 coated tablets. These results demonstrate the ability of obtaining directly compressible tablet formulations using these polymers incorporated by coprecipitation and effectiveness of Aquacoat® as a good sustained release coating agent.

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