

**DESIGN, DEVELOPMENT AND EVALUATION  
OF ENCAPSULATED ORAL CONTROLLED RELEASE  
THEOPHYLLINE MINI-TABLETS**

**THESIS**

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**DALE LESLIE MUNDAY**

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## ABSTRACT

Conventional solid dosage forms often lead to fluctuations which exceed the maximum safe therapeutic level and/or decline below the minimum effective level. It is recognised that many drugs for chronic administration should be administered on a schedule that maintains plasma drug concentration within the therapeutic window. Research in controlled release dosage forms aims at designing a system with a zero-order input (eg, ideally to deliver 8.33% of the dose per hour over a 12 hour duration), producing steady state plasma drug levels. Oral administration of drugs prepared as a controlled release formulation is extremely popular, and has attracted the attention of pharmaceutical scientists during the last decade. This has been due to the simultaneous convergence of various factors (eg, discovery of novel polymers and devices, better understanding of formulation and physiological constraints, expiration of existing patents, prohibitive cost of developing new drug entities), involved in the development of these delivery systems. Controlled release oral products can be formulated as single or multiple unit dosage forms and the relative merits of multiple unit forms with their own rate controlling systems are well established. This work describes the development of a relatively inexpensive multiple-unit capsule dosage form of theophylline containing coated mini-tablets for drug delivery throughout the gastrointestinal tract. Preformulation studies on theophylline anhydrous included solubility and dissolution rate determinations. Techniques including X-ray powder diffraction, differential scanning calorimetry and infrared spectroscopy provided no evidence of true polymorphism after recrystallisation from various solvents. However, scanning electron micrographs showed the effects of solvent polarity and cooling rate on the size and shape of recrystallised particles.

Theophylline granules were manufactured by using various binders and were film coated by fluidised bed technology with various proportions of ethylcellulose, containing varying amounts of PEG 1540. *In vitro* release rates were dependent upon coating thickness and the proportion of PEG, which, being water soluble, created pores in the coating during dissolution studies as observed by a scanning electron microscope. However, substantial proportions of the drug remained unreleased from the granules. In order to overcome the problems of drug retention, plain granules were used and theophylline mini-tablets (3 mm diameter, weighing 15 - 20 mg) were manufactured and film coated with various Eudragits<sup>®</sup> and other polymeric mixtures (soluble and insoluble). *In vitro* dissolution profiles from samples enclosed in hard gelatin capsules were determined using the USPXXI paddle apparatus in test media at pH 1.2 (HCl), pH 5.4 and 7.4 (phosphate buffers) at 37°C. Monitoring of *in vitro* theophylline release over 12 h, under identical hydrodynamic conditions, showed that the dissolution rate at pH 1.2 is substantially greater (95% of total drug content released in < 10 h) than that in phosphate buffers. The maximum release after 12 h was approximately 20 and 30% of total drug content of the tablet at pH 5.4 and 7.4, respectively. However, *in vivo* bioavailability after oral administration of tablets to rabbits corresponded to over 95% of total drug, compared with the same dose administered intravenously. The retarded drug release during *in vitro* dissolution in phosphate buffer was attributed to a possible interaction of phosphate ions with theophylline molecules at the tablet core-coat interface. These findings indicate that both rate and extent of theophylline release from the slow release coated mini-tablets

are highly sensitive to phosphate buffers. The data also emphasise the usefulness of an animal model for assessment of *in vivo* drug release and subsequent absorption during the development of modified release dosage forms. Mini-tablets were subjected to isothermal and cyclic stresses to reach conditions for up to 6 months at different temperatures and relative humidity. The film integrity was maintained but ageing of the coating occurred which impeded dissolution. Reduced drug release was temperature related while the effect of relative humidity was insignificant. Encapsulated mini-tablets (uncoated and coated with Eudragit<sup>®</sup> RL and RS 2% w/w) equivalent to a 300 mg dose, were evaluated both *in vitro* and *in vivo* using beagle dogs. The pharmacokinetic parameters from single and multiple dose studies showed several advantages over Theo-Dur<sup>®</sup> 300 mg tablets. Precise dosage titration is possible by careful adjustment of the number of encapsulated mini-tablets.

This multiple unit mini-tablet delivery system will allow for greater flexibility in dosage adjustment compared to the currently available preparations, allowing individualised fine dose titration in those patients requiring therapeutic drug monitoring. The development of the multiple unit mini-tablet formulation appears to provide an optimal dosage form with maximum flexibility in respect of dose, duration range and ease of production.

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## PREFACE

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## PUBLICATIONS

Parts of this work have been published and presented at international conferences.

1. Oral Controlled Release System: The Use of Multiple Unit Microporous Polymeric Coated Mini-Tablets. Munday, D.L. and Fassihi, A.R., *J. Pharm. Pharmacol.*, 39 (Suppl.)(1987) 129 P. This work was presented at the British Pharmaceutical Society Conference, Manchester. September 1987.
2. Controlled release delivery: effect of coating composition on release characteristics of mini-tablets. Munday, D.L. and Fassihi, A.R., *Int.J.Pharm.*, 52 (1989) 109 - 114.
3. Dissolution of Theophylline from Film Coated Slow Release Mini-tablets in Various Dissolution Media. Fassihi, A.R. and Munday, D.L., *J. Pharm. Pharmacol.*, 41 (1989) 369 - 372.
4. Changes in Drug Release Rate, II Effect of Temperature and Relative Humidity on Polymeric Film Coatings. Munday, D.L. and Fassihi, A.R. Proceedings of the 5th International Conference on Pharmaceutical Technology, Paris. May 1989, Vol. II, 55 - 60.
5. Bioavailability Study of a Theophylline Oral Controlled Release Capsule containing Film Coated Mini-tablets in Beagle Dogs. Munday, D.L., Fassihi, A.R. and de Villiers, C., *Int. J. Pharm.*, Accepted for publication. In press.
6. Multiple Dose in vivo Evaluation of an Oral Controlled Release Capsule Dosage Form for Theophylline containing Film Coated Mini-tablets in Beagle Dogs.



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- 7 Changes in Drug Release Rate: Effect of Stress Storage Conditions on Polymeric Film Coated Mini-tablets. *Drug Dev. Ind. Pharm.* Accepted for publication. In press.

### Presentations at Local Conferences

1. D L Munday and A R Fassihi, An Approach to the Design of a Zero-order Drug Delivery System for Oral Administration. Academy of Pharmaceutical Sciences Conference, March 1987.
2. D L Munday and A R Fassihi, Production of Modified- Release Capsule Dosage Form: Coating of conventional granules with ethylcellulose by Fluidized Bed Technology. Academy of Pharmaceutical Sciences Conference, March 1987.
3. D L Munday and A R Fassihi, Changes in Drug Release Rate Produced by Stress Storage Conditions on Polymeric Film- coated mini-tablets. Academy of Pharmaceutical Sciences Conference, April 1988.
4. A R Fassihi and D L Munday, The Significance of Media Composition in *in vitro* Dissolution Screening of Film-coated Theophylline Tablet. Academy of Pharmaceutical Sciences Conference, April 1988.
5. D L Munday and A R Fassihi, *In vivo* Evaluation of Theophylline Oral Controlled Release Multiple-unit Dosage Form. Academy of Pharmaceutical Sciences Conference, March 1989.
6. D L Munday and A R Fassihi, A Bioavailability Study of a Multiple-unit Oral Controlled Release Theophylline Capsule. Academy of Pharmaceutical Sciences Conference, April 1990.
7. D L Munday and A R Fassihi, Oral Controlled Release Theophylline: A Multiple-Dose *in vivo* Evaluation of a Capsule containing Film Coated Mini-tablets. Academy of Pharmaceutical Sciences Conference, April 1990.

# **CHAPTER ONE**

## INTRODUCTION

### 1.1 ORAL CONTROLLED RELEASE THEOPHYLLINE DOSAGE FORMS

Theophylline (1,3-dimethylxanthine) is closely related chemically to caffeine and theobromine. These three methylated xanthines occur in plants widely distributed geographically and grown specifically for beverage purposes such as tea (leaves of *Thea sinensis*), cocoa and chocolate (seeds of *Theobroma cacao*) and coffee (fruit of *Coffea arabica*). These beverages have central nervous system (CNS) stimulant actions that elevate mood, decrease fatigue and increase capacity for work. Theophylline and caffeine are potent stimulants of the CNS. Although caffeine is probably more potent, theophylline however produces more profound and potentially more dangerous effects (Rall, 1980). Besides their stimulant action on the CNS, they also produce diuresis, stimulate cardiac muscle and relax smooth muscle of the bronchi, especially if the bronchi have been constricted in asthma. Theophylline has the most effective action on bronchial smooth muscle and because it also produces a definite increase in vital capacity, it is of value in the treatment of bronchial asthma. The bronchodilating effects of theophylline were first described as long ago as the 1920's. However in recent years there has been a resurgence of interest in the therapeutic use of theophylline principally as a result of increased knowledge of its cellular basis of action and its pharmacokinetics.

The structural formula of theophylline is shown in Fig 1.1 There is a free proton on the N-7 position which makes theophylline a weak acid with a pKa of 8.8 at 23°C and 8.3 at 37°C (Zuidema, 1983).

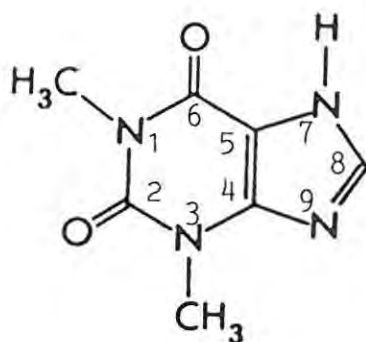


Fig. 1.1 The structural formula of theophylline

Theophylline exists in both the anhydrous and monohydrate forms (Molecular weights 180.2 and 198.2 respectively). The anhydrous form occurs as a white odourless crystalline powder with a bitter taste and a melting point of 270°C - 274°C. It is poorly soluble in water (1 in 120 at 25°C). A full physicochemical and analytical profile on theophylline is well documented (Cohen, 1975). To improve the solubility several so-called "salts" have been produced such as theophylline sodium glycinate, choline theophyllinate and theophylline ethylenediamine (aminophylline). These more soluble forms are used for parenteral preparations whereas for oral administration theophylline anhydrous or monohydrate may be used.

Theophylline is readily absorbed after oral or rectal administration. In general the therapeutic range for theophylline has been recommended to be around 10 to 20  $\mu\text{g}/\text{mL}$ , however studies on asthmatic subjects have shown that the therapeutic effects of theophylline require a plasma concentration of at least 5 to 8  $\mu\text{g}/\text{mL}$  (Jenne et al., 1972; Paifsky and Ogilvie, 1975; Ellis et al., 1976.). Some reports indicate that the toxic effects become apparent at about 15  $\mu\text{g}/\text{mL}$  and are frequent above 20  $\mu\text{g}/\text{mL}$  (Zwillich et al., 1975; Jacobs et al., 1976). These toxic effects include nervousness, restlessness, insomnia, tremors, hyperesthesia and other signs of CNS stimulation (See Fig. 1.2).

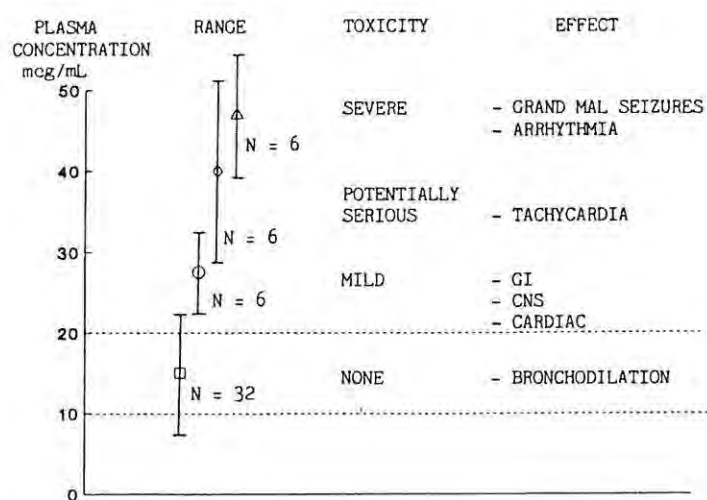


Fig. 1.2 Rank-ordering of the actions of theophylline according to minimum plasma concentrations needed to elicit. (Adapted from Hendeles, L. et al., *Drug Intell. Clin. Pharm.* 11, 12, 1977).

Therapeutic strategies aim therefore at achieving and maintaining average plasma concentrations within a therapeutic range. Within these proper range levels, theophylline is amazingly free of side effects.

Theophylline is eliminated primarily by metabolism in the liver. There is considerable inter-subject variability in plasma concentration in different patients given the same dose. Although theophylline is highly bioavailable ( $F > 0.9$ ; Hendeles et al., 1977) differences in absorption and rates of elimination have been demonstrated (Hendeles et al., 1978; Ogilvie 1978). For example the half-life of theophylline in young children averages about 3.5 hours, while 8 or 9 hours is more typical for adults (Gal et al., 1978). Metabolic pathways of degradation are capacity limited and therefore the rate of elimination cannot increase proportionately to increases in drug dose. Moreover the oxidative systems responsible for liver metabolism may be induced or inhibited. For example, hydrocarbons in cigarette smoke enhance metabolism, whereas certain drugs and diseases reduce elimination resulting in accumulation of the drug. In view of the wide range in elimination rates, it is often difficult to maintain steady state plasma concentrations of this drug, which has a relatively narrow therapeutic range.

The controlled release oral formulations have emerged as the most useful preparations for maintenance therapy in chronic conditions because of their ease of administration and greater therapeutic efficacy. However, physiological factors play a critical role when determining the suitability of using sustained release formulations. For instance, variable GI transit times will affect the time period over which the drug can be absorbed. Moreover, blockage of the GIT might allow release of the drug to occur over a small area and excessive localised concentrations and irritation could damage the surrounding tissue. In addition, the bioavailability of theophylline from sustained release oral formulations may be incomplete and variable (Upton et al., 1980; Spangler et al., 1978; Weinberger et al., 1978).

Food intake affects gastric emptying (Fig.1.3; Fassihi, 1990) which may increase or decrease both the extent and rate of absorption (Melander et al., 1979; Singhvi et al., 1982). Several workers have reported on the influence of food on the bioavailability of theophylline from controlled release preparations with varying conclusions (Lefebvre et al., 1988; Hendeles et al., 1985; Thompson et al.; 1983; Leeds et al., 1982; Pedersen, 1981; Pedersen and Moller-Petersen, 1984; Sips et al., 1984; Jonkman et al., 1981; Lagas and Jonkman, 1983; Macheras et al., 1987).

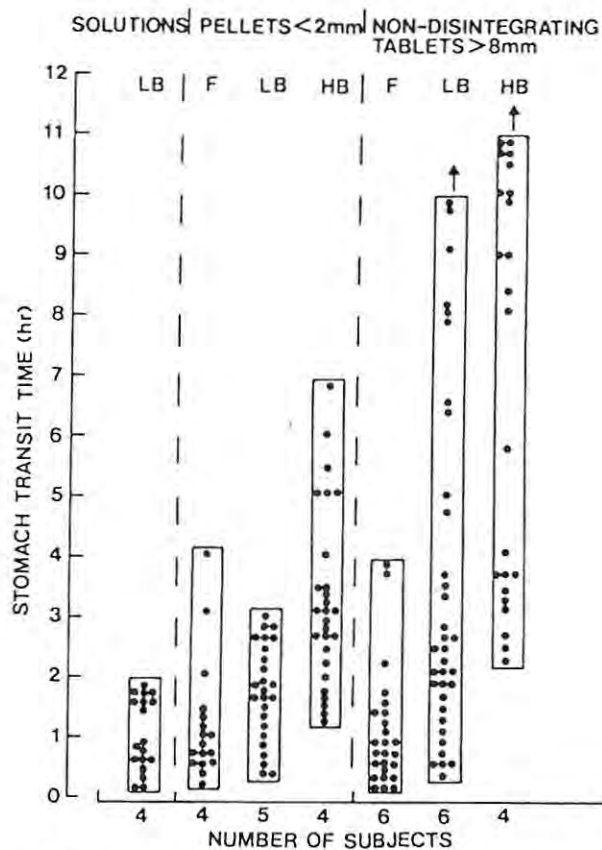


Fig. 1.3 Range of individual data points observed in subjects studied for gastric emptying of pharmaceutical dosage forms according to feeding conditions using gamma scintigraphy.

(Key: F - fasted; LB - light breakfast (~ 1500 kJ); HB - heavy breakfast (~ 3600 kJ)

(Data modified from Davis et al., 1986)

Therapeutic plasma levels must be maintained without repeated peaks and troughs characteristic of conventional dosage forms. Some patients may have subtherapeutic concentrations, while in others the drug concentration may lie above the recommended values. This interpatient variability is due to differences in absorption and different rates of elimination. Elimination is also influenced by other factors such as age, smoking history, diet, concomitant diseases and the concurrent use of certain other drugs.

In particular, the 12-hour controlled release oral dosage preparations of theophylline have been in recent years the focus of great attention. Only patients with a frequently recurring or continuous symptoms are likely to benefit from a controlled release dosage form. In these patients a constant serum level is likely to provide greater



stability of the hyper-reactive airways that characterises this disease than fluctuating concentrations. Rapid release formulations administered at 8 h intervals to patients with rapid elimination will result in unacceptably large fluctuations. A product with complete and slow enough absorption provides more constant serum levels with larger dosing intervals than rapid release formulations (Weinberger et al., 1981).

There are several commercially available slow release theophylline preparations with proven efficacy. However they may differ to clinically important degrees in the extent, rate and consistency of absorption (Weinberger et al., 1978; Fagerstrom and Heintz, 1983). Most of the currently available commercial controlled release oral theophylline preparations are given twice daily (12 hour preparations), but there are a few which are given once daily (24 hour preparations). The oral controlled release theophylline preparations which are currently available in South Africa include the following:

Chronophyllin <sup>®</sup> Capsules	Once daily
Euphyllin Retard <sup>®</sup> Tablets	Twice daily
Microphyllin SR <sup>®</sup> Capsules	Twice daily
Nuelin SA <sup>®</sup> Tablets	Twice daily
Somophyllin CRT <sup>®</sup> Capsules	Twice daily
Theo-Dur <sup>®</sup> Tablets	Twice daily
Theo-Dur <sup>®</sup> Sprinkle Pellets	Twice Daily

The design of the above proprietary products are subject to patent rights and therefore precise details thereof are not known. However they release the drug by mechanisms which will be discussed in the following section of this Chapter.

Dosage regimens have to be carefully adjusted according to particular patient needs. Although oral controlled release theophylline dosage forms are designed to control drug release rate, individual titration of the dose rate is still necessary. However the presently available dosage units cannot be divided into sub-units to meet precise individual needs. This is especially the case with encapsulated pellets, although some tablet formulations may be bisected or trisected. The modern sophisticated methods of therapeutic drug monitoring now available has made precise individual dose titration possible. The need exists therefore for a multiple-unit dosage form which can provide precise dosage titration for a particular patient by accurate adjustment of the dose.

The objectives of this study were to develop an oral controlled release theophylline dosage form which would meet with the following requirements.

1. Maintain plasma concentrations within the therapeutic range ( $10 - 20 \mu\text{g/mL}$ ) for maximum periods of time during successive dosage intervals. Plasma fluctuations should be minimal without the concentration decreasing to subtherapeutic levels or increasing beyond the maximum safe concentration where toxic symptoms are experienced.
2. The dosage form should provide maximal bioavailability of the drug.
3. The design of the dosage form should be such that there is minimal danger due to "dose dumping".

4. Individualised dose titration must be possible to meet patient's precise needs by careful adjustment of the dose required.
5. The preparation must have maximum stability on storage during the shelf life. Changes in drug release profile after the shelf life should be insignificant.
6. The dosage form should be simple in design and hence as inexpensive as possible.

In this thesis the author has carried out work directed toward achieving these objectives. A novel multiple-unit capsule dosage form containing mini-tablets, with each unit providing a precise dose of theophylline in the form of an extended release drug delivery system, has been proposed. The dosage form will be designed, manufactured and its *in vitro-in vivo* performance evaluated.

## 1.2 PRINCIPLES AND RATE CONTROLLING MECHANISMS OF CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

Controlled release of a drug from a delivery system can be established by chemical or physical methods. The chemical methods are based on the chemical or biological degradation of polymers. For example in the pendant-chain system, in which a drug is chemically attached to the backbone of a polymer, the drug is gradually released from the polymer by hydrolysis or enzymatic cleavage (Kim et al., 1980). The overwhelming majority of the marketed oral controlled release systems are based on physical principles (dissolution, diffusion, osmosis and desorption) and can be categorised as those in which drug release is: (i) regulated by dissolution of excipients, (ii) governed by diffusion of the drug; (iii) provided by osmotic pressure; (iv) the result of a desorption reaction from a drug-resin complex; or (v) based on other physical principles e.g. relaxation, swelling, erosion etc.

The mathematical theory of diffusion in isotropic substances is based on the hypothesis that the rate of transfer of diffusing substance through unit area of a section is proportional to the concentration gradient measured normal to the section, i.e.

$$F = -D \frac{\partial C}{\partial x}, \quad (1.1)$$

F is the rate of transfer per unit area of section, C the concentration of diffusing substance, x the space coordinate measured normal to the section, and D is the diffusion coefficient.

The fundamental differential equation of diffusion in an isotropic medium is derived from equation (1.1), a simplified form of which is,

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} \quad (1.2)$$

assuming diffusion to be one-dimensional, i.e. a gradient of concentration along only the x - axis. Expressions (1.1) and (1.2) are usually referred to as Fick's first and second laws of diffusion. Various mathematical solutions to equation (1.2) have provided useful quantitative methods for studying the drug release phenomena. The Fickian diffusion of a soluble drug from monolithic delivery systems may be expressed by equation (1.2) where it is assumed that the diffusion coefficient of the drug, D, is concentration-independent. Release rate from monolithic devices also depends upon their method of preparation. Within this context at least two different types of devices can be envisioned. In the first type the polymeric device is soaked in a drug solution until the polymer is saturated with drug. In the second type, drug is dispersed directly in a polymer to form a dispersed drug delivery system. Under perfect sink conditions diffusion through a plane sheet of thickness l, at x = 0, where region 0 < x < l is initially at a uniform concentration C<sub>0</sub>, and the surfaces are kept at a constant concentration C<sub>1</sub>, the solution of equation (1.2) is given (Crank, 1956) by:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\left[-D(2n+1)^2 \pi^2 t / 4l^2\right] \quad (1.3)$$

where M<sub>t</sub> denotes the total amount of diffusing substance at time t, M<sub>∞</sub> is the corresponding quantity after infinite time, and n is an integer. Equation (1.3) can be approximated over the initial portion of the release profile.

$$\frac{Mt}{M_{\infty}} = 4 \frac{(Dt)^{1/2}}{\pi l^2} \quad \text{for } 0 \leq \frac{Mt}{M_{\infty}} \leq 0.6 \quad (1.4)$$

However, if a drug is dispersed as such in the polymer phase (second type), the release kinetics may be altered when the total amount of the dispersed drug per unit volume of matrix (A) exceeds the amount which is necessary to provide a saturated solution (C<sub>s</sub>) after contact with the medium. The release kinetics for this case have been based on the classical expression derived by Higuchi:

$$Q = [D_s C_s (2A - C_s)t]^{1/2} \quad (1.5)$$

where Q is the amount of drug released per unit area, D the diffusion coefficient of drug in the homogeneous matrix phase, C<sub>s</sub> the solubility of drug in the matrix phase, t is time and A the total amount of drug present per unit volume of matrix.

When  $A \gg C_s$ , equation 1.5 reduces to:

$$Q = (2AD_s C_s t)^{1/2} \quad (1.6)$$

Therefore, plots of the drug release under sink conditions versus the square root of release time should give a straight line if Fickian diffusion is the predominant mechanism of release.

In many experimental situations, including the case of polymeric hydrogels and heterogeneous-matrix systems, the mechanism of drug diffusion deviates from that derived for pure monolithic systems. The increasing release rates from heterogeneous multiphase structure systems may be considered as an approach to achieving a

zero-order (time-independent) release rate. In these cases, a general equation, which is an extension of equation (1.4), can be used:

$$\frac{M_t}{M_\infty} = kt^n \quad (1.7)$$

where  $M_t/M_\infty$  is the fraction of drug released at time  $t$ ,  $k$  is a kinetic constant characteristic of the drug/polymer system, and  $n$  is an exponent which characterises the type of release mechanism operative during the dissolution process. Release rates can be fitted to the equation (1.8), which is obtained upon differentiation of equation (1.7):

$$\frac{dM_t}{sdt} = nAkt^{n-1} \quad (1.8)$$

where " $s$ " is the releasing surface area, and  $A$  is the initial concentration of drug in the polymer matrix. Table 1.1 summarises the general dependence of  $n$  on the diffusional mechanisms (Korsmeyer et al., 1983).

Table 1.1

## ANALYSIS OF DIFFUSIONAL RELEASE MECHANISMS

Value of exponent (n)	Release Kinetics	Time-dependence of solute release rate (dM/dt)
0.5	Fickian diffusion	$t^{-0.5}$
$0.5 < n < 1.0$	Anomalous (non-Fickian) diffusion	$t^{n-1}$
1.0	Case II transport	zero-order (time-independent) release
$n > 1.0$	Super Case II transport	$t^{n-1}$

Many matrix formulations are based on a published model (Higuchi, T., 1963), and the ensuing square root law has been used to describe drug release from inert matrices (Fessi et al., 1978; Roseman, 1975; Fassihi, 1987). In non-swelling monolithic devices, release rates of solutes suspended in the matrix decline throughout the dissolution process. This is a result of both increasing diffusional pathlength and decreasing surface area with time. In addition to the pure monolithic systems, devices possessing other structural features have been suggested and prepared, such as the laminated and hemispherical matrix systems (Paul, 1985; Hsieh et al., 1983), and the multiphase cross-linked polymeric hydrogel systems (Law et al., 1986). Of particular interest is the potential use of these systems as inexpensive devices for delivery of drugs and other bioactive compounds at controlled, and perhaps time-independent, rates.

The other rate controlling mechanisms in slow release preparations are based on (i) the osmotic pump, and (ii) ion-exchange systems.



### (i) Osmotically controlled systems

A publication by Theeuwes, 1975 has reported on the application of osmotic pressure in controlled release systems. These dosage forms have a semipermeable membrane and osmotic pressure provides the driving force to generate controlled release of drugs. The semipermeable membrane is permeable to water but not to the drug. A tablet containing a drug core surrounded by such a membrane is shown in Fig. 1.4. When the device is exposed to water, water will flow into the tablet due to the osmotic pressure difference. The rate of flow,  $dV/dt$ , of water into the device can be expressed

$$\frac{dV}{dt} = \frac{kA}{h} (\Delta\pi - \Delta P) \quad (1.9)$$

where  $k$  is the membrane permeability,  $A$  is the membrane area,  $h$  is the membrane thickness,  $\Delta\pi$  is the osmotic pressure difference, and  $\Delta P$  is the hydrostatic pressure difference.

There are two types of this system (See Fig. 1.4).

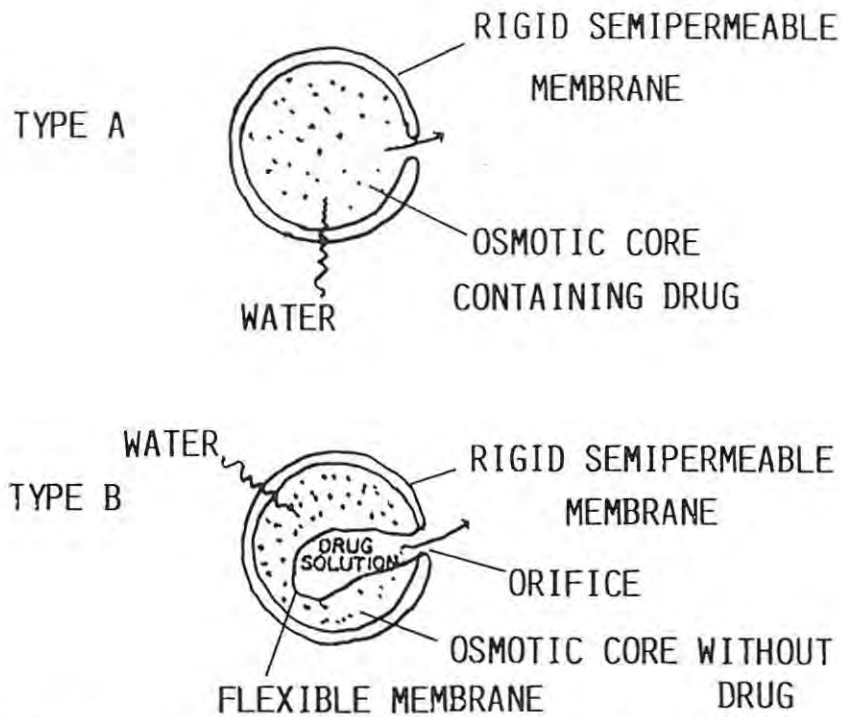


Fig. 1.4 The two types of osmotically controlled systems. Type A contains an osmotic core with drug, while type B contains drug solution in a flexible bag with the osmotic core surrounding.

Type A contains the drug in the form of a solid core associated with electrolyte. The electrolyte is dissolved by the incoming water providing the high osmotic pressure difference. On the other hand, type B contains the drug solution in an impermeable membrane within the device with the electrolyte surrounding the bag. Both types have single or multiple holes bored through the membrane to allow drug release. In type A, the high osmotic pressure can be relieved only by pumping drug containing solution out of the orifice. Similarly with type B, the high osmotic pressure will cause compression of the inner membrane and drug is pumped out the hole. In this case the hydrostatic difference becomes negligible and equation 1.9 becomes

$$\frac{dV}{dt} = \frac{kA}{h} (\Delta \pi) \quad (1.10)$$

The flow rate of water into the tablet therefore is governed by permeability, area and thickness of the membrane. On the other hand, the rate of drug leaving the orifice,

$dM/dt$ , is equivalent to the flow rate of incoming water multiplied by the solution concentration of drug,  $C_s$ , within the device.

$$\frac{dM}{dt} = \frac{dV}{dt} C_s \quad (1.11)$$

With solid drug/electrolyte systems, the size and number of laser drilled holes are the rate-limiting factors for drug release.

There are certain orally administered osmotic systems without a hole. The osmotic pressure causes the tablet to burst, causing the drug to be rapidly released.

The advantages of osmotically controlled systems include:

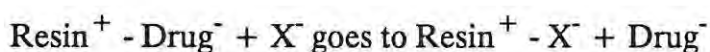
1. Zero-order release is obtainable.
2. Reformulation is not required for different drugs.
3. Drug release is independent of the environment of the system.

There are also some disadvantages:

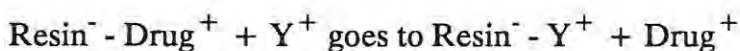
1. The systems are much more expensive than the more conventional counterparts.
2. Quality control is more extensive than most conventional tablets.

## (ii) Ion-Exchange Systems

These systems generally utilise resins composed of water-insoluble cross-linked polymers, which contain salt-forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and is gradually released by exchanging with appropriately charged ions in contact with the ion-exchange groups (Motycka et al., 1985).



or



where  $\text{X}^-$  and  $\text{Y}^+$  are ions in the GIT.

The drug diffusion rate out of the resin is controlled by the area of diffusion, diffusional path length and the rigidity of the resin, which is a function of the amount of cross-linking agent used to prepare the resin.

This system has advantages for drugs that are highly susceptible to degradation by enzymatic processes since it offers a protective mechanism, by temporarily altering the substrate. However since the release rate is proportional to the concentration of the ions present in the area of administration, this approach to sustained release is rather limited. Moreover the release rate of drug can be affected by variability in diet, water intake, and individual intestinal content. A modification is the Pennkinetic system in which the drug-resin complex is embedded in a granule of polyethylene glycol which is then coated with ethylcellulose (Raghunathan et al., 1981). The hydrophobic polymer coat governs the rate of drug availability.

These principles and mechanisms of controlled release drug delivery will be implicated in the design and development of the proposed theophylline dosage forms in this thesis.

## **CHAPTER TWO**

## **PREFORMULATION STUDIES**

Preformulation studies should be carried out on a drug substance prior to its development into different dosage forms in order to optimise those physical and chemical properties that are considered important for the formulation of a stable, effective and safe dosage form (Shami et al., 1976; Nyqvist, 1986). Consideration should also be given to possible interactions with various other components intended for use in the final product. Studies should be made of such aspects as polymorphism, crystal size and shape, pH solubility profile, solubility, dissolution and stability. These factors could have a significant effect on the bioavailability of the dosage form. The integrated information obtained from the preformulation studies is useful in selecting the best form of the drug for presentation in dosage form. The studies performed on theophylline anhydrous are described, together with discussions of the results.

### **2.1 POLYMORPHISM**

In their review article, Haleblan and McCrone (1967) define a polymorph as a "solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state". A compound may have the ability to crystallise as more than one distinct crystal species, termed polymorphs, being different in structure and properties as the crystals of two different compounds. The different properties will include variations in melting point, solubility, dissolution, crystal shape, density, hardness and optical properties. Such changes could produce significant modification of performance properties such as the stability and bioavailability of the dosage form. A different polymorph of the same compound may possess higher solubility and dissolution rates which would result in improved rates and extent bioavailability. In formulating a sustained release

preparation, where dissolution rate is a critical factor, a knowledge of the existence of other possible crystal forms is essential.

Different polymorphs may be prepared by manipulation of conditions of crystallisation such as solvent, temperature and rate of cooling. In order to investigate whether theophylline anhydrous was capable of polymorphism, the drug was recrystallised from several different solvents with varying polarities and at different cooling rates.

### **2.1.1 Materials, Methods and Equipment**

Theophylline Anhydrous B.P. was used as received from Holpro Chemical Corporation (Pty) Ltd. The solvents used were ethyl alcohol (95%), chloroform, acetone and n-propyl alcohol. All were of analytical grade. Quantities of theophylline anhydrous were dissolved with gentle heat in sufficient of each solvent to produce a supersaturated solution. Two such solutions were prepared for each solvent, or mixture of solvents. The hot solutions were filtered (no. 4 sintered glass filter) and one solution of each solvent allowed to self-cool to room temperature, while the other was cooled rapidly on ice. Similar recrystallisations were obtained from a mixture of ethyl alcohol (95%), chloroform, n-propyl alcohol and acetone (equal parts), as well as deionised water. The recrystallised drug was separated by filtration and dried in a dessicator (silica gel) for one week before use. Theophylline samples were also mixed with sucrose and sodium chloride and recrystallised from ethyl alcohol (95%) to investigate the effect of impurities.



### **Differential Scanning Calorimetry**

Differential Scanning Calorimetry (DSC) was performed on 2 - 5 mg quantities of each sample of recrystallised theophylline. A Perkin-Elmer DSC-2 Differential Scanning Calorimeter and Perkin- Elmer Recorder was used with the adjustments set as follows:

Range: 20/20

Chart Speed: 10 mm/min

Heating rate: 20°K/min

Temperature range - Lower limit: 320°K

- Upper limit: 620°K

Indium was used as the reference standard.

### **Infra-red Spectroscopy**

A Pye Unicam SP3-100 I.R. spectrophotometer was used to produce an IR spectrum of each sample using a KBr disc technique.

### **Scanning Electron Microscopy**

Scanning electron micrographs of samples were taken using a Jeol JSM 840 Scanning Electron Microscope at a magnification of 250. Samples were coated with gold prior to the microscopic examination using a Polaron E5100 Sputter coater.

## X-Ray Powder Diffraction

The X-Ray diffraction patterns of the different samples were measured utilizing a Philips PW 1050/70 automatic X-ray powder diffractometer fitted with monochromator and scintillation counter with pulse height selections.

A PW 2233/20 Cu normal focus tube was run at 50 kV and 30 mA and was used with  $1^\circ$  divergence and scatter slits. Diffraction patterns were recorded on a strip chart while scanning the sample through a  $2^\theta$  range of  $10 - 50^\circ$ .

### 2.1.2 Results and Discussion

#### Differential Scanning Calorimetry

There appeared to be no difference in the thermograms of each sample irrespective of the solvent or the rate of crystallisation. A typical thermogram (Fig. 2.1a) is that obtained for theophylline recrystallised from ethyl alcohol (95%) at a rapid cooling rate. An endothermic peak at  $538^\circ\text{K}$  ( $265^\circ\text{C}$ ) corresponding to the melting point of theophylline anhydrous is seen.

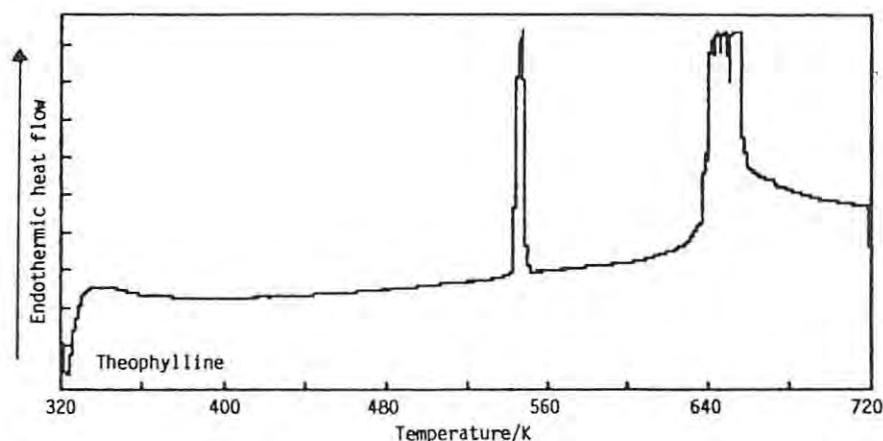


Fig. 2.1a DSC thermogram of a sample of theophylline recrystallised from ethyl alcohol (95%) under rapid cooling conditions. The endothermic peak at  $538^\circ\text{K}$  corresponding to the melting point of theophylline anhydrous is shown.

Since the thermograms are similar, the presence of polymorphic forms of theophylline is unlikely under these conditions of recrystallisation. When an impurity such as sucrose was present, an additional endothermic peak at about 460°K (186 °C) corresponding to sucrose is seen (See Fig. 2.1b).

Further thermograms were obtained of fused mixtures of theophylline with PEG and PVP (Figs. 2.1c, d and e). Endothermic peaks corresponding to the composition of the mixtures are seen. Hence there is no evidence of interactions between theophylline and sucrose, PEG or PVP.

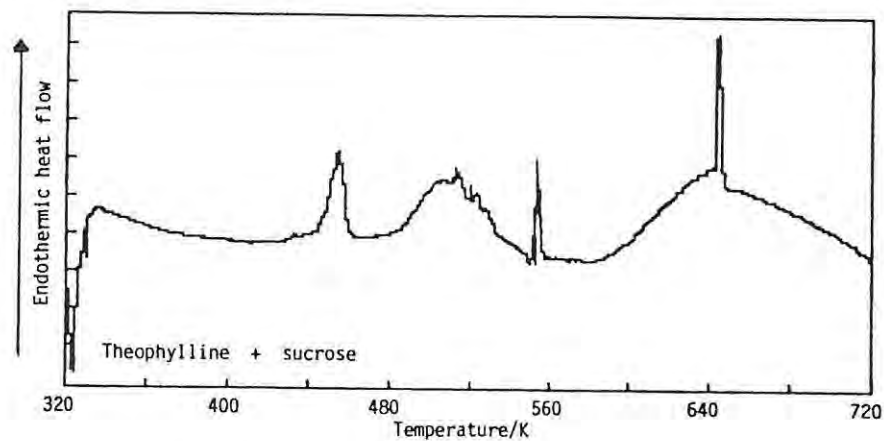


Fig. 2.1b DSC thermogram of a sample comprising a mixture of theophylline anhydrous and sucrose. In addition to the endothermic peak for theophylline at about 460°K corresponding to sucrose is shown.

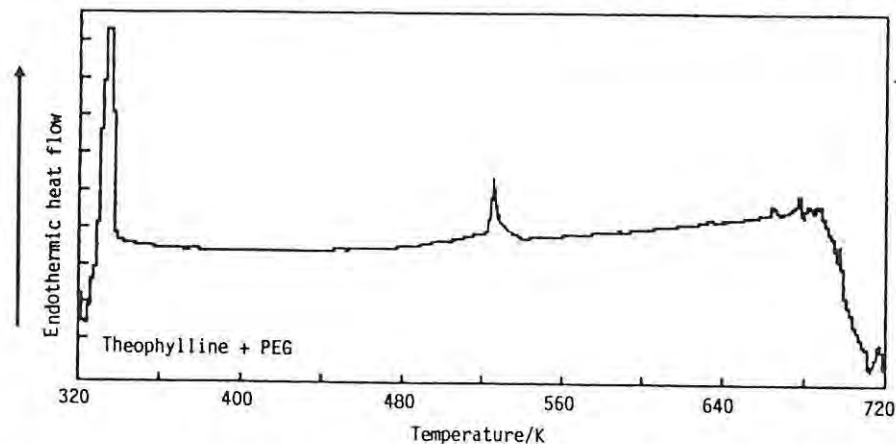


Fig. 2.1c DSC thermogram of a fused mixture of theophylline and polyethylene glycol (PEG). In addition to the characteristic peak for theophylline, an additional endothermic peak corresponding to PEG around 350°K is seen.

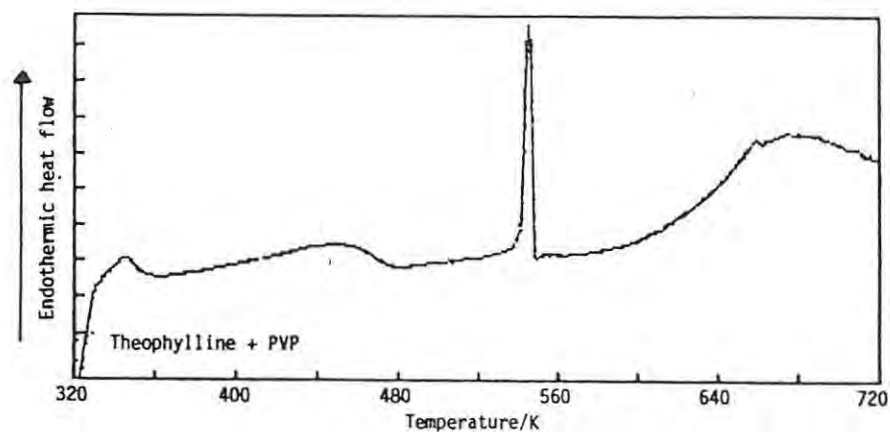


Fig. 2.1d DSC thermogram of a fused mixture of theophylline and polyvinylpyrrolidone (PVP). In addition to the characteristic peak for theophylline, an additional broad endothermic peak corresponding to PVP is seen.

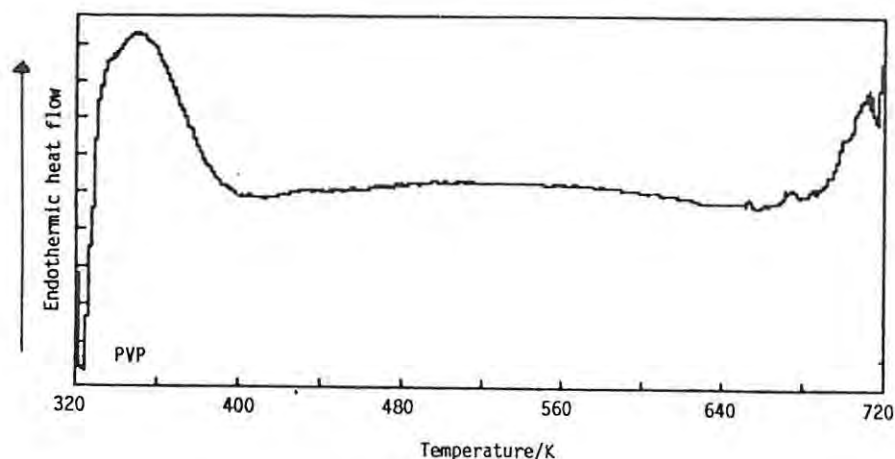


Fig. 2.1e DSC thermogram of a pure sample of PVP.

### Infra-red Spectroscopy

The infra-red spectra were identical for each sample of recrystallised theophylline. A typical spectrum is shown in Fig.2.2 which was obtained from theophylline recrystallised from water at a rapid rate by cooling on ice. The spectrum shows typical principal

peaks for theophylline anhydrous at A1660, B1720 and C1440 or 1560. The IR spectra demonstrate that no polymorphic changes are evident.

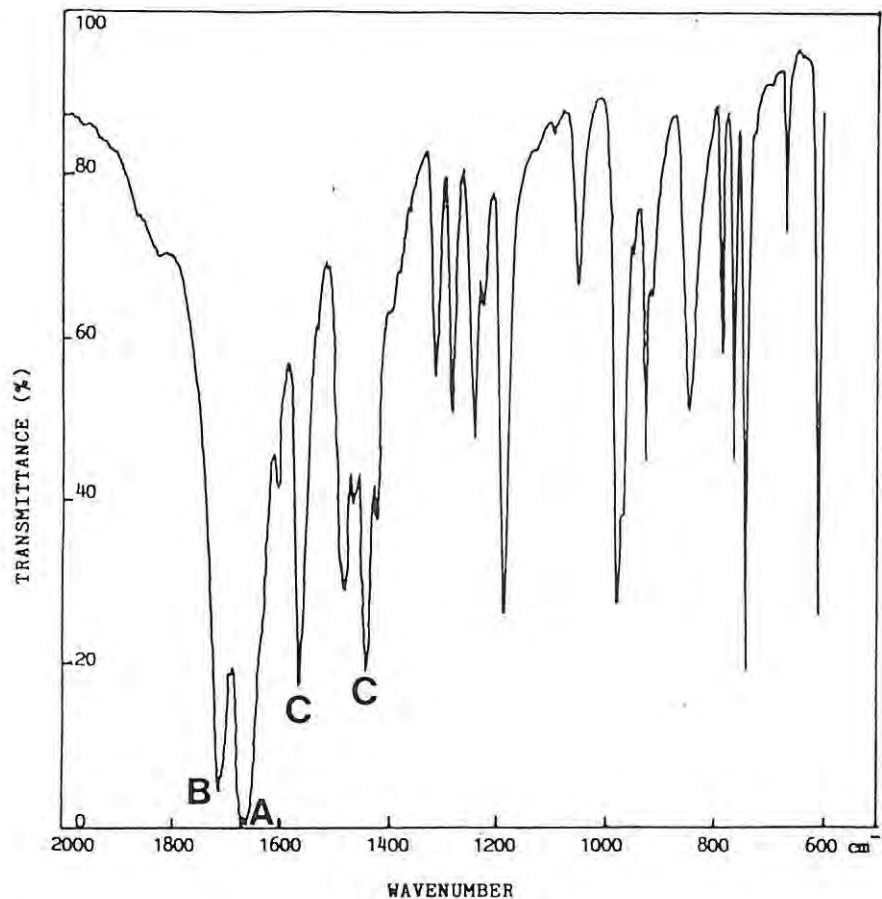


Fig. 2.2 Infra-red spectrum obtained from a sample of theophylline anhydrous recrystallised from water at a rapid cooling rate. The spectrum shows typical principal peaks for theophylline anhydrous at A1660, B1720 and C1440 or 1560.

### Scanning Electron Microscopy

The photomicrographs shown in Fig. 2.3a - i reveal differences in particle shape and size due apparently to differences in the polarity of the solvents and the rates of cooling. Samples recrystallised from polar solvents such as water and ethyl alcohol produced needle-like crystals with relatively smooth surfaces, whereas more non-polar solvents such as acetone, chloroform and n-propyl alcohol yielded crystals which were plate-like and irregular. The cooling rate appeared to influence the size of crystals produced. A slow cooling rate produced larger crystals while those recrystal-

lised rapidly on ice resulted in smaller crystals. The effects that polarity and cooling rate produce on the shape and size of the crystals formed are illustrated in Fig. 2.4, and Table 2.1 is a tabulated summary of these effects. The presence of sucrose and sodium chloride as impurities produced imperfections on the crystal surface (See Fig. 2.3h and i).

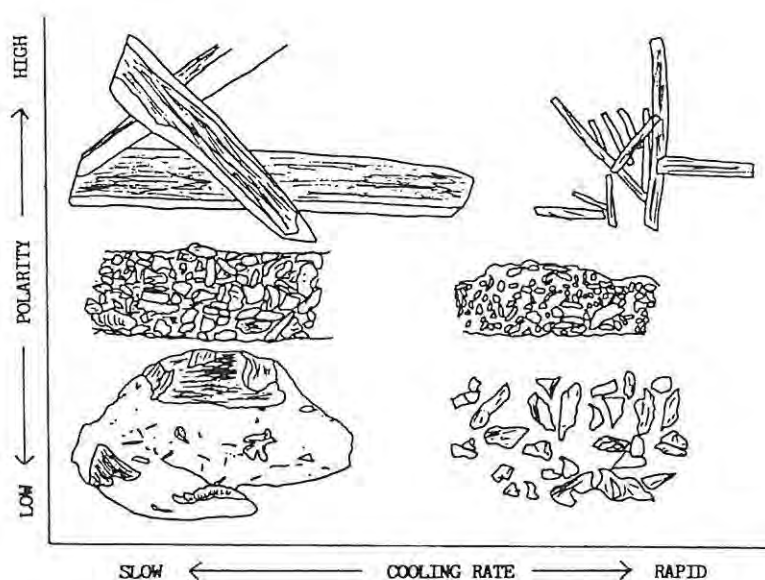


Fig. 2.4 Effect of polarity of solvent and rate of cooling on the size and shape of theophylline particles recrystallised from solutions in various solvents.

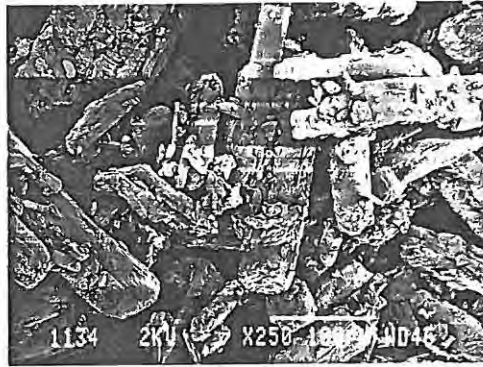
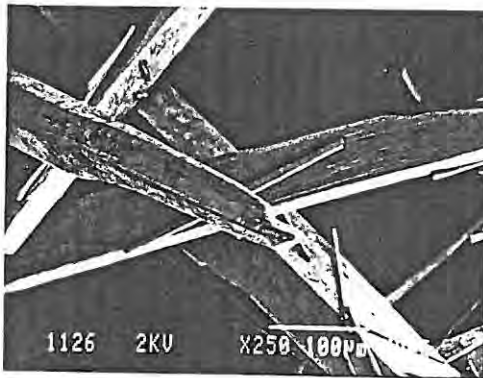


Fig. 2.3 a Scanning electron micrograph of theophylline anhydrous particles as received from Holpro Chem. Corp. at a magnification X250. The white bars represent 100  $\mu\text{m}$ .

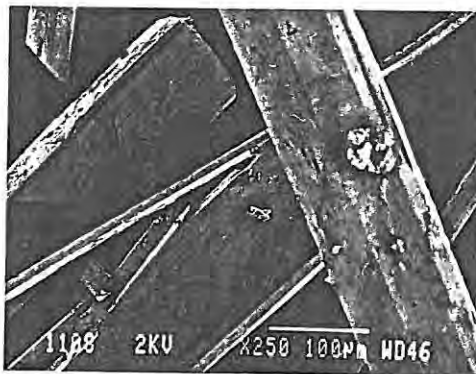


slow cooling rate



rapid cooling rate

Fig 2.3 b Scanning electron micrographs of theophylline particles recrystallised from water at two different cooling rates. Magnification X250. White bars represent 100  $\mu\text{m}$ .



slow cooling rate

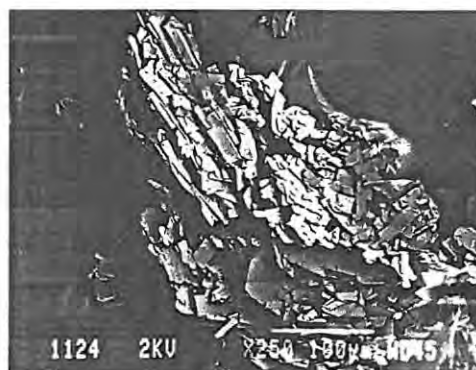


rapid cooling rate

Fig. 2.3 c Scanning electron micrographs of theophylline particles recrystallised from ethyl alcohol (95%) at two different cooling rates. Magnification X250. White bars represent 100  $\mu\text{m}$ .



slow cooling rate



rapid cooling rate

Fig. 2.3 d Scanning electron micrographs of theophylline particles recrystallised from n-propyl alcohol at two different cooling rates. Magnification X250. White bars represent 100  $\mu\text{m}$ .

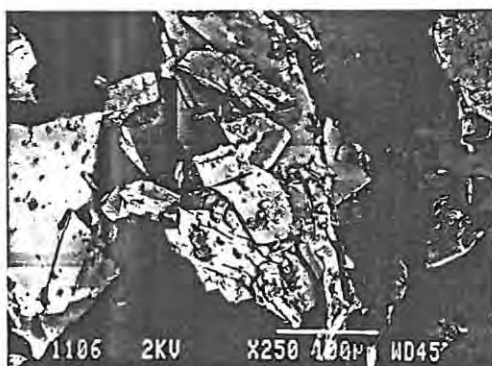


slow cooling rate



rapid cooling rate

Fig. 2.3 e Scanning electron micrographs of theophylline particles recrystallised from Acetone at two different cooling rates. Magnification X250. White bars represent 100  $\mu\text{m}$ .



slow cooling rate



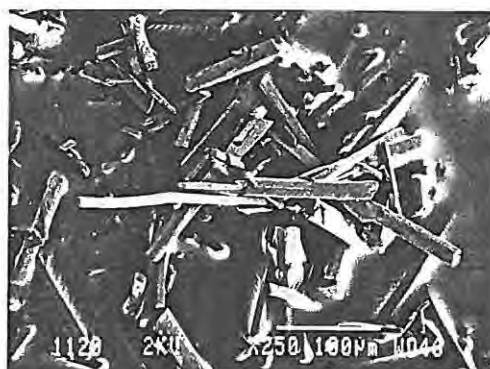
rapid cooling rate

Fig. 2.3 f Scanning electron micrographs of theophylline particles recrystallised from chloroform at two different cooling rates. Magnification X250. White bars represent 100  $\mu\text{m}$ .





slow cooling rate



rapid cooling rate

Fig. 2.3 g Scanning electron micrographs of theophylline particles recrystallised from a solvent mixture comprising ethyl alcohol (95%), chloroform, n-propyl alcohol and acetone in equal parts at two different cooling rates. Magnification X250. White bars represent 100  $\mu\text{m}$ .



Fig. 2.3 h Scanning electron micrograph of particles of theophylline containing sucrose as an impurity recrystallised from ethyl alcohol (95%) at a slow cooling rate. Imperfections on the crystal surfaces are seen. Magnification X250. White bars represent 100  $\mu\text{m}$ .

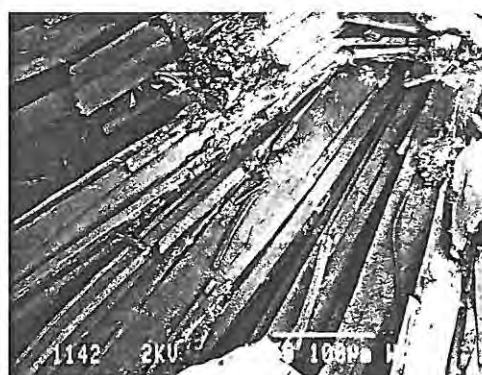


Fig. 2.3 i Scanning electron micrographs of particles of theophylline containing sodium chloride as an impurity recrystallised from ethyl alcohol (95%) at a slow cooling rate. Imperfections on the crystal surfaces are seen. Magnification X250. White bars represent 100  $\mu\text{m}$ .

**TABLE 2.1 A** tabulated summary of the relative shapes and sizes of theophylline crystals recrystallised from various solvents at different cooling rates.

SOLVENT	SHAPE AND SIZE					
	Needles		Plates		Plates arranged in needle form	
	Large (width $\mu\text{m}$ )	Small (width $\mu\text{m}$ )	Large (width $\mu\text{m}$ )	Small (width $\mu\text{m}$ )	Large (width $\mu\text{m}$ )	Small (width $\mu\text{m}$ )
<b>WATER</b>						
Rapid cooling	-	+(16)	-	-	-	-
Slow cooling	+(65)	-	-	-	-	-
<b>ETHYL ALCOHOL (95%)</b>						
Rapid cooling	-	+(8)	-	-	-	-
Slow cooling	+(110)	-	-	-	-	-
<b>n - PROPYL ALCOHOL</b>						
Rapid cooling	-	-	-	+(15)	-	-
Slow cooling	-	-	+(90)	-	-	-
<b>ACETONE</b>						
Rapid cooling	-	-	-	+(24)	-	-
Slow cooling	-	-	-	-	-	+(16)
<b>CHLOROFORM</b>						
Rapid cooling	-	-	-	-	-	+(24)
Slow cooling	-	-	-	-	+(52)	-
<b>ETHYL ALCOHOL (95%), CHLOROFORM, ACETONE, AND n-PROPYL ALCOHOL (EQUAL PARTS)</b>						
Rapid cooling	-	+(12)	-	-	-	-
Slow cooling	+(50)	-	-	-	-	-

Note: The sizes indicated in brackets are an average of 5 readings. Refer to individual scans for actual sizes.

+ = crystal formation

- = no crystal formation

## **X-Ray Powder Diffraction**

X-Ray powder diffraction studies were carried out on only three samples:

**Sample labelled "T"** - Theophylline anhydrous as received from supplier

(Holpro Chem. Corp)

**Sample labelled "WS"** - Theophylline recrystallised from water under slow conditions

**Sample labelled "PR"** - Theophylline recrystallised from n-propyl alcohol under  
rapid conditions on ice

The X-ray powder diffraction data for the above theophylline samples are tabulated in Tables 2.2 and 2.3. These data showing peak positions and intensities were obtained from diffraction patterns recorded on a strip chart. The data shows that samples "T" and "PR" have identical crystal structures. However the diffraction pattern recorded for sample "WS" shows several different features from those obtained for the other two samples (See Tables 2.2 and 2.3). These differences occur mainly in the  $2\theta$  range  $10 - 24^\circ$  (Fig. 2.5 and 2.6). Since none of the previous study methods revealed the presence of polymorphic changes it was considered possible that the differences occurring in Sample "WS" may be a hydrated form of theophylline. The presence of trace levels of solvent (in this case water) as a residue from the precipitation process may change the physicochemical properties of a substance by becoming a molecular addition to the crystal.

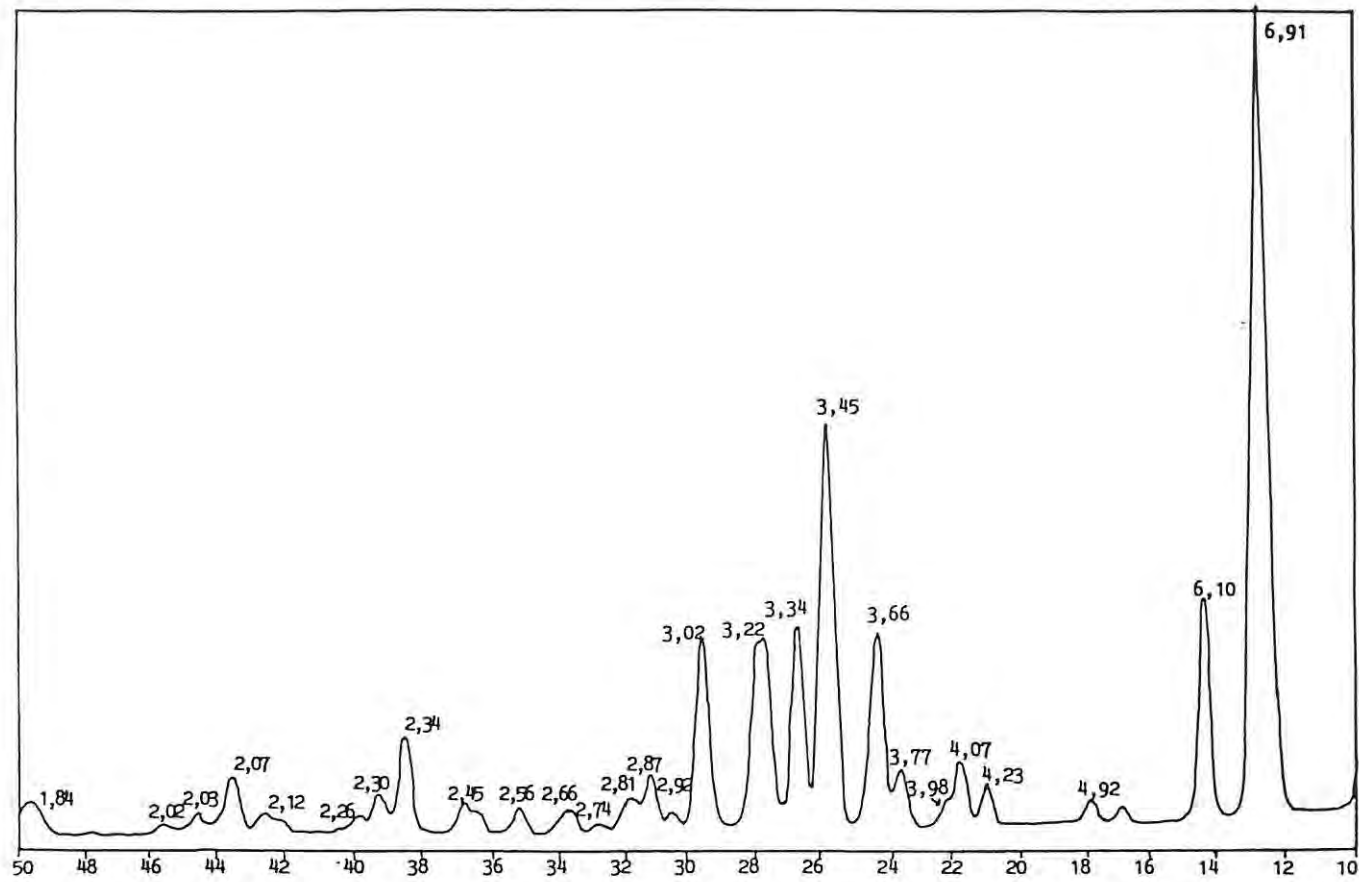


Fig. 2.5 X-Ray powder diffraction pattern (peak positions and intensities) recorded on a strip chart while scanning sample "I" through a  $2\theta$  range of  $10 - 50^\circ$ .

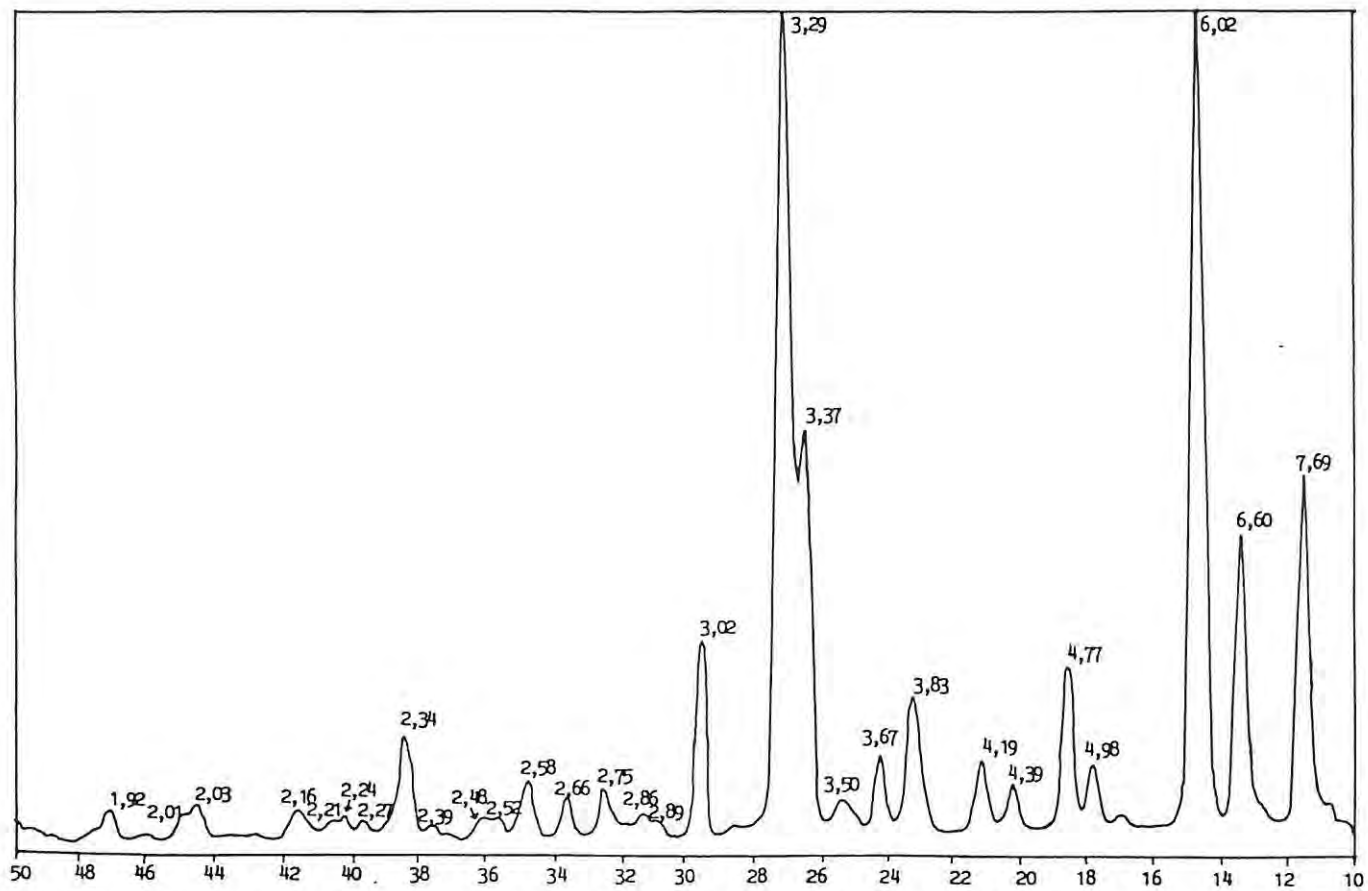


Fig. 2.6 X-Ray powder diffraction pattern (peak positions and intensities) recorded on a strip chart while scanning sample "WS" through a  $2\theta$  range of  $10 - 50^\circ$ .

TABLE 2.2 X-Ray powder diffraction data for theophylline samples "T" and "PR"

Sample "T"		Sample "PR"	
$d^\alpha$	$I^\beta$	$d^\alpha$	$I^\beta$
6.91	VS	6.96	VS
6.10	M	6.10	VS
-	-	-	-
4.92	VW	4.95	VW
-	-	-	-
-	-	-	-
4.23	VW	4.23	VW
-	-	-	-
4.07	W	4.09	S
-	-	3.83	M
3.77	W	3.78	VW
3.66	M	3.67	S
-	-	-	-
3.45	MS	3.46	MS
3.34	M	3.35	MW
3.22	M	3.23	M
3.02	M	3.06	M
2.92	VW	2.94	VW
2.87	W	2.88	M
2.81	VW	-	-
2.74	VW	-	-
2.66	VW	2.66	VW
2.56	VW	2.56	VW
-	-	-	-
2.45	VW	2.45	M
-	-	2.39	VW
2.34	MW	2.34	M
2.30	W	2.30	VW
2.26	VW	-	-
-	-	-	-
2.12	VW	2.12	VW
2.07	W	-	-
2.03	VW	2.03	VW
2.02	VW	1.99	VW
1.84	VW	1.83	VW

$^\alpha d$ : interplanar spacing (Å)

$^\beta I$ : intensities graded as S (STRONG), M (MEDIUM), W (WEAK) V (VERY)

TABLE 2.3 X-Ray powder diffraction data for theophylline samples "WS" and "WS DRIED".

Sample "WS" $d^\alpha$	$I^\beta$	Sample "WS DRIED" $d^\alpha$	$I^\beta$
7.69	S	-	-
-	-	7.02	VS
6.60	S	-	-
-	-	6.15	MS
6.02	VS	-	-
-	-	5.57	VW
4.98	W	4.95	W
4.77	M	-	-
4.39	VW	-	-
-	-	4.21	W
4.19	W	-	-
-	-	4.07	W
-	-	3.98	W
-	-	3.77	M
3.67	W	3.66	S
3.50	VW	-	-
-	-	3.46	VS
3.37	S	3.35	VS
3.29	VS	3.23	S
-	-	3.21	S
3.02	MS	3.04	S
2.89	VW	2.94	VW
2.86	VW	2.88	W
-	-	2.82	W
2.75	VW	2.74	VW
2.66	VW	2.67	W
2.58	VW	2.56	W
2.52	VW	-	-
2.48	VW	2.47	W
-	-	2.45	W
2.34	MW	2.34	S
2.27	VW	2.30	MW
2.24	VW	2.24	W
2.21	VW	2.23	VW
2.16	VW	2.14	W
-	-	2.12	W
-	-	2.07	MW
2.03	VW	2.03	MW
2.01	VW	1.99	W

$\alpha^\alpha d$ : interplanar spacing (Å)

$\beta^\beta I$ : intensities graded as S (STRONG), M (MEDIUM), W (WEAK) V (VERY)

To investigate this possibility sample "WS" was dried in an oven at 100°C for 1 hour and a sample of this dried material was submitted to X-ray powder diffraction as before. Results showed that there was no significant difference in diffraction patterns compared to samples "T" and "PR" (see Table 2.2 and Table 2.3). This evidence therefore supports the view that differences in crystal structure between the freshly recrystallised sample "WS" and the dried sample is due to pseudopolymorphism resulting from the presence of water as a molecular addition to the crystal in the freshly re-crystallised material.

## CONCLUSION

Attempts to recrystallise theophylline from various solvents, both polar and non-polar, did not produce polymorphic changes to the theophylline crystal, although there was evidence of pseudopolymorphism in the sample recrystallised from water. Significantly the use of polar and non-polar solvents resulted in differences in the shape and size of the crystals as shown in SEM techniques. In the absence of evidence of the existence of any other polymorphic forms under these conditions of recrystallisation, it was concluded that further attempts to alter the dissolution characteristics of the drug by this means should be discontinued.

## 2.2 CRYSTAL SIZE, SHAPE AND DISSOLUTION

Attempts were then made to investigate the affect of crystal size and shape on the dissolution properties of theophylline obtained by recrystallisation from solvents as described in Section 2.1.1. In the case of poorly or sparingly soluble drugs, absorption is often dissolution rate limited. It is also well known that the size and shape of a drug particle has a profound influence upon its dissolution rate consequently affecting its



rate of absorption and onset of action (Staniforth, 1988). In certain cases the size of the drug particle may be modified in order to obtain the desired physicochemical characteristics. It is essential therefore that during early preformulation studies the particle size and distribution be determined, optimised and controlled when applicable. Samples of theophylline used for dissolution rate determinations were:

1. Crystals as received from Holpro Chemical Corporation.

Short, rod-like particles variable in size from about 100 - 500  $\mu\text{m}$  long and 50 - 100  $\mu\text{m}$  wide.

2. Crystals recrystallised from water under slow cooling conditions.

Long, needle-like crystals averaging about 1000  $\mu\text{m}$  in length and about 100  $\mu\text{m}$  in width.

3. Crystals recrystallised from n-propyl alcohol by cooling rapidly on ice.

Thin, plate-like fragments of irregular shape ranging in length from less than 10  $\mu\text{m}$  to about 80 - 100  $\mu\text{m}$ .

### 2.2.1 Sieve Analysis

There are a number of methods of particle size analysis of a powder. One of the most commonly used methods is employing a variety of sieves. The sieve analysis is usually carried out using dry powders with metal sieves of known aperture diameters. A series or a nest of sieves which have the smallest mesh above a collector tray followed by meshes which get progressively coarser towards the top of the series. In this analysis four stainless steel sieves of mesh sizes 390  $\mu\text{m}$ , 250  $\mu\text{m}$ , 190  $\mu\text{m}$  and 75  $\mu\text{m}$ , and a

Erweka AR 400 mechanical shaker was used. Samples of known mass of each of the above three types of crystal were subjected to sieve analysis to determine the size distribution of each. About 5g of sample, accurately weighed, was loaded on to the top coarsest sieve of the assembled stack and the nest was subjected to mechanical vibration for 10 minutes. The particles are considered to be retained on the sieve mesh with an aperture corresponding to the minimum or sieve diameter. For a comparison to be made of the characteristics of the powders, the size distribution can be broken down into different size ranges which can be presented in the form of a histogram. Such a histogram enables the percentage of particles having a given equivalent diameter to be determined and allows different particle size distributions to be compared.

### **Results of Sieve Analysis**

A histogram of each sample indicating the percentage of powder lying between different mesh sizes is shown (Fig. 2.7 to 2.9). The size distribution of the drug sample recrystallised from water as well as the sample recrystallised from n-propyl alcohol contain a larger proportion of large particles than the powdered theophylline as received from Holpro in which the particles are almost normally distributed. Both recrystallised samples exhibit skewness of the frequency distributions. Both frequency curves have an elongated tail toward the smaller size ranges and are therefore negatively skewed.

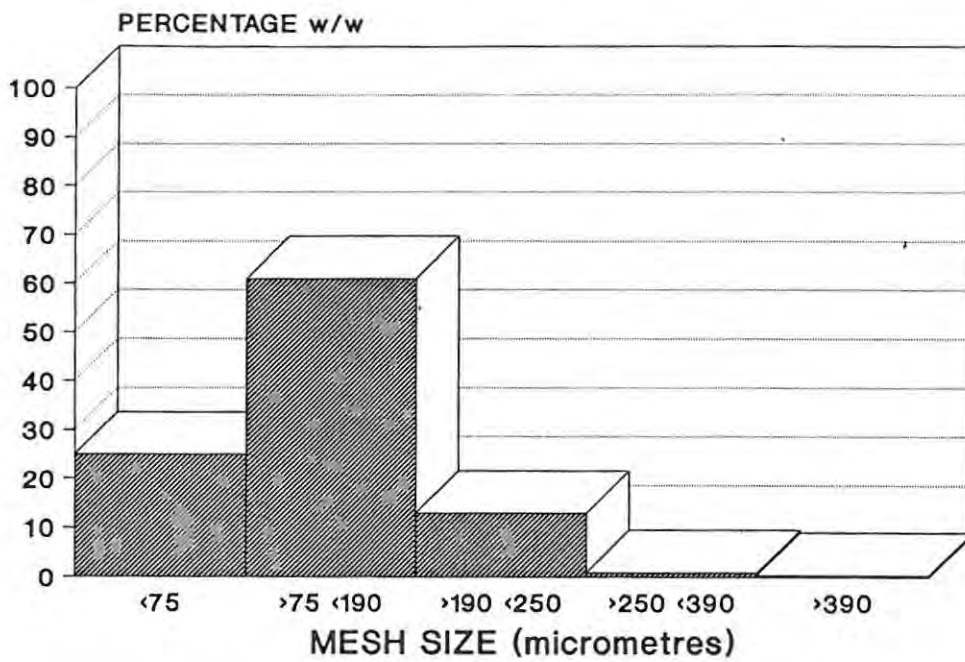


Fig. 2.7 Histogram of sample 1 indicating the percentage of powder lying between different mesh sizes.

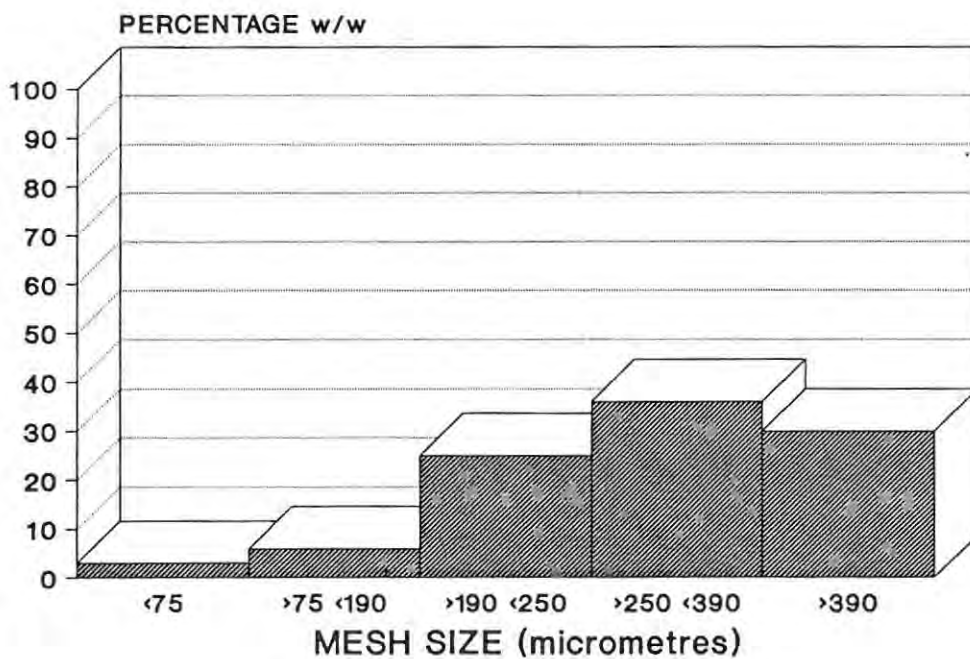


Fig. 2.8 Histogram of sample 2 indicating the percentage of powder lying between different mesh sizes.

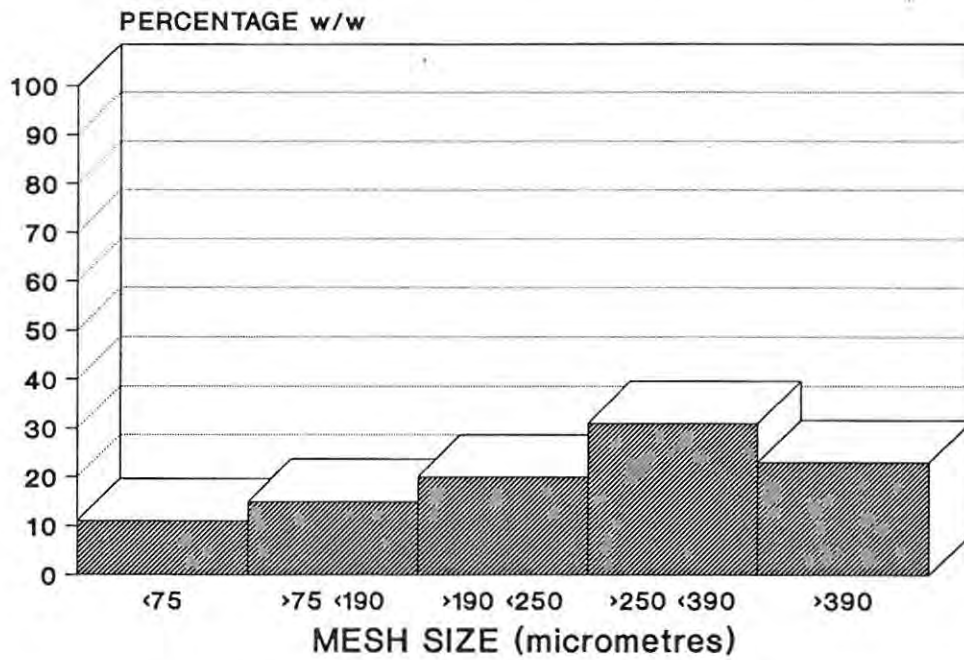


Fig. 2.9 Histogram of sample 3 indicating the percentage of powder lying between different mesh sizes.

## 2.2.2 EFFECT OF PARTICLE SIZE ON DISSOLUTION RATE

In instances where the bioavailability of a drug is dissolution rate limited, absorption into the system may be increased by a reduction in drug particle size and hence an increase in total surface area. For sustained release dosage forms of the drug, it may be possible to reduce absorption by increasing the particle size. This is clear from the Noyes-Whitney equation

$$\frac{dm}{dt} = \frac{DA}{h} (C_s - C)$$

where  $dm/dt$  is the rate of dissolution,  $D$  is the diffusion coefficient,  $A$  is the effective surface area of the drug particles,  $h$  is the diffusion layer thickness,  $C_s$  is the saturation solubility of the drug in the diffusion layer and  $C$  is the concentration of drug in solution. The following study was performed to determine the effect of particle size on the dissolution rate of the three recrystallised theophylline samples subjected to sieve analysis.

### Method

A beaker containing 200 mL of distilled water was placed on a magnetic stirrer with the stirring rate adjusted to 32 rpm. The distilled water was used as received from the reservoir of the still at a temperature of 19°C. Exactly 0.5 g of the first sample was then quickly added all at one time to the water. A stop watch was started immediately the solid entered the water. At exactly one minute, 1 mL of the solution was removed and passed through a 0.45  $\mu\text{m}$  membrane filter (Millipore) to remove undissolved solids from the solution. An equivalent volume of distilled water at 19°C was added to maintain constant volume. The 1 mL sample was diluted to 100 mL with water and

the theophylline concentration determined by UV spectrophotometry at 271 nm. The above sampling procedure was repeated at 2, 4, 6, 8 and 10 minutes. The dissolved theophylline (mg) was plotted against time (minutes). The above method was repeated with 0.5 g quantities of samples 2 and 3.

### **Results and Discussion**

The dissolution profiles of each sample are shown in Fig. 2.10. The dissolution profiles show that the plate-like particles (sample 3) have a faster rate of dissolution than those particles received from the supplier (Holpro) (Sample 1). The latter in turn have a faster dissolution rate than the long needle-like particles (Sample 2). The differences in the rates of dissolution can be explained in terms of the differences in surface area of the particles. The large needle-like crystals having the smallest surface area will produce the slowest dissolution rate, whereas the plate-like particles although intermediate in size have the largest surface area and hence a faster dissolution rate. The smallest particles (sample 1) are rod-like. Because of their shape the surface area of the short rods is smaller than the plates.

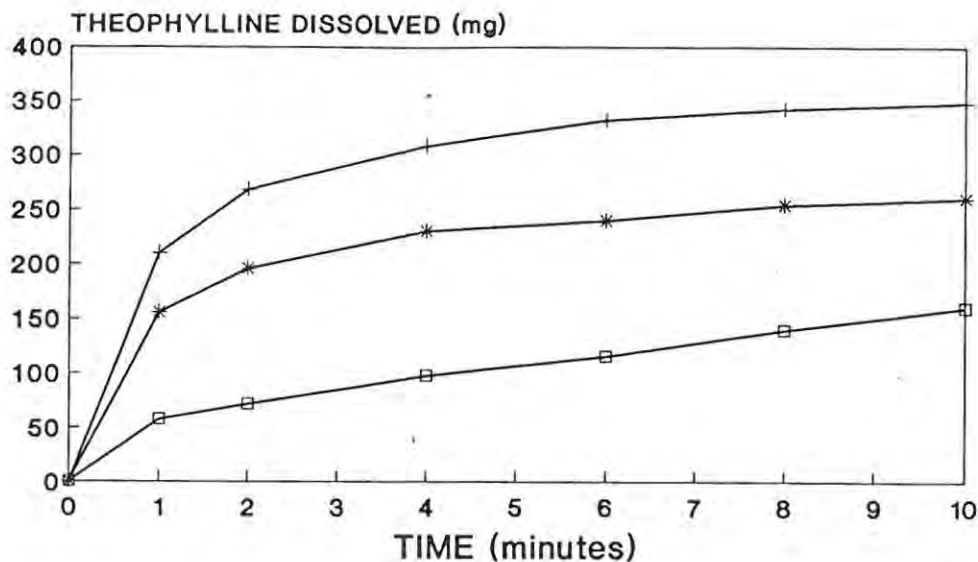


Fig. 2.10 The effect of particle size and shape on the dissolution rate of theophylline in distilled water at 19°C.

- + , drug particles recrystallised from n-propyl alcohol
- \* , drug particles as received from supplier (Holpro Chem. Corp.)
- , drug particles recrystallised from water.

### Conclusion

The graph (Fig.2.10) shows significant differences in dissolution rate of the drug particles over a relatively short time period of 10 minutes. However when formulating sustained release dosage forms designed to release the drug constantly over 12 hour time periods, these differences might therefore be considered insignificant.

### 2.3. pH SOLUBILITY PROFILE

A drug must possess some aqueous solubility, irrespective of the route of administration, in order to be physiologically active. Aqueous solubility is however not the only factor influencing absorption. Other factors such as degree of ionisation and lipid solubility can also be important.

The aqueous solubility of many drugs will vary according to the pH of its environment. It is clear therefore that the solubility of a drug may vary at different positions along

the gastro- intestinal tract. The gastric juice has a pH of 1 - 3 with the pH increasing gradually toward the distal regions of the intestine where the pH could be as high as 8. A study was performed to determine the pH solubility profile for theophylline anhydrous.

### **Method**

The method employed was based on equilibrium solubility. An excess of theophylline anhydrous (5 g) was added to 200 mL of 0.05 M phosphate buffer at pH 1.5 in a beaker. The suspension at 37°C was stirred on a magnetic stirrer until equilibrium was achieved (about 24 hours). At equilibrium 5 mL of suspension was withdrawn and quickly filtered through a 0.45  $\mu$ m membrane filter. The 5 mL of filtered solution was diluted to 200 mL with water. A 5 mL volume of this diluted solution was then further diluted to 250 mL. The absorbance of this solution was measured at 271 nm and the concentration of theophylline calculated. Appropriate quantities of 0.1 M NaOH was added to the suspension to raise the pH to suitable higher levels. After equilibrium was reached each time (24 hours) the above sampling and diluting procedure was repeated and the diluted solution assayed for theophylline.



## Results and Discussion

The pH solubility profile for theophylline is illustrated in Fig. 2.11.

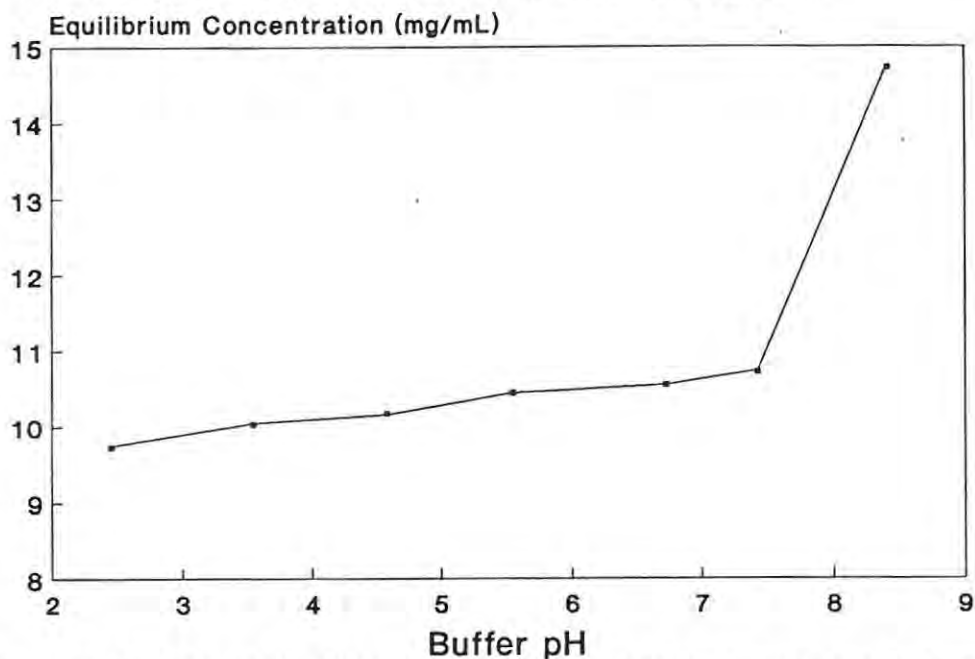


Fig. 2.11 Curve showing the pH solubility profile of theophylline anhydrous B.P. in phosphate buffer. These results show that there is little change in equilibrium solubility over the pH range about 2 - 7. There is however a significant increase in solubility at pH values above 7.4. The greater solubility of theophylline at pH values above 7.4 would probably indicate that theophylline would have a greater solubility in the alkaline intestinal fluid. Thus the drug would be more rapidly absorbed in this region of the GIT since the drug is non-ionising and has a pKa value of 8.3 at 37°C (Zuidema J., 1983).

### 2.4 INTRINSIC DISSOLUTION

It is a well established fact that an orally administered drug must first dissolve in the gastrointestinal fluids for absorption to take place. The dissolution rate data as well as the information on the solubility, pKa and partition coefficient of the drug will provide useful insight into its potential *in vivo* absorption characteristics. The dissol-

ution rates of theophylline from different crystal forms and particle sizes have already been demonstrated under a previous section entitled "Crystal Size, Shape and Dissolution". The intention of this study was to determine the intrinsic dissolution rate of theophylline by the constant surface method under sink conditions. Moreover solid dispersions of theophylline with certain polymeric substances were prepared and the intrinsic dissolution rate similarly determined.

#### **2.4.1 Measurement of the Intrinsic Dissolution Rate of Theophylline Anhydrous**

##### **Materials and Method**

A compression die similar to Wood's Apparatus (Wood et al., 1965) was designed (Fig. 2.12). A disc (11 mm diameter) of pure anhydrous theophylline powder (Holpro) was prepared by slow compression using an Instron machine. A high compaction pressure to ensure zero porosity was employed together with a long dwell time.

Employing the USP XXI paddle method of dissolution, the intrinsic dissolution rate of theophylline was determined using 1 L of distilled water as dissolution medium. The brass holder containing the disc was positioned as shown in Fig. 2.12. The temperature of the water was  $37 \pm 0.5^\circ\text{C}$  and the paddle was rotated at 50 rpm. The amount of drug released was monitored with time by U.V. spectrometry at 271 nm and removing samples of dissolution medium at 5 minute intervals during the first hour of release. Sink conditions were prevailing throughout the dissolution measurements. An equivalent volume of water at  $37^\circ\text{C}$  was added to maintain constant volume. The above determinations were carried out in quadruplicate and the mean theophylline concentrations (mg/L) were plotted against time (minutes).

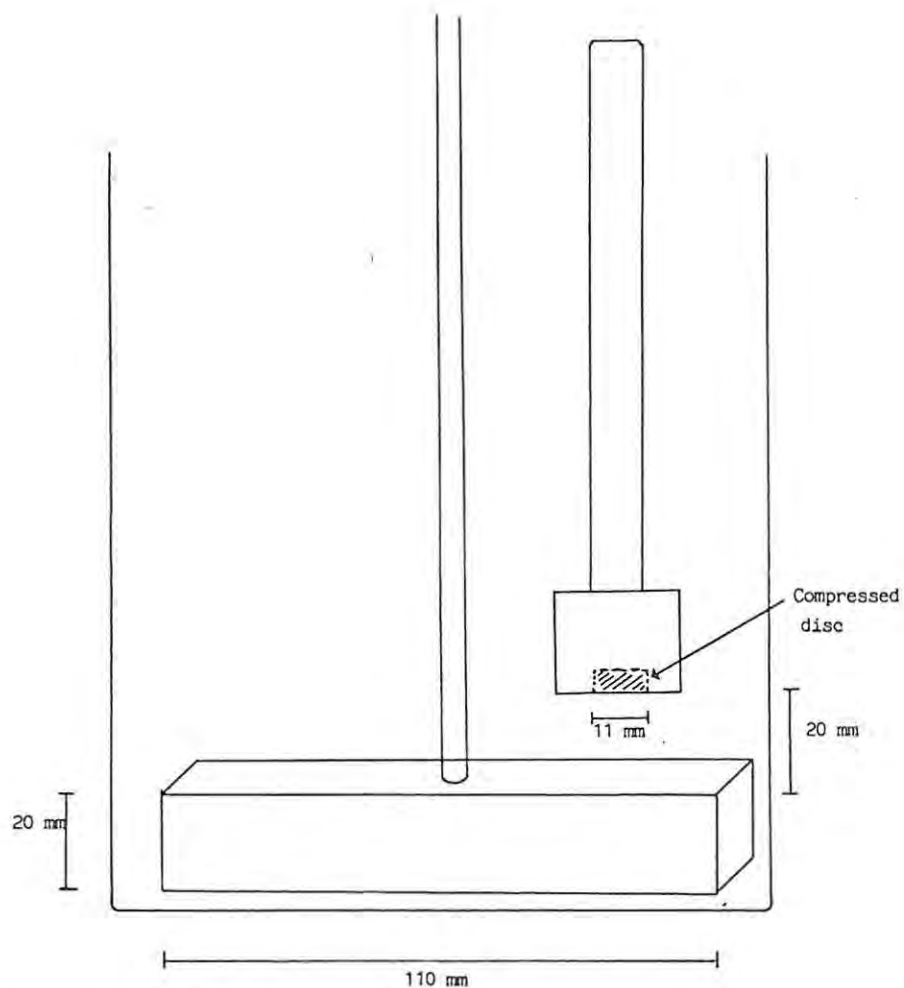


Fig. 2.12 Diagram showing the apparatus used to determine intrinsic dissolution of theophylline. The compressed disc is shown fitting into the brass holder. The perspex paddle is driven at 50 rpm by a variable speed motor.

### Results and Discussion

The plot of theophylline concentration against time was linear (Fig. 2.13) indicating that sink conditions were maintained.

The slope of the line divided by the exposed surface area gives the intrinsic dissolution rate expressed in  $\text{mg}/\text{cm}^2 \cdot \text{min}$ .

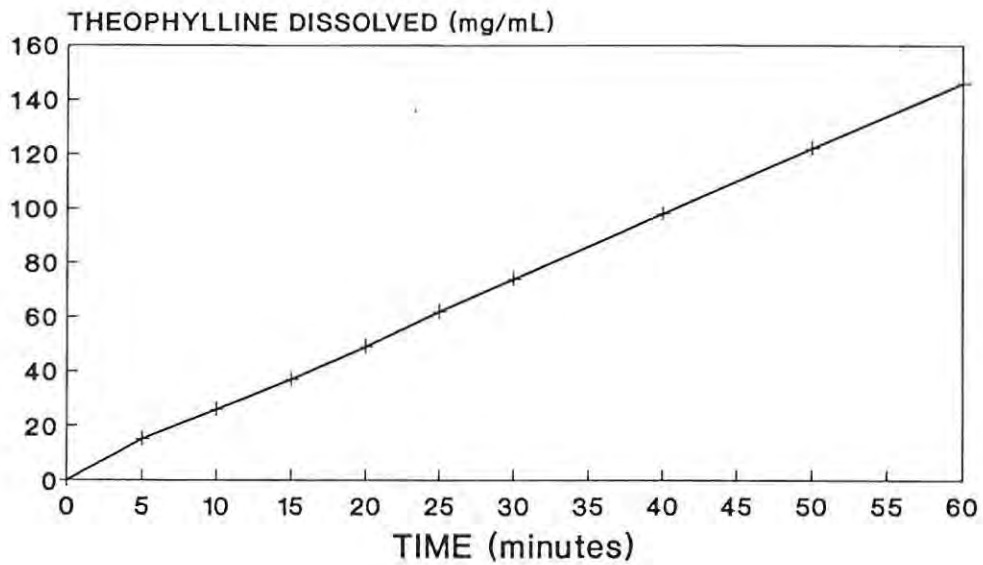


Fig. 2.13 Plot illustrating the intrinsic dissolution profile of theophylline in water by the constant surface method.

The surface area of the exposed disc surface was  $0.951 \text{ cm}^2$ . The intrinsic dissolution rate  $K$  was calculated using the equation:

$$K = W/tA \quad \text{where } W \text{ is the quantity of drug}$$

dissolved in time  $t$

and  $A$  is the surface area of the disc surface.

The calculated intrinsic dissolution rate for theophylline under the above conditions was  $2.54 \text{ mg/cm}^2 \cdot \text{min}$ . However, it should be noted that there are a number of factors

which significantly influence the calculated intrinsic dissolution rate of a substance. These include the agitation rate and the position of the disc holder. It is absolutely essential therefore when making comparisons of intrinsic dissolution rates to ensure that dissolution conditions are exactly similar.

It was noted that during the dissolution process more erosion occurred along the disc surface nearer to the side of the flask. (Fig. 2.14).

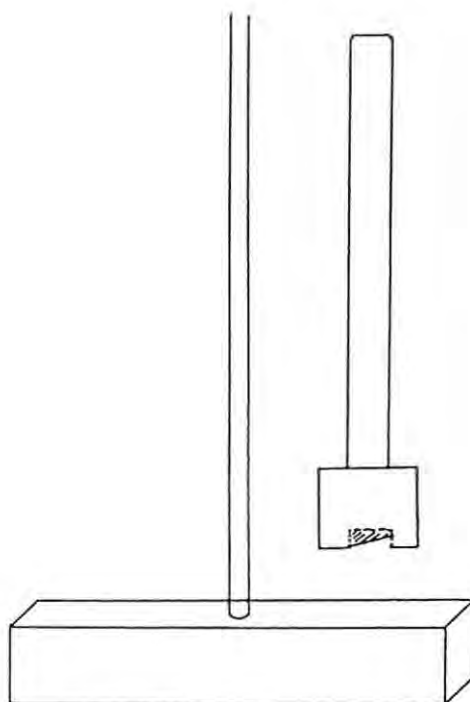


Fig. 2.14 Diagram illustrating the greater erosion rate occurring on the disc surface nearer to the side of the dissolution flask.

This phenomenon can be attributed to the fact that the moving pattern of the dissolution medium becomes progressively faster from the centre where the paddle shaft joins the paddle towards the sides of the flask where the moving pattern is at its highest speed. This would increase the dissolution rate of the drug along the outer surface. Therefore the exact position of the solid surface in relation to the paddle is

an important factor influencing the intrinsic dissolution rate. Since the rate of dissolution is not constant over the entire disc surface area, it would seem that eccentrically mounted discs as proposed by Nicklasson and Magnusson, (1985) would result in a more constant fluid flow over the disc surface. Rotating disc methodology was also employed by Dubois and Ford, (1985) when examining the dissolution rates of 10 drugs which were solid dispersed by fusion in polyethylene glycol 6000.

#### **2.4.2 Measurement of the Intrinsic Dissolution Rate of Theophylline from Solid Dispersions.**

A solid dispersion has been defined by Chiou and Riegelman, (1971) as "dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method." The concept of solid dispersions was introduced in order to increase the bioavailability of many poorly water-soluble drugs which are dissolution rate limited. However research conducted in the area of solid dispersions encompasses both fast release as well as sustained release products. Work done by Simonelli et al., (1969) has shown that large increases in the dissolution rates of drugs from solid dispersions have occurred. The mechanisms involved in the increased dissolution rates are discussed by Ford, (1986) in his review article on the current status of solid dispersions. The drug must be transferred to a higher energy form to produce more rapid dissolution and this is most easily accomplished at high carrier levels when the carrier dissolves rapidly bringing the dispersed drug into solution. Examples of such carriers include polyethylene glycols and polyvinyl- pyrrolidones. It follows that the presence of insoluble polymers such as ethylcellulose and Eudragit<sup>®</sup> would proportionately reduce the dissolution rate of

the drug from a solid dispersion where soluble carriers were also present. Solid dispersions of drugs in carriers of low solubility offer the potential for sustained release. This work was carried out to demonstrate the affect of both soluble and insoluble polymers on the dissolution rate of theophylline from solid dispersion. A knowledge of the dissolution behaviour could be applied in the design of sustained release dosage forms.

### **Materials and Method**

The constant surface method eliminates changes in surface area and surface electrical charge as dissolution variables. Solid dispersions of theophylline with various polymers were prepared by the fusion method. The composition of each of the two solid dispersion formulations are given below.

#### **Formulation 1**

Theophylline anhydrous 2.0 g

Polyvinylpyrrolidone 2.0 g

Polyethylene glycol 1540 7.0 g

#### **Formulation 2**

Theophylline anhydrous 2.0 g

Ethylcellulose 2.0 g

Polyethylene glycol 6000 7.0 g

The solid dispersions were made by slowly melting the polyethylene glycols on a hot plate at a low temperature and then stirring in the other two components to produce a smooth suspension in the molten mixture. The molten mixtures were then poured carefully into the same brass holders used for the measurement of the intrinsic dissolution rate of theophylline anhydrous described previously. After solidifying the surplus dispersion was gently scraped away to yield a surface completely flush with the brass holder. Employing the USP XXI paddle method as before, the intrinsic dissolution rate of theophylline from each solid dispersion formulation was determined in triplicate. Distilled water (IL) at  $37 \pm 0.5^\circ\text{C}$  was used as dissolution medium. The paddle was rotated at 50 rpm during each determination except for one determination using formulation 2 where the paddle speed was 100 rpm. The sampling of dissolution medium and the assay for theophylline was performed as described previously. The mean percent of theophylline dissolved was plotted against time (minutes).

### **Results and Discussion**

The plots of percentage drug dissolved against time are shown in Fig. 2.15. Because of the water solubility of the polymers polyvinylpyrrolidone and polyethylene glycol in Formulation 1, the theophylline present in this formulation dissolves more rapidly in comparison to Formulation 2 containing the insoluble polymer ethylcellulose which tends to impede the dissolution process significantly. However, increasing the rotational speed of the paddle to 100 rpm increases the dissolution rate of theophylline from Formulation 2. Fig. 2.15 also shows the dissolution profile of pure theophylline anhydrous. It can be clearly seen that the presence of theophylline in the form of a solid dispersion with various polymers resulted in a great increase in the rate of



dissolution which depended upon the composition of the fused solid dispersion as well as the agitation speed.

The intrinsic dissolution rates of theophylline from the two solid dispersion formulations were calculated and compared.

Formulation 1    Intrinsic dissolution rate (50 rpm)  $4.2 \text{ mg/cm}^2 \text{min}$

Formulation 2    Intrinsic dissolution rate (50 rpm)  $1.9 \text{ mg/cm}^2 \text{min}$

Formulation 2    Intrinsic dissolution rate (100 rpm)  $3.2 \text{ mg/cm}^2 \text{min}$

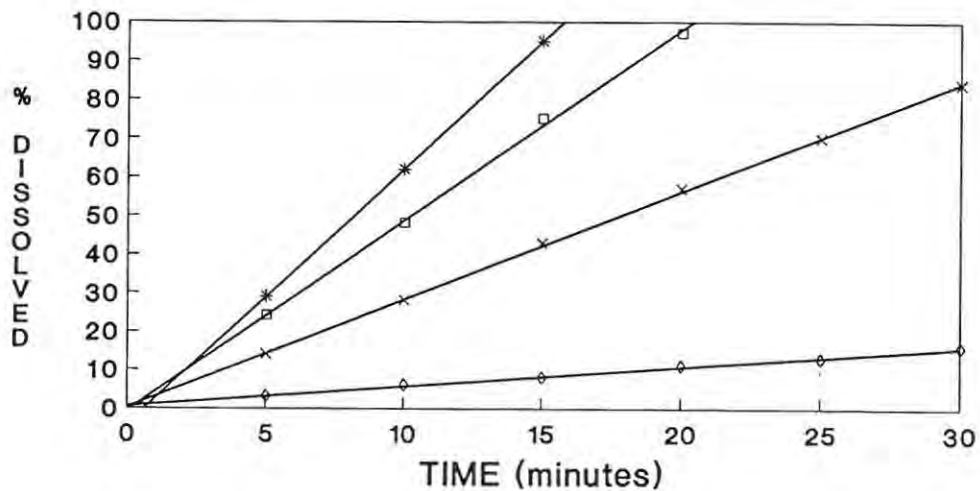


Fig 2.15 Dissolution profiles showing the % of theophylline released against time (minutes) from discs by the constant surface method.

- \* Theophylline in solid dispersion with PVP and PEG 1540 (50 rpm)
- Theophylline in solid dispersion with ethylcellulose and PEG 6000 (100 rpm)
- × Theophylline in solid dispersion with ethylcellulose and PEG 6000 (50 rpm)
- ◇ Theophylline Anhydrous (pure) (50 rpm)

### Conclusion

The presence of a soluble polymer, such as PEG and PVP, significantly increased the dissolution rate of theophylline from solid dispersion. The incorporation of an insoluble polymer, ethylcellulose, however significantly decreased the dissolution rate

and demonstrates that ethylcellulose will be useful in impeding the drug dissolution rate in sustained release formulations. It is also noteworthy that the dissolution rate depends largely on the speed of agitation. Ethylcellulose and PEG were used because they are commonly used non-toxic polymers in sustained release technology and will feature prominently in certain parts of the work that follows.

# CHAPTER THREE

## **GRANULATION, FILM COATING OF GRANULES AND ASSESSMENT OF DRUG RELEASE FROM GRANULES**

Fluidised bed film coating technology was used to film coat granules of theophylline with polymeric materials. These granules contained a high proportion of the drug and were sufficiently hard to prevent fracture or powdering during the film coating process when the granules are in constant rapid motion. Work was carried out therefore to determine which of the binders in general pharmaceutical use would produce granules possessing sufficient hardness.

### **3.1 GRANULE PRODUCTION**

#### **3.1.1 Materials and Methods**

The binding materials investigated were acacia, gelatin and maize starch, each of which were according to B.P. 1980 specifications. Other binders used were sodium carboxymethylcellulose (Holpro), sucrose (BDH) and polyvinylpyrrolidone 40 000 (Sigma).

A sufficient quantity of an aqueous solution of each binder was added to 50 g theophylline anhydrous in fine powder while mixing to produce a wet mass. The concentrations and volumes of the aqueous solutions of the binders used are provided in Table 3.1. Acacia and gelatin were each used at two different concentrations. The soft masses were passed through a sieve (2 mm) and dried at 55°C for 8 hours. After drying the coarse granules were passed through a sieve (2 mm with 1.25 mm underneath). The granules produced were in the range  $< 2 \text{ mm} > 1.25 \text{ mm}$ . The approximate concentration (% w/w) of each binder in the dried granulated material is shown in Table 3.2.

**Table 3.1** Concentrations and volumes of binder solutions required to mix with 50 g of anhydrous theophylline to produce a suitable wet mass

Binder and concentration of solution (% w/v)	Volume or weight of solution required (mL or g)
Acacia 20%	12.5 mL
Gelatin 20% (> 45°C)	12.5 mL
Sucrose 60%	13.5 mL
Sodium carboxymethylcellulose 5% paste	15.0 g
Polyvinylpyrrolidone 15%	12.5 mL
Starch paste 10%	15.0 g
Acacia 40%	15.0 mL
Gelatin 40% (> 45°C)	15.0 mL

### 3.1.2 Hardness Testing

A comparison of the hardness of the various granules was made utilising a Erweka TBH 28 Tablet Hardness Tester. Since the granules were less than 2 mm in diameter, a stainless steel strip 5 mm thick was used to line the pressure plate making it possible for the granule to be crushed before the plate returned to its resting position.

Ten granules of each sample were tested and the pressure (Newtons) required to fracture each granule was recorded. The mean pressure for each sample is shown in Table 3.2 in order of decreasing hardness.

**TABLE 3.2**

Binder (%w/w in dried granules)	Mean pressure (Newtons) ±S.D.
Gelatin 10.7%	30.2 ±6.3
Sodium carboxymethylcellulose 1.5%	20.8 ±7.0
Gelatin 4.7%	16.3 ±4.2
Acacia 10.7%	15.9 ±3.9
Starch 2.9%	12.0 ±2.7
Acacia 4.7%	11.0 ±3.8
PVP 3.6%	7.8 ±1.8
Sucrose 13.8%	7.2 ±1.8

Although gelatin 10.7% produced the hardest granule (30.2N), a limitation to its use was its relatively high viscosity and concentration. The aim was to produce a granule sufficiently hard yet retaining as high a theophylline content as possible. The hardness value for sodium carboxymethylcellulose was significantly lower (20.8N) yet the granules were sufficiently hard for fluidised bed techniques and with a much lower concentration of binder (1.5%). Therefore granules of theophylline prepared using sodium carboxymethylcellulose were considered the most suitable. These granules had a theophylline content of not less than 98% w/w.

### 3.2 FILM COATING PROCESS

Using sodium carboxymethylcellulose as binder, granules of theophylline in the size range of <1.25 mm > 0.8 mm were produced. The granules in this size range were suitable for coating and encapsulation, although for practical reasons it was only

possible to test for hardness the granules in the size range 1.25 - 2.0 mm. Batches of granules were film coated with ethylcellulose and polyethylene glycol (PEG) under the optimally controlled coating conditions shown in Table 3.3.

The composition, concentration and volume of polymer solution delivered was adjusted so as to produce three batches of granules differing in the composition and amount of coating (expressed as % w/w) as follows:

1. Ethylcellulose 5%
2. Ethylcellulose 5% + PEG 1540 2%
3. Ethylcellulose 5% + PEG 1540 5%

The ethylcellulose 10 cps used was obtained from Hercules Inc., Wilmington and the PEG 1540 from Riedel-De Haen AG, Seelze- Hannover.

**TABLE 3.3** Conditions under which the granules were film coated by fluidised bed technology (upward spray method)

Granule bed weight	50 g
Coating solution	5 - 10% w/v of total polymer in isopropanol:acetone 1:1
Solution delivery rate	8 - 10 mL/min
Atomising air pressure	1.8 - 2.0 kg/cm <sup>2</sup>
Rated value drying temperature	45°C
Drying temperature	50°C
Outlet air temperature	40°C
Fluidising air flow rate	80 - 100 m <sup>3</sup> /h

The solvents isopropanol and acetone were of analytical reagent grade. An Aero-matic AG Film Coating Dryer was utilised for the fluidised bed coating process (Muttenez, Switzerland).

### **3.3 *In Vitro* DRUG DISSOLUTION STUDIES**

#### **3.3.1 Method**

The modified USP XXI paddle method was utilised for the *in vitro* dissolution studies of theophylline from 0.5 g samples of coated granules contained in the stainless steel meshed basket. The apparatus used was a Hanson Dissolution Drive Control and Multiple Spindle Drive (Northridge Ca.) with a constant temperature water bath at  $37 \pm 0.5^\circ\text{C}$ . The dissolution medium consisted of 1 L of dilute hydrochloric acid pH 1.2, deionised water and phosphate buffers of pH 2.6 - 5.4. The paddles were rotated at a speed of  $50 \pm 1$  rpm. Suitable volumes of dissolution medium were removed at 30 minute time intervals, diluted appropriately with the dissolution medium and the absorbance measured at 271 nm using a Beckman Model 25 spectrophotometer. An equal volume of dissolution medium was added at  $37^\circ\text{C}$  in order to maintain constant volume in each case. Exhausted granules remaining in the baskets after dissolution were dried carefully on filter paper and examined by scanning electron microscopy using a JEOL JSM 840 scanning electron microscope. Samples were quench-frozen in sub-cooled nitrogen ( $< -200^\circ\text{C}$ ), freeze-fractured, sputter-coated with gold making use of a HEXLAND CT 1000 cold stage and cryo preparation accessory.

#### **3.3.2 Results and Discussion**

Dissolution profiles showing the concentration of theophylline (mg/L) against time (minutes) are shown in Fig. 3.1. Consistent with the findings of other workers



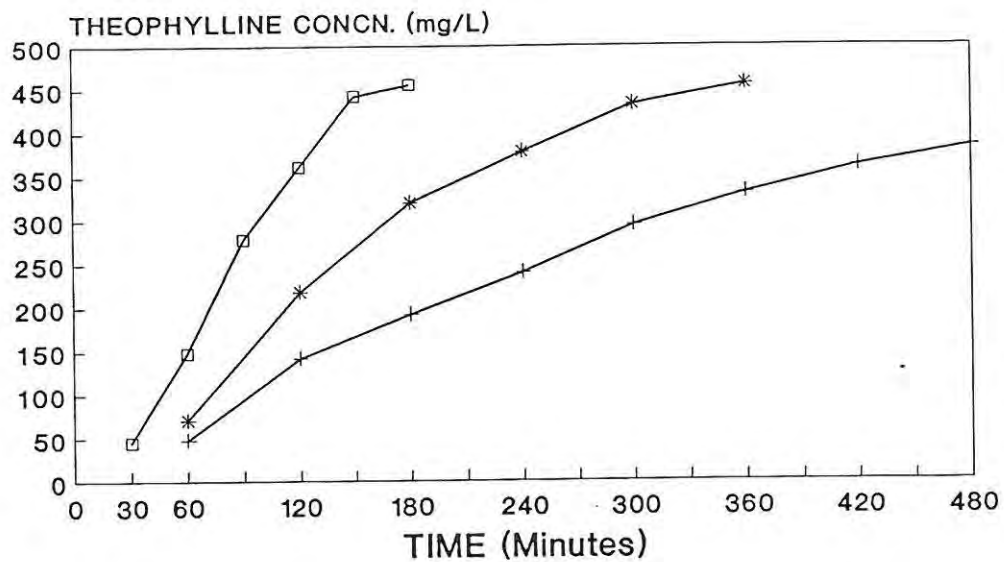
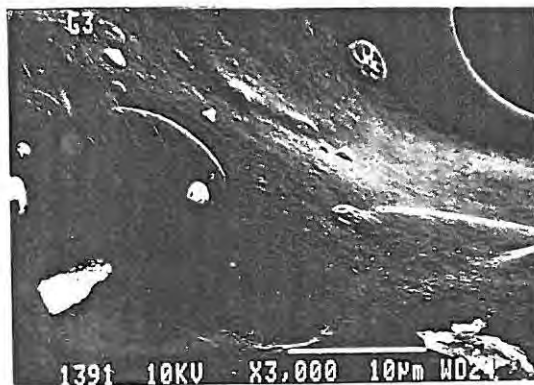


Fig 3.1 In vitro dissolution profile of theophylline from granules coated with ethylcellulose and PEG 1540 in dilute hydrochloric acid pH 1.2

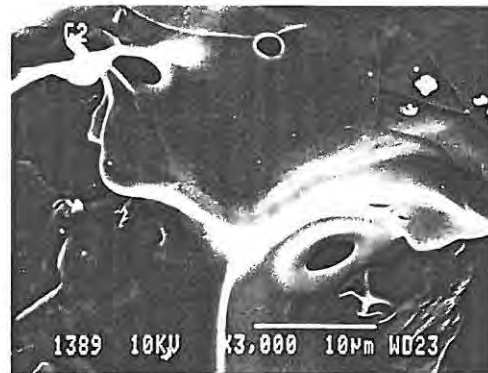
+ Ethylcellulose 5% w/w

\* Ethylcellulose 5% + PEG 1540 2% w/w

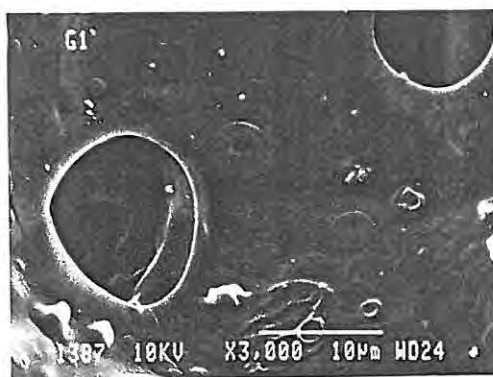
□ Ethylcellulose 5% + PEG 1540 5% w/w



A



B



C

Fig 3.2 Scanning electron micrographs of the insoluble ethylcellulose coatings remaining after dissolution testing from theophylline granules coated with:

A Ethylcellulose 5%

B Ethylcellulose 5% + PEG 1540 2%

C Ethylcellulose 5% + PEG 1540 5%

(Lippold and Förster., 1982; Donbrow and Friedman., 1975; Samuelov et al., 1979) it can be seen that the presence of PEG in ethylcellulose films significantly increases the rate of drug release through the polymeric membrane compared with that when PEG is absent. Moreover an increase in PEG concentration will directly increase the rate of release. The water-soluble PEG is rapidly leached out of the coating film producing pores or channels through which the dissolved theophylline may pass. The presence of pores is confirmed on inspection of the SEM's of the exhausted granules (See Fig. 3.2). The mechanism by which the drug molecules pass through the ethylcellulose membrane coating is by diffusion and this would account for the much slower release rate from granules coated with ethylcellulose only.

### **3.4 CAST POLYMER FILMS**

To demonstrate the geometry and nature of pores formed in films consisting of a mixture of ethylcellulose (insoluble polymer) and PEG 1540 (soluble channelizing agent) after exposure to various dissolution media, films were prepared, immersed in dissolution medium, dried and examined by scanning electron microscopy. The effect of a soluble liquid channelising agent such as polysorbate 20 was also investigated.

#### **3.4.1 Preparation**

Utilising a mixture of equal parts of acetone and isopropanol as solvents, solutions containing a mixture of ethylcellulose and PEG 1540 or polysorbate 20 at different concentrations were prepared. Table 3.4 shows the concentrations of ethylcellulose, PEG 1540 and polysorbate 20 in the solvent mixture.

**TABLE 3.4**

The concentrations of ethylcellulose, PEG 1540 and polysorbate 20 in the solvent mixture (% w/v)

	Ethylcellulose	PEG 1540	Polysorbate 20
A	3	2	-
B	5	2	-
C	10	2	-
D	3	5	-
E	5	5	-
F	10	5	-
G	3	10	-
H	5	10	-
I	10	10	-
J	5	-	-
K	5	-	5

Using a pipette 1 mL of each solution was placed into the centre of glass rings (30 mm in diameter) resting horizontally and evenly on a smooth clean glass surface. Evaporation of the solvents took place overnight (18 hours) at room temperature (16 - 19°C). The dried cast films were then carefully removed from the glass surface and two small strips measuring about 12mm x 4mm were cut from near the centre of each film. Specially designed plastic clips were used as film holders for dissolution studies.

### 3.4.2 Dissolution

The dissolution apparatus with paddle was used. One dissolution beaker contained 1 L of deionised water (pH 6.8) while the other contained 1 L of 0.1 M phosphate buffer at pH 2.3. One strip from each film was immersed in the water while the other in the phosphate buffer. The dissolution media were maintained at 37°C and the paddles rotated at 50 rpm to maintain circulation for 1 hour. As a control a film prepared from

a solution of ethylcellulose (no channelising agent) was cut similarly into strips and immersed in the dissolution media. The strips were then air-dried on filter paper and examined by scanning electron microscopy. The SEM photomicrographs are shown in Fig.3.3.

### 3.4.3 Results and Discussion

The immersion of the strips in aqueous fluid caused the soluble channelising agents, PEG 1540 and polysorbate 20, to dissolve producing pores or channels in the insoluble ethylcellulose film. In general the numerical distribution of these pores was directly proportional to the PEG concentration. An unexpected result was the tendency for thicker films to yield smaller diameter pores in comparison to the thinner films yielding larger pore diameters.

The explanation for this unexpected result is probably that the arbitrarily chosen immersion time of one hour was possibly insufficient for moisture to penetrate the thicker films and dissolve the soluble constituents completely (See Fig. 3.3 C and F which show indentations or craters on the film surface). The average approximate pore diameters and thicknesses of the films are shown in Table 3.5. In the case of the film containing polysorbate 20, a liquid channelising agent, the SEM at higher magnification (X5000) (Fig. 3.3 K) shows pores which are much more numerous but also very much smaller in diameter (0.1 - 0.4  $\mu\text{m}$ ) than the comparable film (Fig. 3.3 E) comprising ethylcellulose and PEG 1540. The film without channelising agent (Fig. 3.3 J) produced no pores at the same magnification (X3000). The pH of the dissolution medium does not appear to produce any significant difference on the size or numerical distribution of the pores. Therefore it appears that the solubility of the

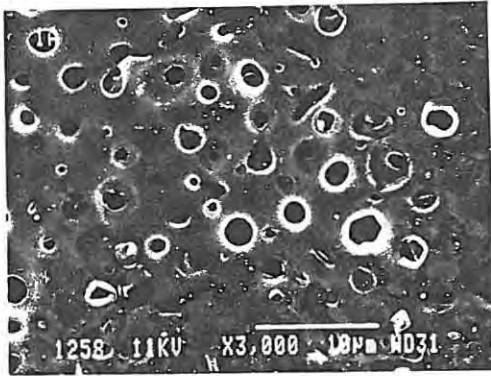
channelising agents used was not affected by the differences in the pH and composition of the medium.

**TABLE 3.5**

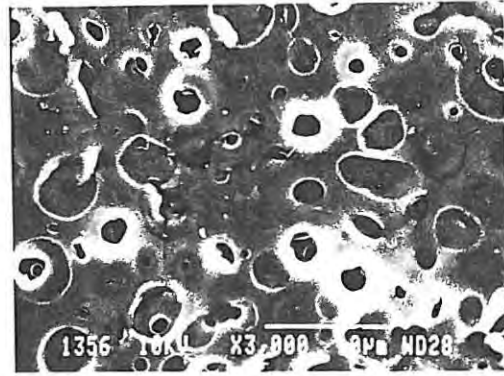
The average pore diameters ( $\pm$ S.D.) and the thicknesses of the polymer films cast from various solutions of ethylcellulose and PEG 1540 after immersion in dissolution medium

Ethylcellulose concentration (% w/v)	3	5	10
Pore diameter ( $\mu\text{m}$ )	$4.8 \pm 3.1$	$2 \pm 0.8$	$0.9 \pm 0.7$
Film thickness ( $\mu\text{m}$ )	60	85	145

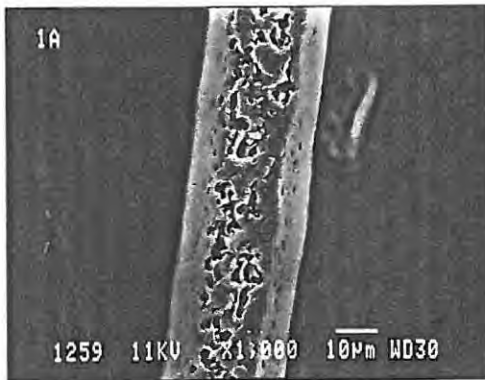
NOTE: Concentrations of 2%, 5% and 10% PEG 1540 were used in these films.



1



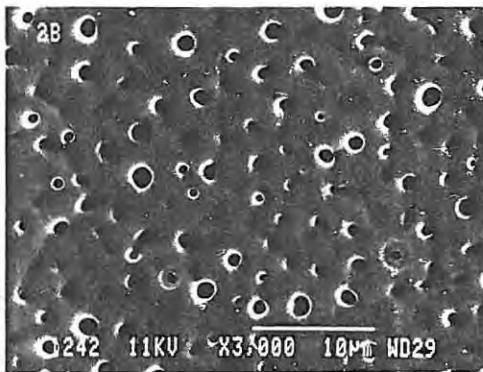
2



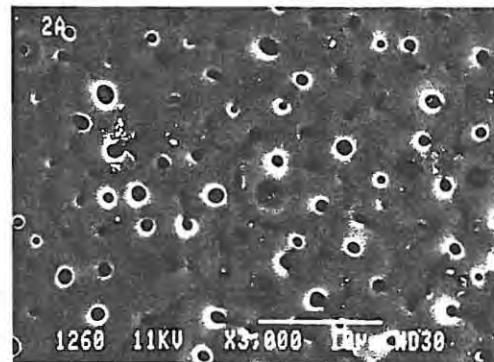
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Fig. 3.3A SEM's of cast polymer films produced from a solution of ethylcellulose 3% and PEG 1540 2% in isopropanol: acetone 1:1

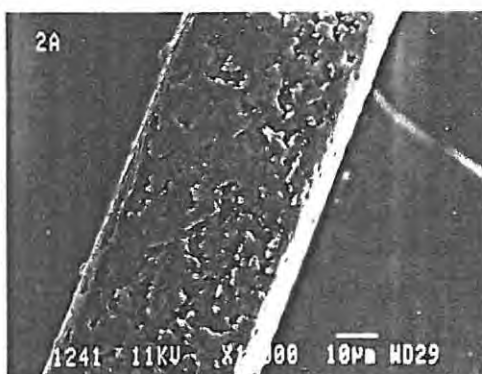
- 1 After dissolution in water (pH 6.8) - surface view
- 2 After dissolution in buffer solution (pH 2.3) - surface view
- 3 Cross section through film



1



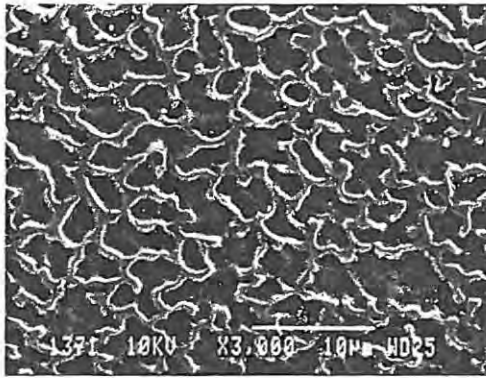
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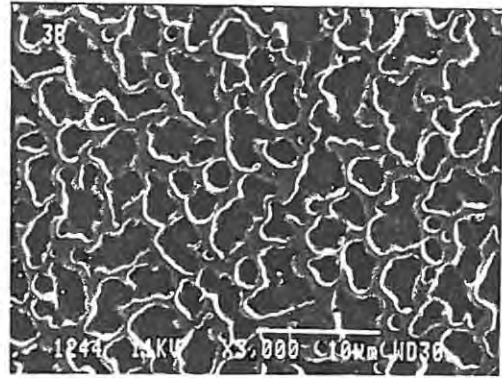
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Fig. 3.3B SEM's of cast polymer films produced from a solution of ethylcellulose 5% and PEG 1540 2% in isopropanol: acetone 1:1

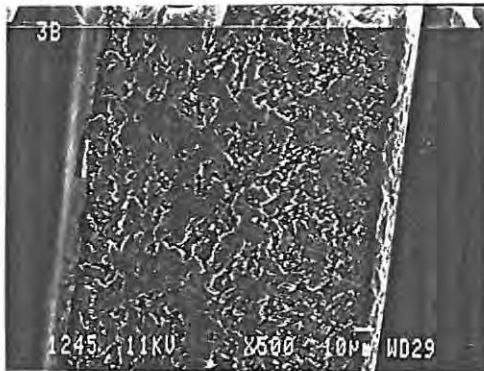
- 1 After dissolution in water (pH 6.8) - surface view
- 2 After dissolution in buffer solution (pH 2.3) - surface view
- 3 Cross section through film



1



2



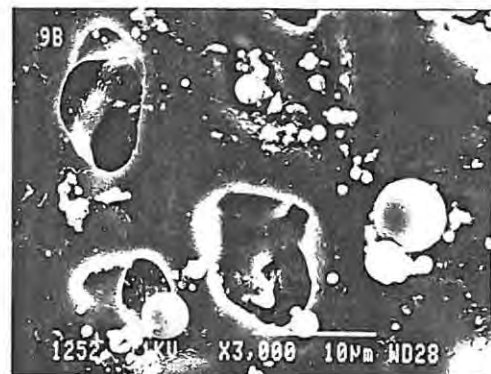
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Fig. 3.3C SEM's of cast polymer films produced from a solution of ethylcellulose 10% and PEG 1540 2% in isopropanol: acetone 1:1

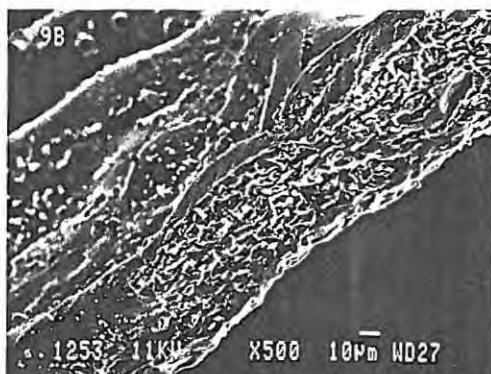
- 1 After dissolution in water (pH 6.8) - surface view
- 2 After dissolution in buffer solution (pH 2.3) - surface view
- 3 Cross section through film



1



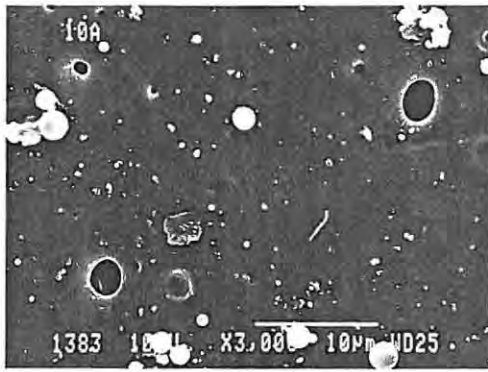
2



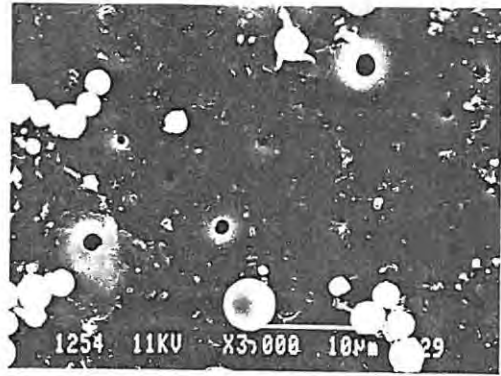
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Fig. 3.3D SEM's of cast polymer films produced from a solution of ethylcellulose 3% and PEG 1540 5% in isopropanol: acetone 1:1

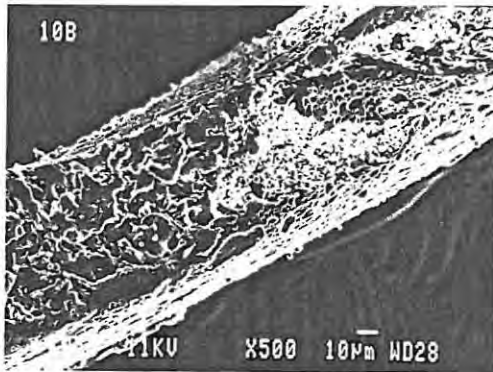
- 1 After dissolution in water (pH 6.8) - surface view
- 2 After dissolution in buffer solution (pH 2.3) - surface view
- 3 Cross section through film



1



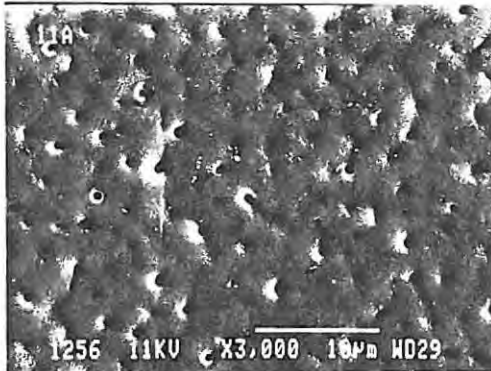
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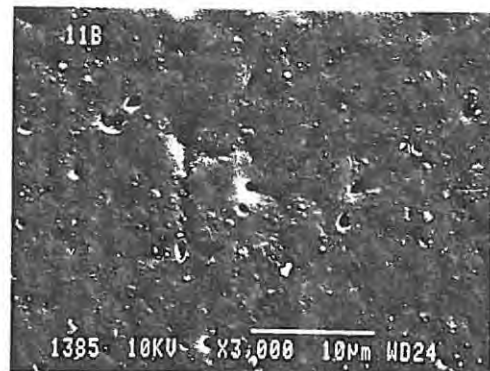
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Fig. 3.3E SEM's of cast polymer films produced from a solution of ethylcellulose 5% and PEG 1540 5% in isopropanol: acetone 1:1

- 1 After dissolution in water (pH 6.8) - surface view
- 2 After dissolution in buffer solution (pH 2.3) - surface view
- 3 Cross section through film



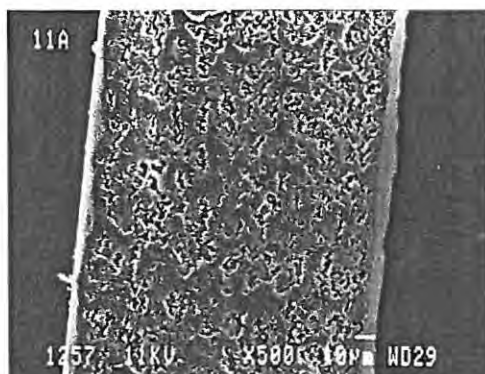
1



2

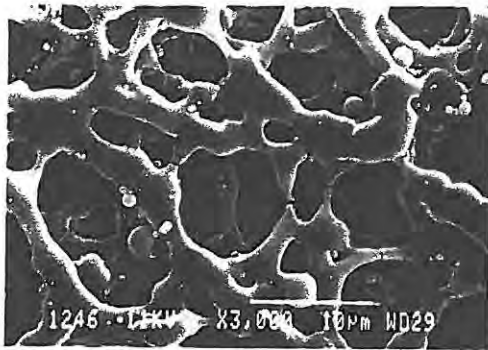
Fig. 3.3F SEM's of cast polymer films produced from a solution of ethylcellulose 10% and PEG 1540 5% in isopropanol: acetone 1:1

- 1 After dissolution in water (pH 6.8) - surface view
- 2 After dissolution in buffer solution (pH 2.3) - surface view
- 3 Cross section through film

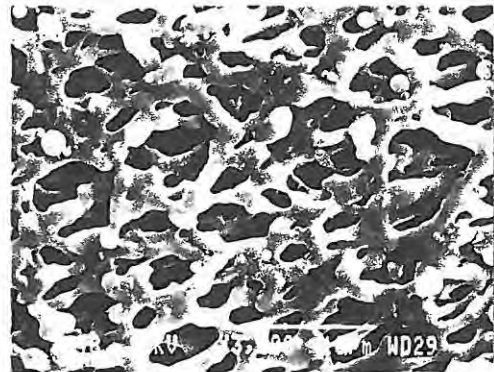


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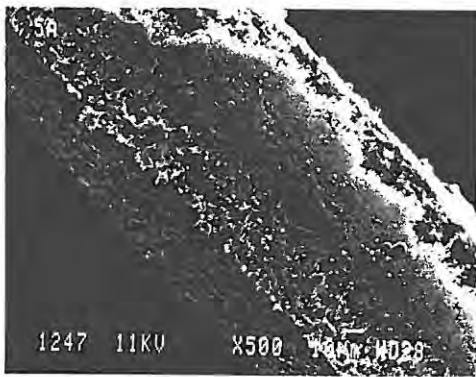




1



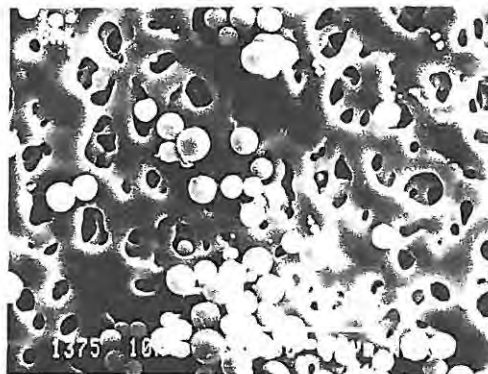
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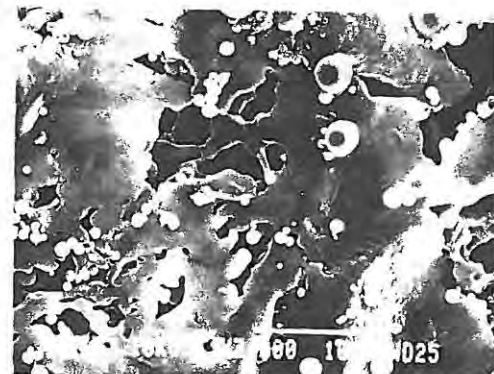
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Fig. 3.3G SEM's of cast polymer films produced from a solution of ethylcellulose 3% and PEG 1540 10% in isopropanol: acetone 1:1

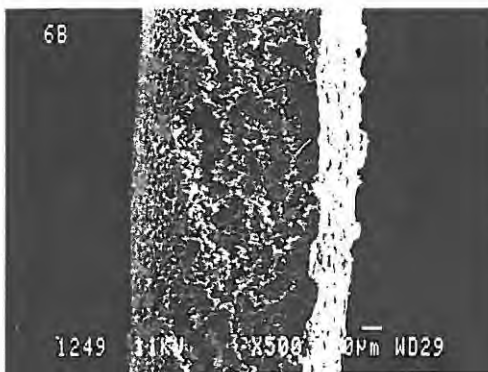
- 1 After dissolution in water (pH 6.8) - surface view
- 2 After dissolution in buffer solution (pH 2.3) - surface view
- 3 Cross section through film



1



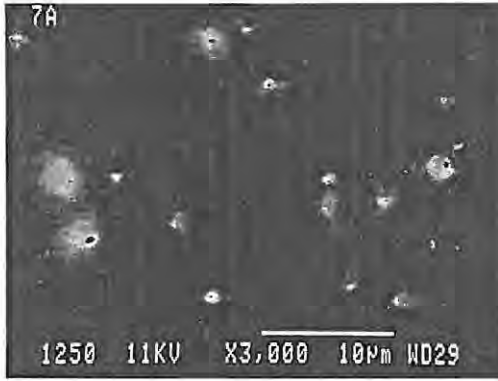
2



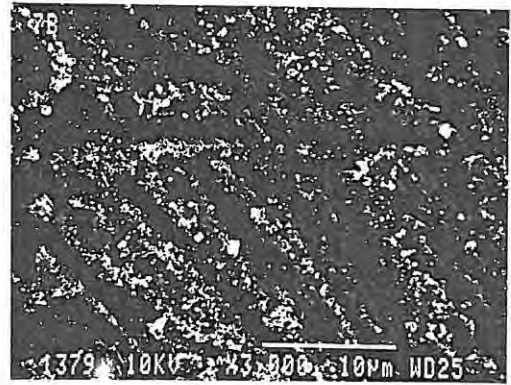
3

Fig. 3.3H SEM's of cast polymer films produced from a solution of ethylcellulose 5% and PEG 1540 10% in isopropanol: acetone 1:1

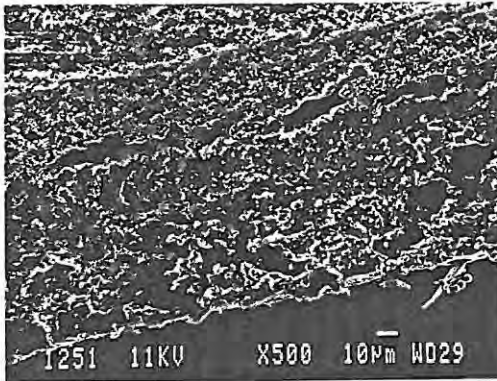
- 1 After dissolution in water (pH 6.8) - surface view
- 2 After dissolution in buffer solution (pH 2.3) - surface view
- 3 Cross section through film



1



2



3

Fig. 3.3I SEM's of cast polymer films produced from a solution of ethylcellulose 10% and PEG 1540 10% in isopropanol: acetone 1:1

- 1 After dissolution in water (pH 6.8) - surface view
- 2 After dissolution in buffer solution (pH 2.3) - surface view
- 3 Cross section through film

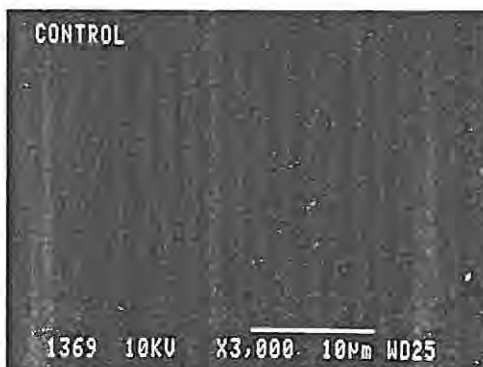


Fig. 3.3J SEM of a cast polymer film produced from a solution of ethylcellulose 5% in isopropanol:acetone 1:1 (No PEG 1540 included) Surface view after dissolution in water

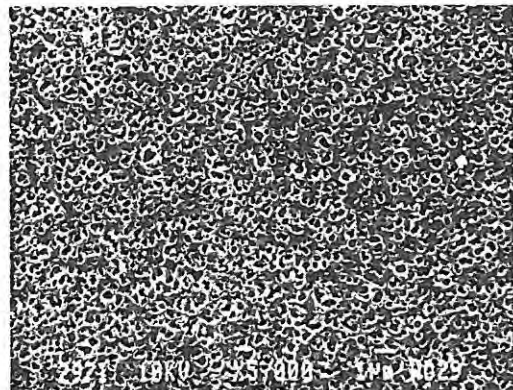


Fig. 3.3K SEM of a cast polymer film produced from a solution of ethylcellulose 5% and polysorbate 20 5% in isopropanol: acetone 1:1 Surface view after dissolution in water

### **3.5 INFLUENCE OF POLYMER COATING, DISSOLUTION MEDIUM AND pH VARIATION ON THEOPHYLLINE RELEASE FROM ENCAPSULATED GRANULES**

In recent years a number of solid orally administered dosage forms have been produced in the form of coated granules or pellets that can be enclosed in hard gelatin capsules (Lippold and Förster, 1982; Alkan et al., 1988; Kawashima et al., 1985; Motycka et al., 1985; Herman et al., 1988; Kohri et al., 1989; Suryakusuma and Jun, 1984; Mehta and Jones, 1985; Beckett et al., 1989). Coated granules or pellets possess distinct advantages over conventional dosage forms in that the release characteristics can be more precisely controlled and hence utilised in the design of modified release drug delivery systems. To achieve these ends the coating process and the evaluation of the coating is critical. The following study investigates the production of film coated granules by the direct application of ethylcellulose coatings (multilayered) to hard granules of theophylline. Ethylcellulose is a typical example of a polymer used for such a purpose as it remains intact throughout its passage through the GIT but permits the diffusion of digestive fluid. This infused fluid dissolves the drug material and then diffuses out again. The air suspension coating process has been utilised because the method is flexible, versatile and the variables can be easily controlled.

#### **3.5.1 Experimental**

Theophylline granules ( $1.6 \pm 0.4$  mm in diameter) with sufficient hardness (average 20 N) were prepared in the same manner as described in the previous section using sodium carboxymethylcellulose as binder (theophylline content not less than 98% w/w). Batches of granules were film coated (fluidised bed technology) under opti-

mally controlled conditions to maintain reproducibility (see Table 3.3 for coating conditions).

The process involved spray coating of the granules with a 5% w/v solution of ethylcellulose in equal parts of isopropanol/acetone providing final amounts of ethylcellulose coating of 5%, 10%, 12.5% and 15% w/w on the granules. Adequate drying times (15 minutes at 50°C) were allowed between successive coatings in order to achieve the final levels of coatings.

The theophylline content in each batch was determined by the method of the BP 1980 (Vol 11) under the monograph of Aminophylline tablets.

*In vitro* drug dissolution tests on 300 mg of encapsulated samples (size 0 hard gelatin capsules) were carried out using the USP XXI paddle method. The paddle speed was 50 rpm and the dissolution medium was in most instances 1 L distilled water at 37°C. Phosphate buffer (0.1 M) at three different pH's (7.5, 5.0 and 2.5) as well as acidified water (dilute HCl) at pH 5.0 and pH 2.4 were also used as dissolution media. As a control the dissolution rate of uncoated granules was also monitored. At suitable time intervals the dissolution medium was sampled, diluted appropriately and the UV absorbance measured at 271 nm. Equivalent volumes of dissolution medium were added to maintain constant volume. The experiments were carried out under identical hydrodynamic conditions.

Scanning electron micrographs of coated granules, both before and after dissolution, were made using a JOEL JSM 840 scanning electron microscope. Samples were quench-frozen in sub-cooled nitrogen (< -200°C), freeze-fractured, sputter-coated

with gold making use of a HEXLAND CT 1000 cold stage and cryo preparation accessory.

### 3.5.2 Results and Discussion

The percentage of theophylline dissolved against time in hours and the release rate (mg/hour) are represented in Figs. 3.4 and 3.5 respectively which shows the values for granules coated with an amount of 5%, 10%, 12.5% and 15% w/w of ethylcellulose. These values each represent the means of three determinations. Pseudo-steady state release of theophylline was obtained from granules coated with 15% w/w of ethylcellulose over a period of 12 hours (See Fig. 3.6). However, there was an initial lag time of 1 - 2 hours before any drug was released. This lag time was the time required for the aqueous medium to diffuse through the membrane, dissolve the drug and pass back through the membrane by diffusion. Moreover the maximum percentage of drug released over the 12 hour period for granules coated with 15% polymer was slightly less than 50%. Even after a 24 hour period only 65% of the drug was dissolved (Fig. 3.7). Despite these limitations the *in vitro* release rate from these 15% coated granules was constant over the time period 3 - 12 hours (varied in the range 17 - 28 mg/hour).

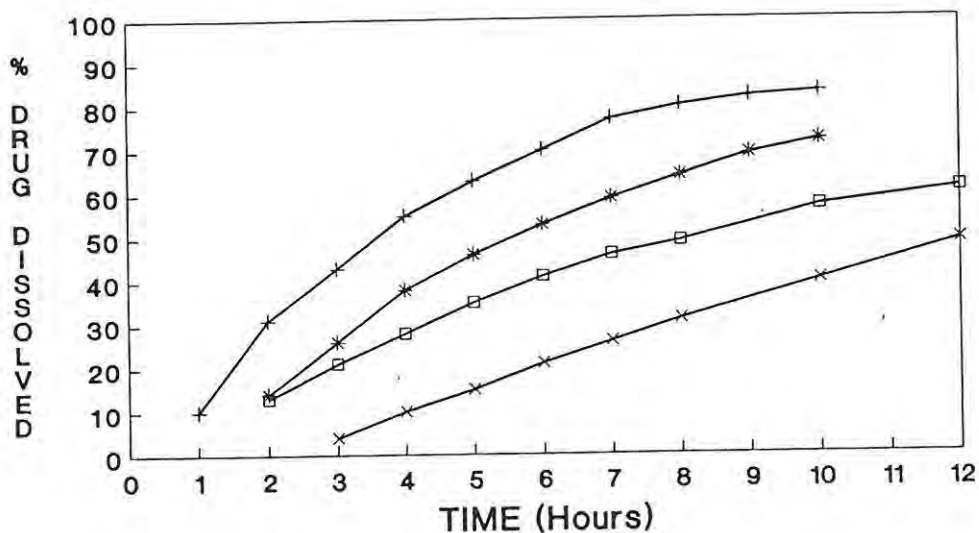


Fig 3.4 Dissolution of theophylline from granules coated with various amounts of ethylcellulose.

- + 5% w/w Ethylcellulose
- \* 10% w/w Ethylcellulose
- 12.5% w/w Ethylcellulose
- x 15% w/w Ethylcellulose

In the case of granules coated with 12.5% and 15% w/w ethylcellulose, the total amount of theophylline released within 10h did not exceed a maximum of 60% which indicates that such high concentrations should not be used unless modified by the addition of desirable channelising agents.

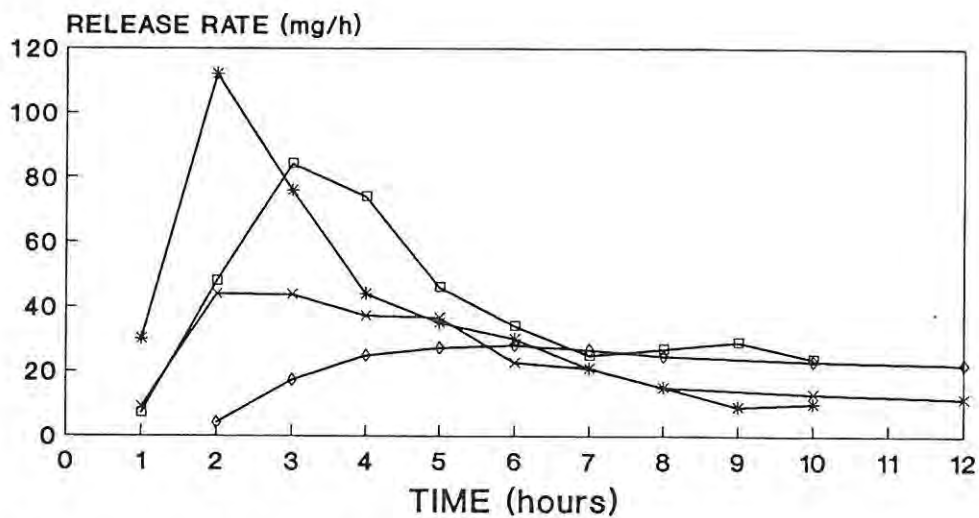


Fig. 3.5 Release rate (mg/h) of theophylline from granules coated with:

- \* 5% w/w Ethylcellulose
- 10% w/w Ethylcellulose
- x 12.5% w/w Ethylcellulose
- ◇ 15% w/w Ethylcellulose

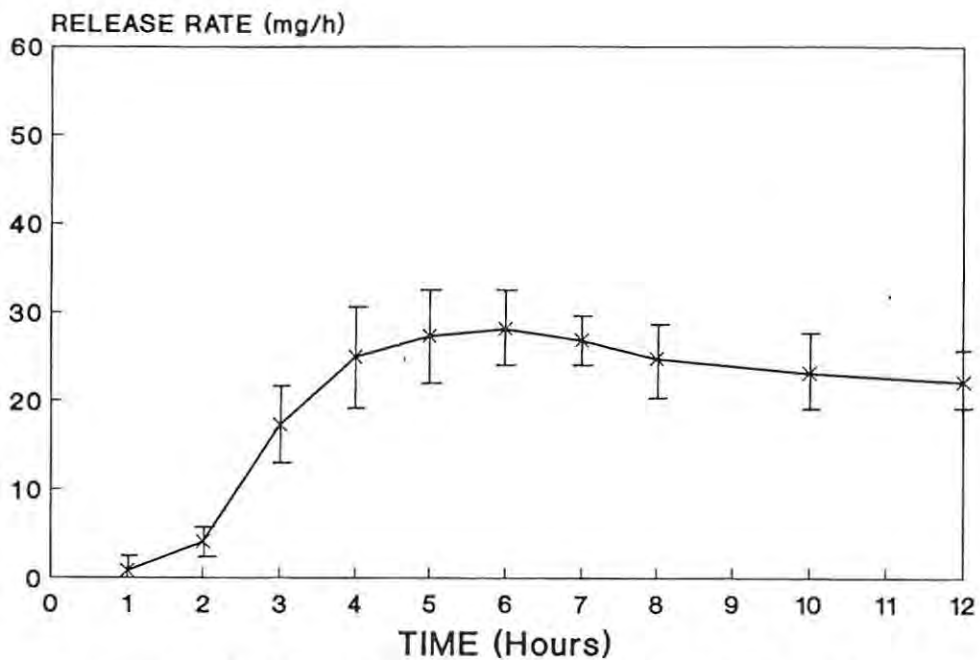


Fig. 3.6 Release rate (mg/h) of theophylline from granules coated with 15% w/w of ethylcellulose.

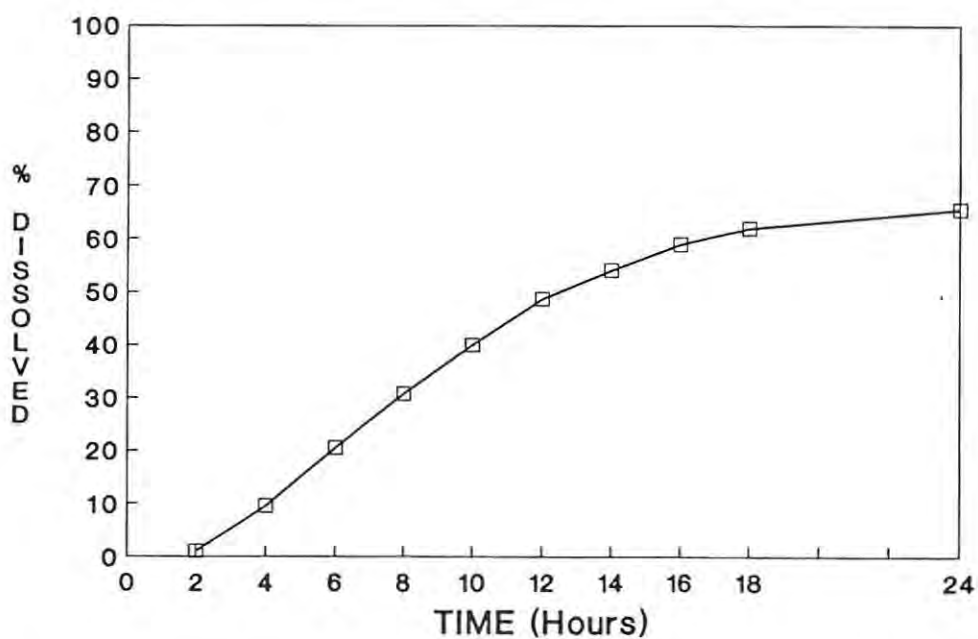


Fig.3.7 Dissolution of theophylline from granules coated with 15% w/w of ethylcellulose over a 24 hour period . No significant variations were observed from 14 hours onwards.

An attempt was made to overcome the above limitations by determining the release from granule samples consisting of a mixture of equal parts of granules coated with 5%, 10% and 15% w/w ethylcellulose. Five determinations were done and the dissolution profile showing the mean percent theophylline released with standard deviations against time (hours) is illustrated in Fig. 3.8. In this case after 10 hours nearly 70% of drug was released and a shorter lag time was shown.

The effect of the retardation of drug release from particles coated with ethylcellulose is clearly demonstrated by comparing the dissolution profile of theophylline from uncoated granules of the same mesh size. For the uncoated granules 90% dissolution was achieved after 45 minutes (Fig. 3.9).

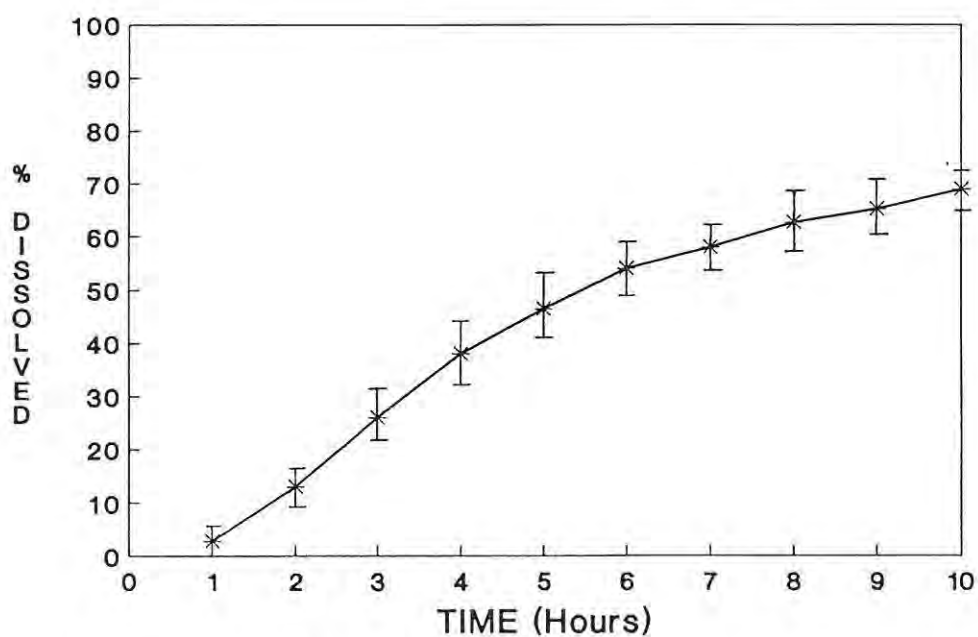


Fig. 3.8 Dissolution of theophylline from a mixture of equal parts of granules coated with 5%, 10% and 15% w/w of ethylcellulose using water as dissolution medium.



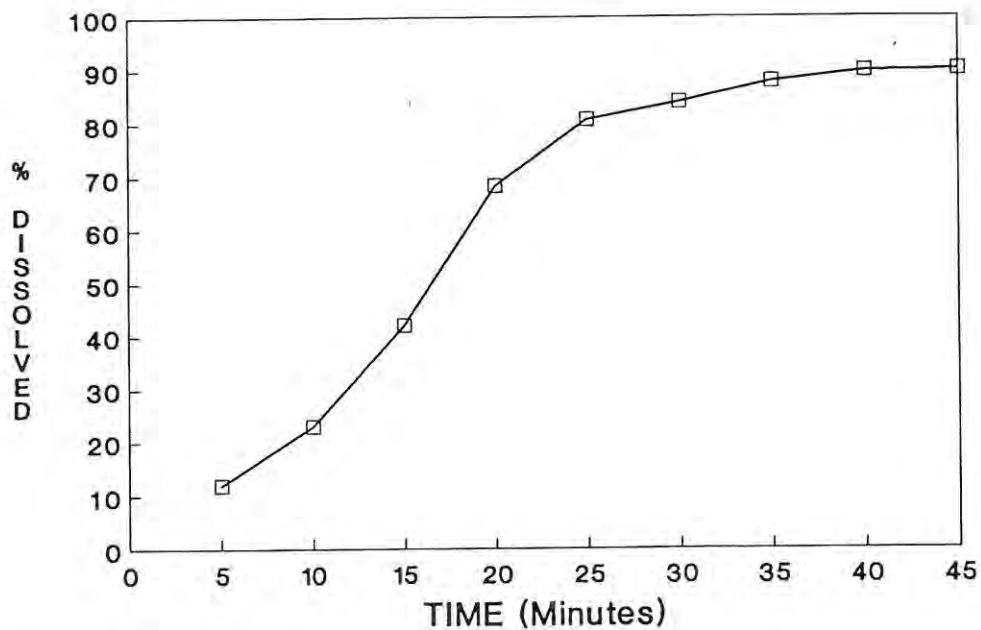


Fig. 3.9 Dissolution of theophylline from uncoated granules.

The percentages of drug released after 5 hours were obtained from the plots of percent drug dissolved versus time (hours) for each amount of coating with ethylcellulose (5%, 10%, 12.5% and 15% w/w) (see Fig. 3.10). These percentages were plotted against the amount of coating (% w/w) (Fig. 3.11). The percentage of drug released after 5 hours decreased almost linearly with increased amounts of coating material.

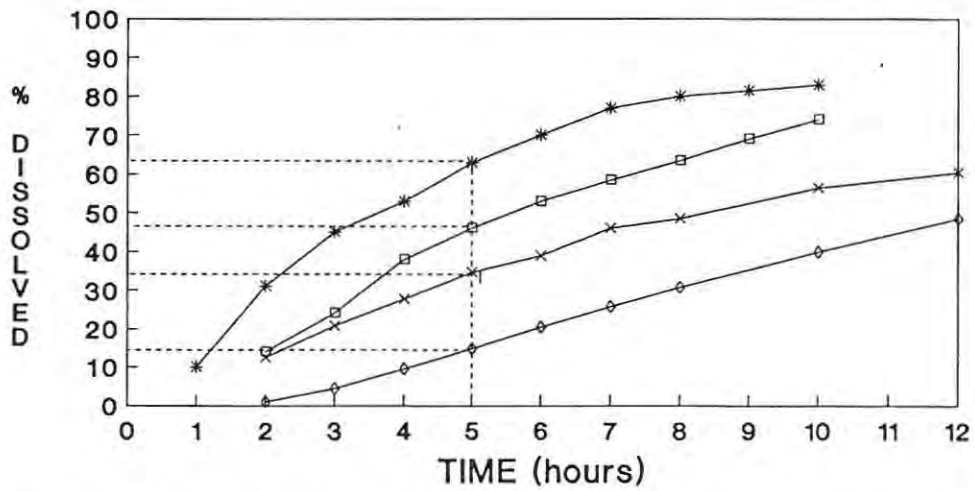


Fig. 3.10 Dissolution of theophylline from granules coated with various amounts of ethylcellulose.

\* 5% w/w ethylcellulose

□ 10% w/w ethylcellulose

x 12.5% w/w ethylcellulose

◇ 15% w/w ethylcellulose

The dotted lines show the % of drug released after 5 h.

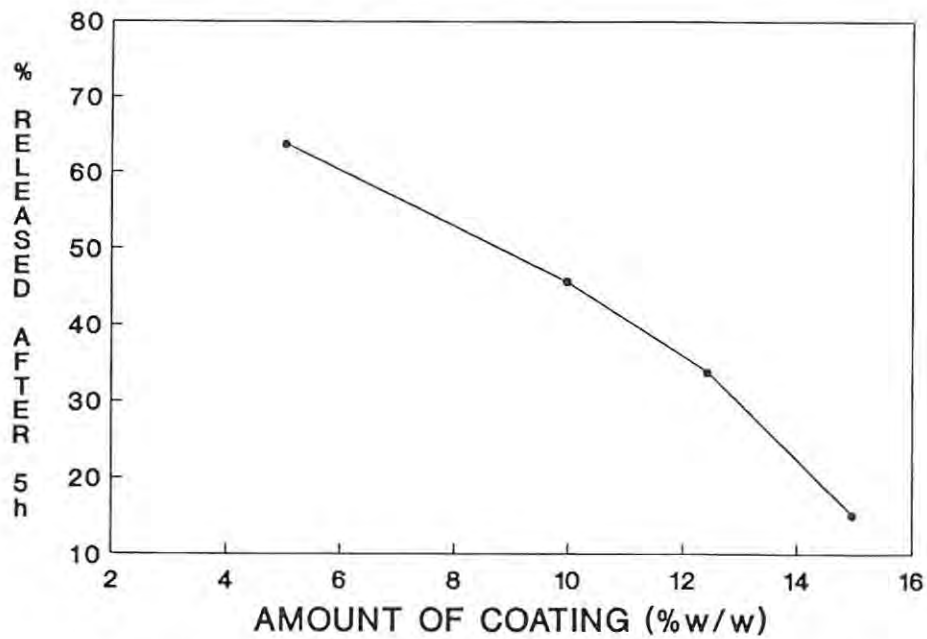


Fig. 3.11 The effect of increasing ethylcellulose coating amount on the percentage of theophylline released after 5 hours.

Experiments performed using phosphate buffer as the dissolution medium in place of distilled water produced unexpected results. The dissolution profile obtained using a sample consisting of a mixture of equal parts of granules coated with 5%, 10% and 15% w/w of polymer using 0.1M phosphate buffer at pH 5.0 as dissolution medium is shown in Fig. 3.12. Similar profiles were obtained with phosphate buffers at pH 7.5 and 2.5. It appears that the dissolution of theophylline in phosphate buffer is greatly impeded (10% was released in 8 hours). Possible reasons for the slow release of the drug through the ethylcellulose coating in phosphate buffer will be examined in detail in Chapter 6.

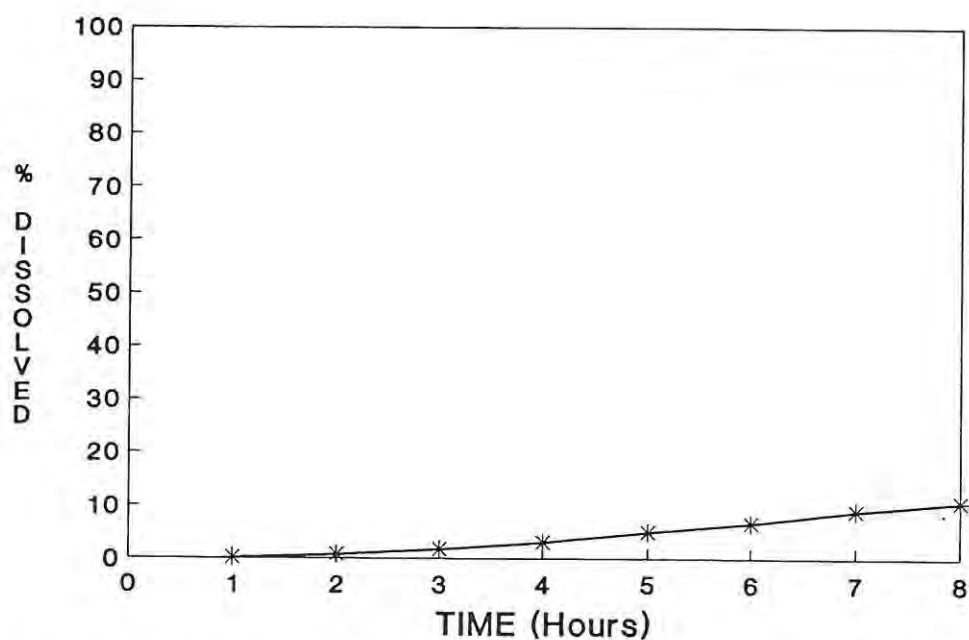
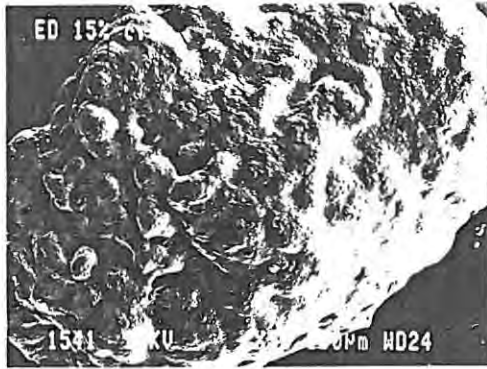


Fig 3.12 Dissolution profile obtained from an equal part mixture of coated granules (5%, 10% and 15% ethylcellulose) using 0.1M phosphate buffer pH 5.0 as dissolution medium.

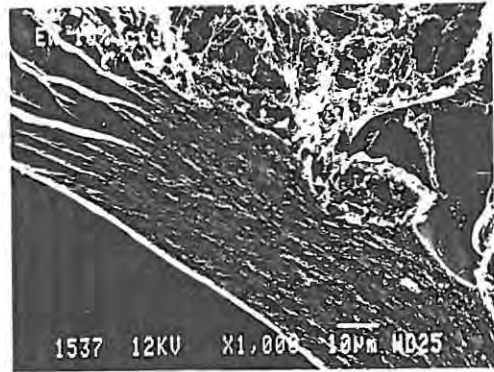
However it is necessary to point out at this stage that the reason for impeded release is not related to pH since a further similar experiment was carried out using acidified water (dilute HCl) at pH 2.0 and 5.0. In these cases the profiles obtained were similar to that achieved in distilled water. Changing the pH during the dissolution time period

also produced no hindrance to the dissolution process. During the first hour dissolution was carried out in acidified water (pH 2.4), then at pH 5.1 for a further 20 minutes and then in distilled water for the remaining period. Dissolution under these circumstances was not impeded.

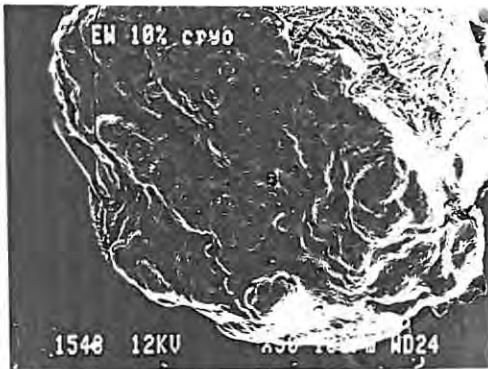
Scanning electron micrographs of exhausted granules remaining after the dissolution process are shown in Fig. 3.13. Both surface and cross sectional views are shown. The dissolution medium used was distilled water.



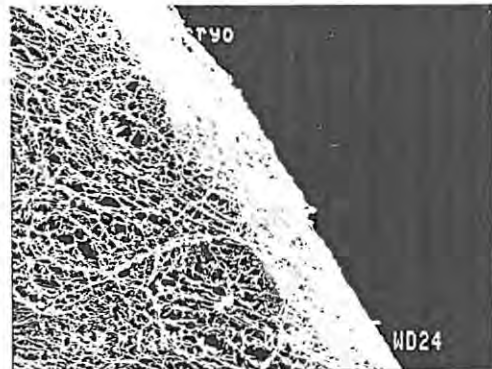
A Eth.cell. 15%  
Surface view x 50



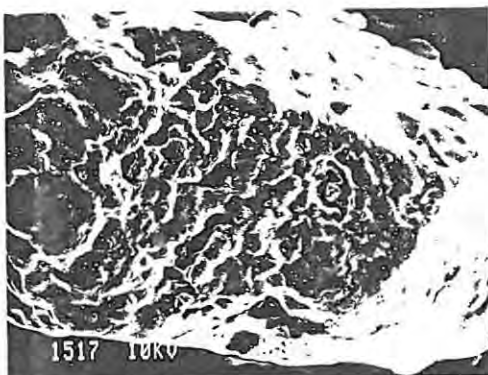
B Eth.cell. 15%  
Cross section x 1000



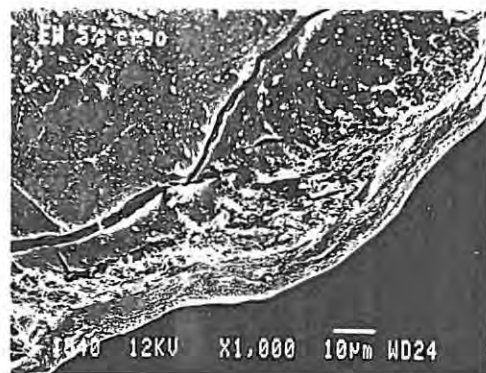
C Eth.cell. 10%  
Surface view x 50



D Eth.cell. 10%  
Cross section x 1000



E Eth.cell. 5%  
Surface view x 50



F Eth.cell. 5%  
Cross section x 1000

Fig. 3.13 Scanning electron micrographs of exhausted granules remaining after dissolution testing. The granules were coated with various amounts of ethylcellulose (expressed as % w/w).

## **CHAPTER FOUR**

## DEVELOPMENT OF THEOPHYLLINE MINI-TABLETS FOR CONTROLLED RELEASE DELIVERY: EFFECT OF COATING COMPOSITION AND DISSOLUTION MEDIUM ON RELEASE CHARACTERISTICS OF MINI-TABLETS

### 4.1 INTRODUCTION

The development of an ideal orally administered drug delivery system providing constant release of drug has been the focus of recent research activity (e.g. Källstrand and Ekman, 1983; Suryakusuma and Jun, 1984; Baveja et al., 1987). The objective is to provide constant drug delivery during passage through the gastrointestinal tract (GIT) irrespective of variations in pH, surface tension and viscosity within the GIT. In certain cases like theophylline, which has a narrow therapeutic range, constant plasma levels should be strictly maintained during the intervals between doses. Various attempts have been made to produce slow-release preparations of theophylline. Some of these have been single-unit dosage forms (SUDF) such as tablets where the drug is incorporated in a polymeric matrix (McGinity et al., 1983; Cameron and McGinity, 1987 a and b; Nakano et al., 1983; Parab et al., 1986), while others are multiple-unit dosage form (MUDF) products consisting of pellets, granules or particles which can be enclosed in gelatin capsules (Lippold and Förster, 1982; Kawashima et al., 1985; Motycka et al., 1985; Chang and Hsiao, 1989). The MUDF products have definite advantages over the SUDF (Bechgaard, 1982; Beckett, 1981). Previous attempts at developing MUDF and SUDF preparations have not achieved the ideal characteristics of zero-order release between dosage intervals over almost the entire drug content of the dosage form, as demonstrated by numerous *in vitro* dissolution tests (Simons et al., 1984; Chung and Shim, 1987; Summers et al., 1986; Buckton et al., 1988). A possible reason for non-uniform release rates of the medicament may

be due to the irregularity in shape of the pellets or granules. Every film-coated pellet or granule is different in size, shape and coating thickness, which could produce erratic release rates.

In order to regularise the coated unit in respect of size, shape and coating thickness and to determine the resulting effect on theophylline release, mini-tablets (0.3 cm diameter,  $20 \pm 1$  mg) were produced and film-coated with a variety of polymers (insoluble and soluble). The *in vitro* dissolution rate of theophylline from 20 tablets enclosed in a hard gelatin capsule was monitored at regular intervals over a 12 hour period. Differences in release profiles depending on the composition and the thickness of the polymer film are demonstrated.

## 4.2 MATERIALS AND METHODS

### 4.2.1 Chemicals

Theophylline anhydrous was received from Holpro Chemical Corporation. Sodium carboxymethylcellulose (Holpro Chemical Corporation) was the binder and magnesium stearate was the lubricant during tablet production. Ethylcellulose 10 cps (Hercules Inc., Wilmington), Eudragit<sup>®</sup> RS 100 and Eudragit<sup>®</sup> RL 100 (Röhm Pharma, Darmstadt) were chosen as the water-insoluble polymers while the water-soluble polymers included PEG 1540 (Riedel-De Haen AG, Seelze-Hannover) and Polysorbate 20 (Honeywell-Atlas, U.K.). Cellulose acetate phthalate (CAP; Eastman Chemical International, U.K.) is soluble in dilute aqueous alkalis, while Eudragit<sup>®</sup> L (Röhm Pharma) is soluble in a neutral to weakly alkaline milieu. Isopropanol and acetone (AR) were used as solvents.



#### 4.2.2 Preparation of the mini-tablets

The theophylline anhydrous powder was granulated using sodium carboxymethylcellulose in the form of a 5% w/v aqueous paste. After drying the granules were lubricated with 0.5% w/w magnesium stearate and compressed to form 3 mm diameter mini-tablets using a Manesty F3 single punch tablet machine (Manesty Machines Ltd., Liverpool) having an average hardness of 25 N and weighing  $20 \pm 1$  mg. The tablet hardness was measured using a Erweka TBH 28 Tablet Hardness Tester, F.R.G.

#### 4.2.3 Film coating of mini-tablets

Film coating using an Aeromatic AG Film Coating Dryer (bottom spray) was carried out under optimum carefully controlled conditions (see Table 4.1). Various batches of mini-tablets were coated, each differing in the composition and thickness of the polymeric coating mixture.

TABLE 4.1 Coating conditions controlled during film coating of mini-tablets by fluidised bed technology.

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Bed weight	60 g
Coating solution	5 - 8% w/v total polymer in isopropanol:acetone 1:1
Solution delivery rate	8 - 10 mL/min
Atomizing air pressure to spray	2 kg/cm <sup>2</sup>
Rated value drying temperature	55°C
Drying temperature	60°C
Outlet air temperature	45°C
Fluidizing air flow rate	100 - 120 m <sup>3</sup> /h

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#### **4.2.4 Assay for theophylline content**

The theophylline released into the dissolution medium was, after suitable dilution, assayed by UV spectrophotometric determinations of absorbance measured at 271 nm using a Beckman Model 25 Spectrophotometer (Beckman Instruments Co., Irvine).

#### **4.2.5 Drug dissolution studies**

The USP XXI paddle method was utilised for *in vitro* dissolution studies of theophylline from 20 coated mini-tablets enclosed in a hard gelatin capsule (size 0). Apparatus used was a Hanson Dissolution Drive Control and Multiple Spindle Drive (Northridge, Ca) with a constant temperature water bath at  $37 \pm 0.5^\circ\text{C}$ . Deionized water (pH 6.8), Simulated Intestinal Fluid USP XXI without pancreatin (pH 7.5) and Simulated Gastric Fluid USP XXI without enzymes (pH 1.2) at volumes of 900 mL were used as dissolution media. The paddles' rotational speed was  $50 \pm 1$  rpm. The encapsulated mini-tablet samples were contained in mesh stainless-steel baskets, which were firmly attached to the holders by means of spring steel clips. Determinations were carried out in triplicate in most cases and the mean values calculated for plotting. Suitable volumes (about 2 mL) of dissolution medium were removed at appropriate intervals, filtered through a membrane filter ( $0.22 \mu\text{m}$ ), a 1 mL aliquot diluted and the absorbance measured at 271 nm. An equal volume of dissolution medium at  $37^\circ\text{C}$  was added to maintain constant volume.

#### **4.2.6 Scanning electron microscopy**

Photomicrographs of fractured mini-tablets of different coating thickness were taken using a JEOL JSM 840 Scanning Electron Microscope at magnification 25 X and 500

X, as well as a surface view at 25 X. Samples were sputter-coated with gold prior to microscopic examination.

### 4.3 RESULTS AND DISCUSSION

The release *in vitro* of theophylline from samples of encapsulated film coated mini-tablets from batches differing in composition and thickness of the polymeric coating mixture was investigated and percent drug released as a function of time was calculated. Some batches were coated with ethylcellulose only (no channelizing agent) at amounts of 5%, 7.5% and 10% w/w, while others coated with ethylcellulose contained a water-soluble polymer (eg. PEG 1540 and polysorbate 20) as a channelizing agent in the ratio of ethylcellulose: water-soluble polymer 2:1. Batches were also coated with the insoluble but permeable polymethacrylate materials Eudragit<sup>®</sup> RL 100 and Eudragit<sup>®</sup> RS 100. No channelizing agents were incorporated in these polymethacrylate materials.

Dissolution of theophylline from mini-tablets coated with ethylcellulose only (5%, 7.5% and 10%) was not significant even after 6 hours when using deionised water as dissolution medium. The diffusion of water and drug through the ethylcellulose membrane was too slow for any meaningful release to occur. However the release of theophylline was greatly enhanced by the presence of soluble channelizing agents. The dissolution profiles for mini-tablets coated with ethylcellulose and PEG 1540 at different amounts using deionised water as dissolution medium are shown in Fig. 4.1 where the effect of thickness on the initial lag period (time for water to pass through the membrane to the drug core) is clearly demonstrated.

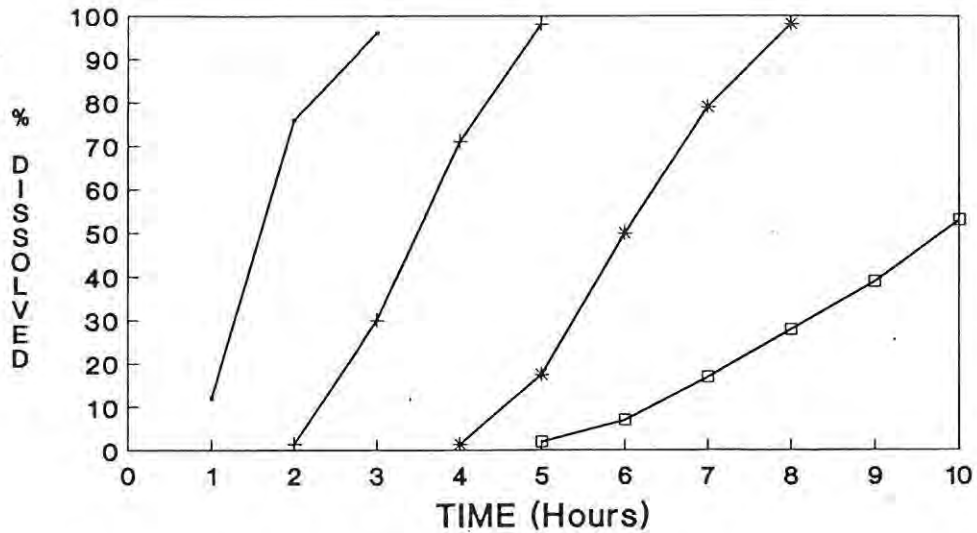


Fig. 4.1 % Theophylline dissolved as a function of time from mini-tablets coated with ethylcellulose and PEG 1540 (2:1) at amounts expressed as % w/w. Dissolution medium: water.

- ♦ Ethylcellulose 1.7% + PEG 0.85%
- + Ethylcellulose 3.3% + PEG 1.7%
- \* Ethylcellulose 5.0% + PEG 2.5%
- Ethylcellulose 5.0% (No PEG)

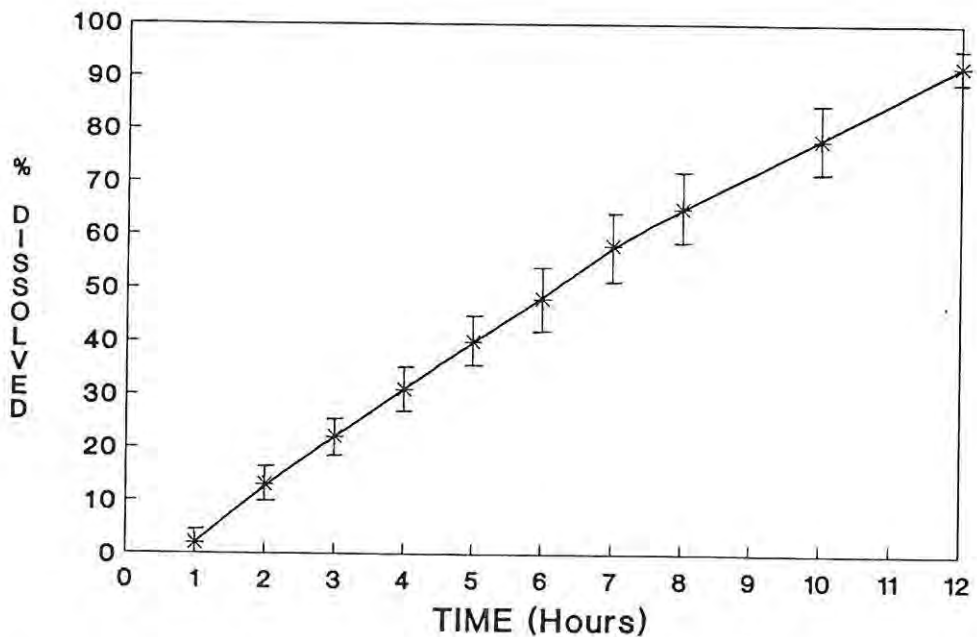


Fig. 4.2 % Theophylline dissolved as a function of time from a mixture of 20 mini-tablets coated with different amounts (% w/w) of an ethylcellulose:PEG 1540 (2:1) mixture. Vertical bars indicate approximate S.D. Dissolution medium: water. The mini-tablet mixture per capsule consisted of eth.cell. 1.7% + PEG 0.85% 2 tablets, eth.cell. 3.3% + PEG 1.7% 3 tablets, eth.cell. 5% + PEG 2.5% 6 tablets, and eth.cell. 5% (NO PEG) 4 tablets.

The initial leaching away of the soluble PEG creates channels or pores in the ethylcellulose membrane during the initial lag period during which time no significant release occurs. When the pores are formed the dissolved drug passes rapidly through into the dissolution medium until over 95% of the drug is released. The following approximate times (h) were required to achieve 95% release.

Mini-tablets coated with:

ethylcellulose 1.7% + PEG 0.85% 3 h

ethylcellulose 3.3% + PEG 1.7% 5 h

ethylcellulose 5.0% + PEG 2.5% 8 h

The mini-tablets coated with ethylcellulose 5.0% (NO PEG) released only about 50% of drug after 10 hours.

By the selection of a definite number of mini-tablets from each coating thickness making a total of 20 mini-tablets enclosed in a hard gelatin capsule (size 1), a constant release profile could be obtained (Fig. 4.2). Theophylline dissolution profiles are shown for mini-tablets coated with ethylcellulose containing Eudragit<sup>®</sup> L, CAP and polysorbate 20 (Figs. 4.3, 4.4 and 4.5 respectively). Again it appears in each instance that after an initial lag period (during which time pores are formed as a result of the leaching of the soluble component), there is a gradual release of drug into the dissolution medium up to 95% in certain instances of the total drug content. This is considerably higher than total release for some of the commercially available sustained release preparations of theophylline (eg. Simons et al., 1984). It was noted,

however, that the rate of drug dissolution into simulated intestinal fluid was significantly reduced under identical hydrodynamic conditions.

This reduction in dissolution rate may be due to molecular interaction at the core-coat interface between theophylline and the phosphate ions leading to the inhibition of the transport process. A fuller discussion of the reasons for this reduced drug release will be presented in chapter 6.

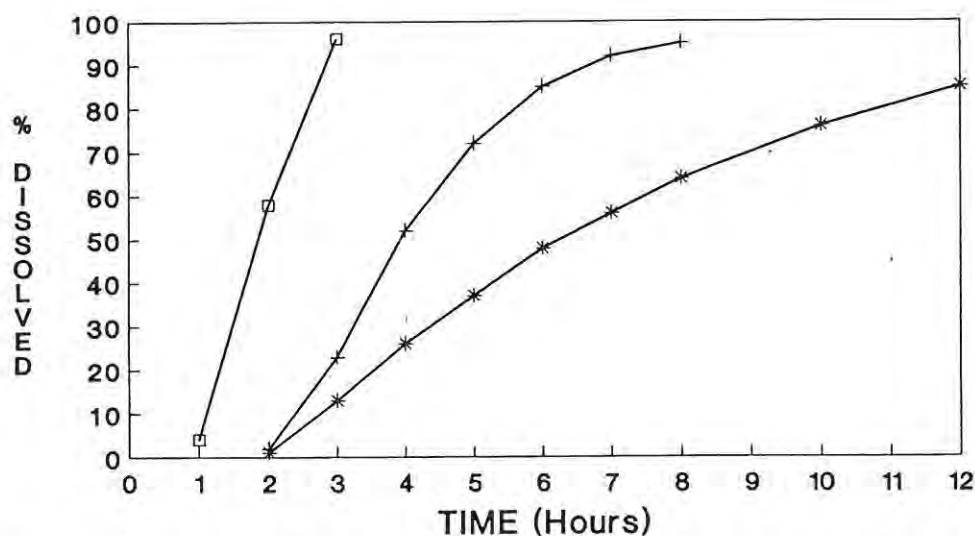


Fig. 4.3 % Theophylline dissolved as a function of time from mini-tablets coated with ethylcellulose and Eudragit<sup>®</sup>L (2:1) at amounts expressed as % w/w. Dissolution medium in parenthesis.

- Ethylcellulose 2% + Eudragit<sup>®</sup>L 1% (water)
- + Ethylcellulose 3% + Eudragit<sup>®</sup>L 1.5% (water)
- \* Ethylcellulose 3% + Eudragit<sup>®</sup>L 1.5% (Sim.Int.Fl,pH 7.5)

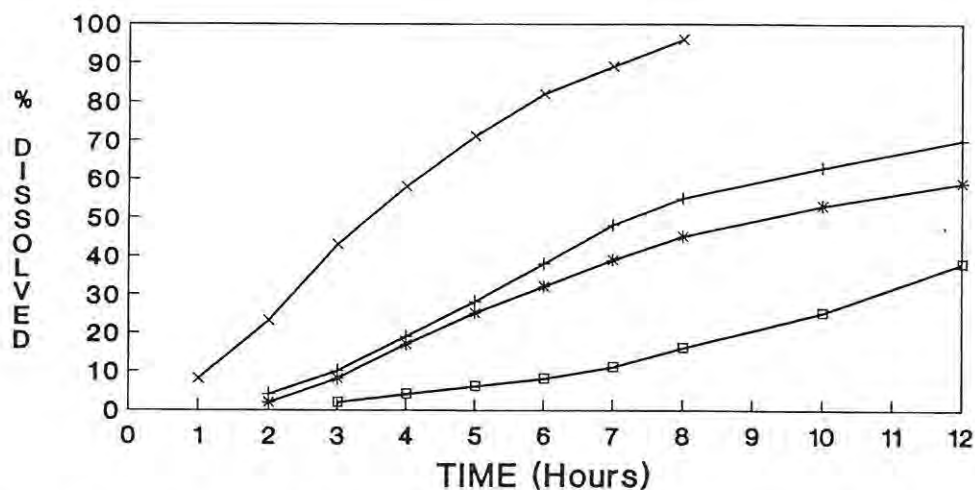


Fig. 4.4 % Theophylline dissolved as a function of time from mini-tablets coated with ethylcellulose and C.A.P. (2:1) at amounts expressed as % w/w. Dissolution medium in parenthesis.

- x Ethylcellulose 2% + C.A.P. 1% (water)
- + Ethylcellulose 3% + C.A.P. 1.5% (water)
- \* Ethylcellulose 2% + C.A.P. 1% (Sim.Int.Fl.)
- Ethylcellulose 3% + C.A.P. 1.5% (Sim.Int.Fl.)



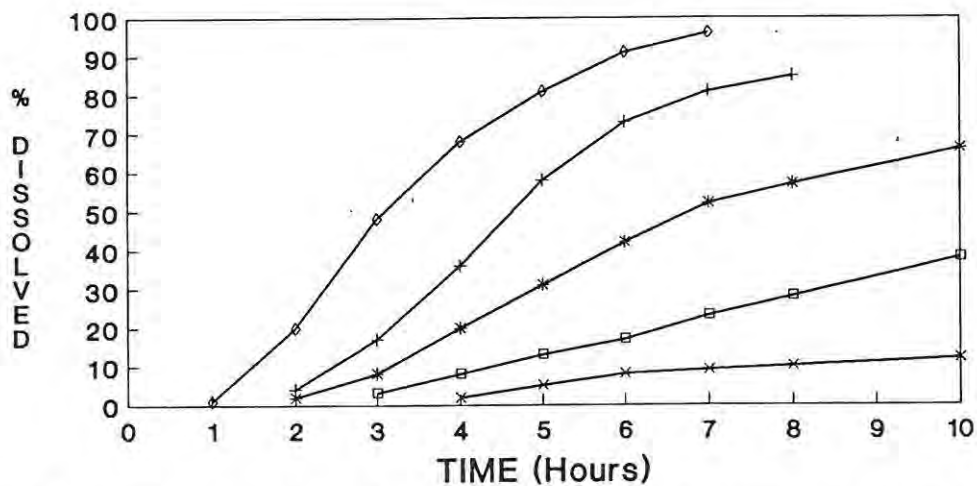


Fig. 4.5 % Theophylline dissolved as a function of time from mini-tablets coated with ethylcellulose and Polysorbate 20 (2:1) at amounts expressed as % w/w. Dissolution medium in parenthesis.

- ◇ Ethylcellulose 2% + Polysorbate 20 1% (water)
- + Ethylcellulose 3% + Polysorbate 20 1.5% (water)
- \* Ethylcellulose 4% + Polysorbate 20 2% (water)
- Ethylcellulose 2% + Polysorbate 20 1% (Sim.Int.Fl.)
- x Ethylcellulose 3% + Polysorbate 20 1.5% (Sim.Int.Fl.)

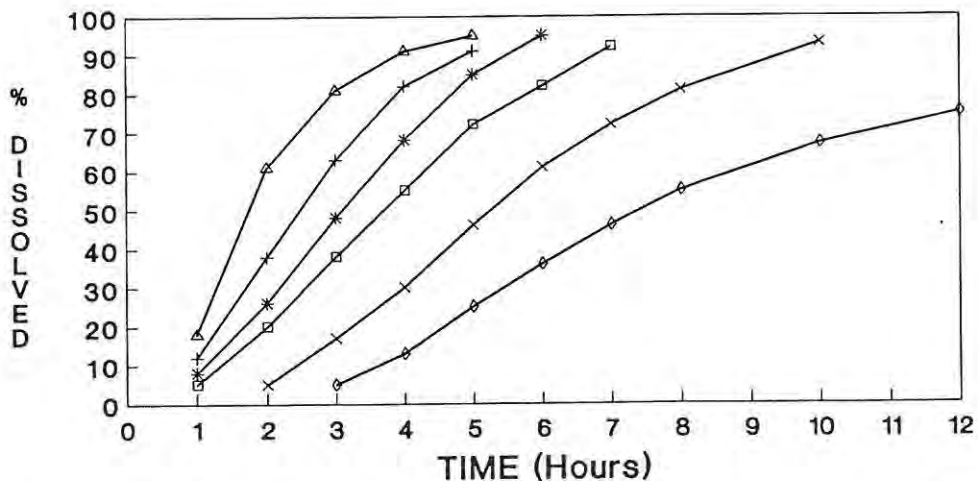


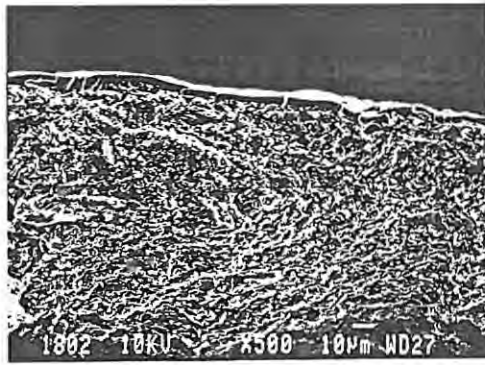
Fig. 4.6 % Theophylline dissolved as a function of time from mini-tablets coated with Eudragit<sup>®</sup> RL and RS at amounts expressed as % w/w. Dissolution medium : water.

- △ Eudragit<sup>®</sup> RL 2%
- + Eudragit<sup>®</sup> RL 4%
- \* Eudragit<sup>®</sup> RL 6%
- Eudragit<sup>®</sup> RS 2%
- x Eudragit<sup>®</sup> RS 4%
- ◇ Eudragit<sup>®</sup> RS 6%

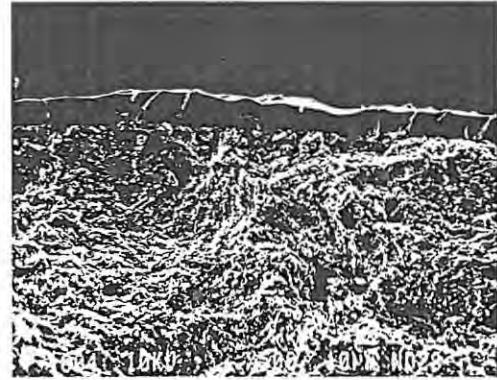
It is noteworthy that for equivalent coating amounts the mini-tablets coated with Eudragit<sup>®</sup> RL and Eudragit<sup>®</sup> RS produced dissolution curves with a shorter lag period and generally a more constant rate of release (Fig. 4.6) compared with those coated with ethylcellulose. As expected the Eudragit<sup>®</sup> RL films by virtue of the content of quaternary ammonium groups it contains are, in contrast to Eudragit<sup>®</sup> RS, freely permeable to water and dissolved drugs. The *in vitro* dissolution profile for mini-tablets coated with Eudragit<sup>®</sup> RL confirms this fact.

Electronmicrographs of Eudragit<sup>®</sup> RS - coated mini-tablets show the uniformity of the polymer film coatings around the tablet (Fig. 4.7) illustrating the reproducibility and efficiency of this coating method.

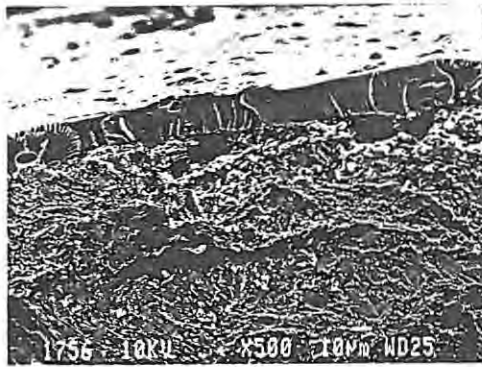
Utilising mini-tablets coated with various amounts of ethylcellulose and PEG 1540 (2:1) the dissolution of theophylline from capsules containing specifically selected numbers of film coated mini-tablets at various thicknesses was monitored. These *in vitro* dissolution profiles from various mini-tablet mixtures are shown in Figs. 4.8, 4.9, 4.10 and 4.11.



A



B



C

Fig. 4.7 SEM's of fractured mini-tablets coated with various amounts of Eudragit®RS seen in cross-sectional view. Magnification x 500.

A: 2% w/w coating

B: 4% w/w coating

C: 6% w/w coating

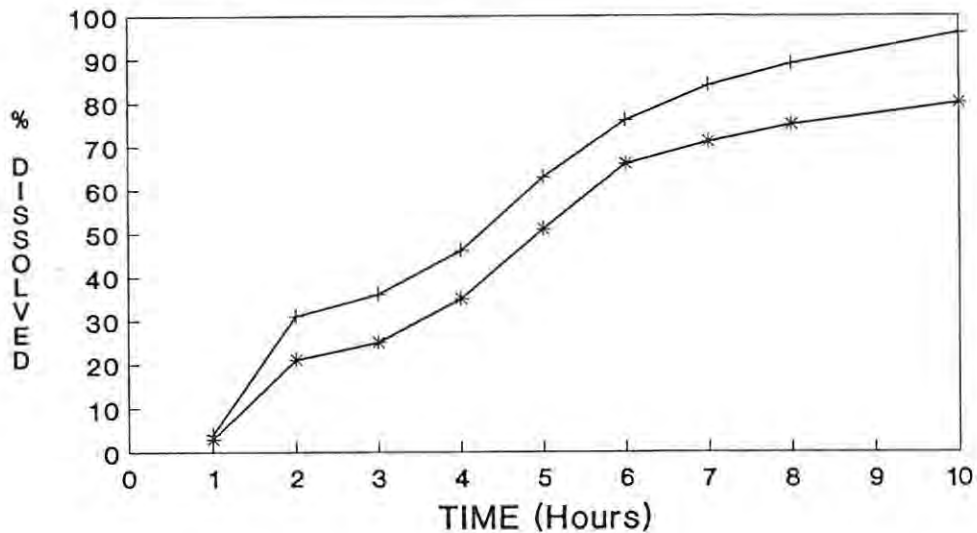


Fig.4.8 Dissolution profiles of theophylline from mini-tablet mixtures coated with ethylcellulose and PEG 1540 (2:1) in various amounts expressed as % w/w. Dissolution medium: water.

+	{	Eth.cell. 1.7% + PEG 0.85% 5 mini-tablets	*	{	Eth.cell. 1.7% + PEG 0.85% 4 mini-tablets
		Eth.cell. 3.3% + PEG 1.7% 5 mini-tablets			Eth.cell. 3.3% + PEG 1.7% 4 mini-tablets
		Eth.cell. 5.0% + PEG 2.5% 5 mini-tablets			Eth.cell. 5.0% (no PEG) 4 mini-tablets

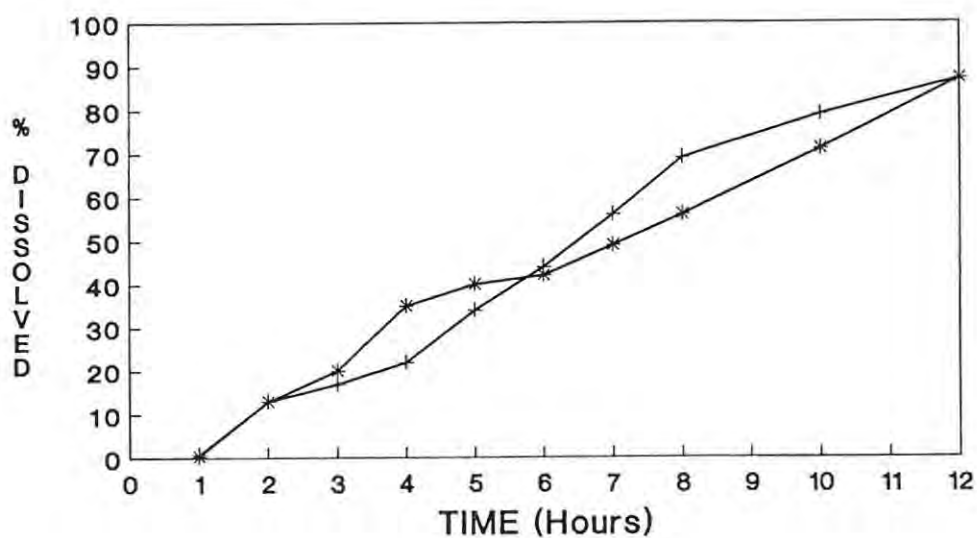


Fig. 4.9 Dissolution profiles of theophylline from mini-tablet mixtures coated with Ethylcellulose and PEG (2:1) in various amounts expressed as % w/w. Dissolution medium: water.

- |   |   |   |   |
|---|---|---|---|
| + | Eth.cell. 1.7% + PEG 0.85% 2 mini-tablets | * | Eth.cell. 1.7% + PEG 0.85% 2 mini-tablets |
|   | Eth.cell. 3.3% + PEG 1.7% 3 mini-tablets  |   | Eth.cell. 3.3% + PEG 1.7% 3 mini-tablets  |
|   | Eth.cell. 5.0% + PEG 2.5% 5 mini-tablets  |   | Eth.cell. 5.0% + PEG 2.5% 6 mini-tablets  |
|   | Eth.cell. 5.0% (No PEG) 5 mini-tablets    |   | Eth.cell. 5% (No PEG) 4 mini-tablets      |

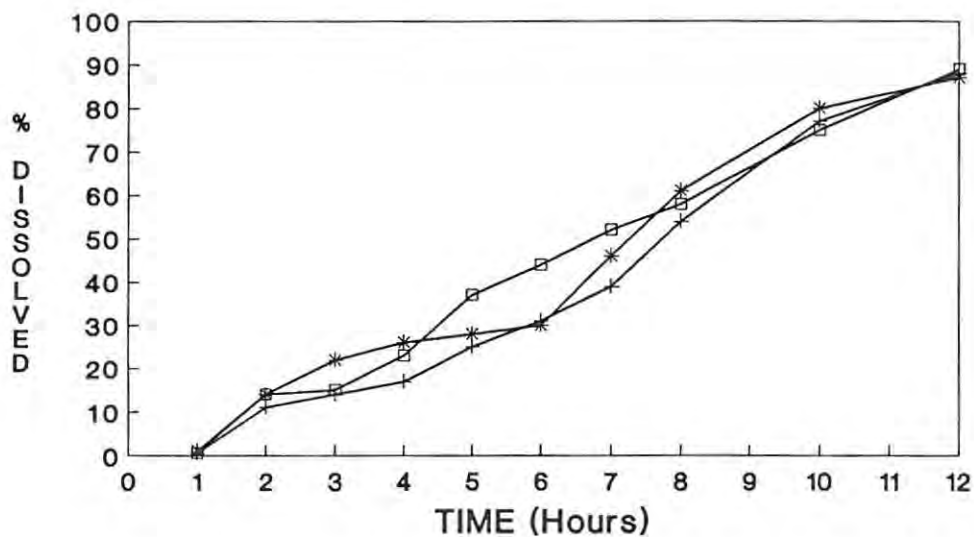


Fig. 4.10 Dissolution profiles of theophylline from mini-tablet mixtures coated with ethylcellulose and PEG (2:1) in various amounts expressed as % w/w. Dissolution medium: water.

- |   |   |   |   |   |   |
|---|---|---|---|---|---|
| * | { | Eth.cell. 1.7% + PEG 0.85% 2 mini-tablets | + | { | Eth.cell. 1.7% + PEG 0.85% 2 mini-tablets |
|   |   | Eth.cell. 3.3% + PEG 1.7% 2 mini-tablets  |   |   | Eth.cell. 3.3% + PEG 1.7% 2 mini-tablets  |
|   |   | Eth.cell. 5.0% + PEG 2.5% 5 mini-tablets  |   |   | Eth.cell. 5.0% + PEG 2.5% 4 mini-tablets  |
|   |   | Eth.cell. 5.0% (No PEG) 6 mini-tablets    |   |   | Eth.cell. 5.0% (no PEG) 7 mini-tablets    |
- 
- |   |   |   |
|---|---|---|
| □ | { | Eth.cell. 1.7% + PEG 0.85% 2 mini-tablets |
|   |   | Eth.cell. 3.3% + PEG 1.7% 3 mini-tablets  |
|   |   | Eth.cell. 5.0% + PEG 2.5% 4 mini-tablets  |
|   |   | Eth.cell. 5.0% (No PEG) 6 mini-tablets    |

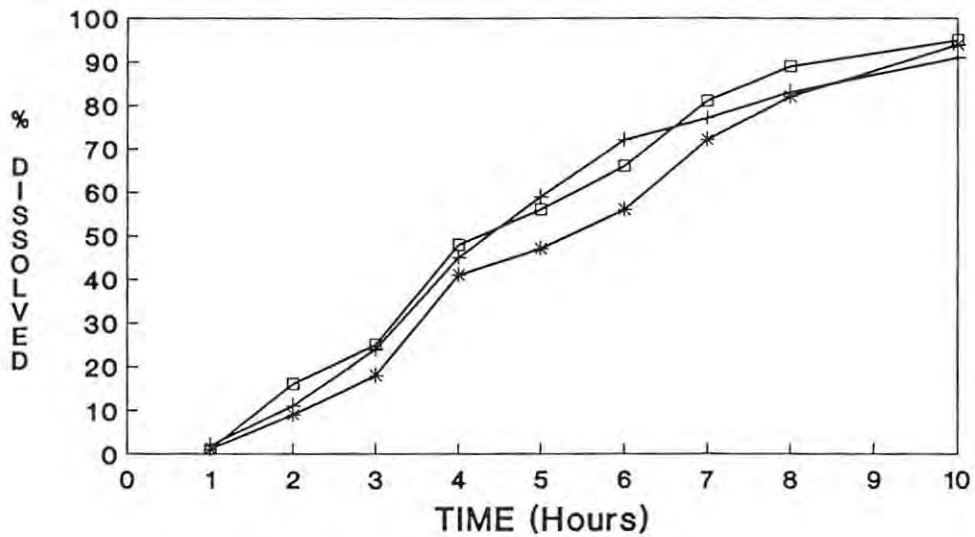


Fig. 4.11 Dissolution profiles of theophylline from mini-tablet mixtures coated with ethylcellulose and PEG (2:1) in various amounts expressed as % w/w. Dissolution medium: water.

- |   |   |   |   |
|---|---|---|---|
| + | Eth.cell. 1.7% + PEG 0.85% 2 mini-tablets<br>Eth.cell. 3.3% + PEG 1.7% 6 mini-tablets<br>Eth.cell. 5.0% + PEG 2.5% 7 mini-tablets | □ | Eth.cell. 1.7% + PEG 0.85% 3 mini-tablets<br>Eth.cell. 3.3% + PEG 1.7% 4 mini-tablets<br>Eth.cell. 5.0% + PEG 2.5% 6 mini-tablets<br>Eth.cell. 5.0% (no PEG) 2 mini-tablets |
| * | Eth.cell. 1.7% + PEG 0.85% 2 mini-tablets<br>Eth.cell. 3.3% + PEG 1.7% 5 mini-tablets<br>Eth.cell. 5.0% + PEG 2.5% 8 mini-tablets |   |   |

By carefully adjusting the exact number of mini-tablets of each thickness, various dissolution profiles can be obtained and Fig. 4.12 shows the combination producing the most constant drug release using water as dissolution medium. Similarly mini-tablets coated with various amounts of Eudragit<sup>®</sup> RS and RL were combined in certain numbers (Fig. 4.13).

Batches of mini-tablets of theophylline were also film coated with a polymeric mixture of Eudragit<sup>®</sup> RS and ethylcellulose (6:1) at three thicknesses. The dissolution profiles are shown in Fig. 4.14. Specific mini-tablet combinations of various coating thicknesses of these were also investigated (Fig. 4.13). Similarly combinations of Eudragit<sup>®</sup> RL and ethylcellulose (3:1) were prepared and dissolution profiles produced (Fig. 4.15).

Dissolution tests were also carried out under the same hydrodynamic conditions on a commercially available controlled release preparation (Theo-Dur<sup>®</sup> tablets 300 mg and 200 mg) (Figs. 4.16 and 4.17). In these cases the release was up to about 70% of the total drug content after 12 hours. Moreover the release appeared to be biphasic, an initial peak at 1 hour and then a second at 8 hours. When simulated intestinal fluid (pH 7.5) was used as the dissolution medium in place of water, the rate at which the theophylline was released was significantly greater (see Fig. 4.17). This may be due to the fact that theophylline is more soluble in an alkaline medium.

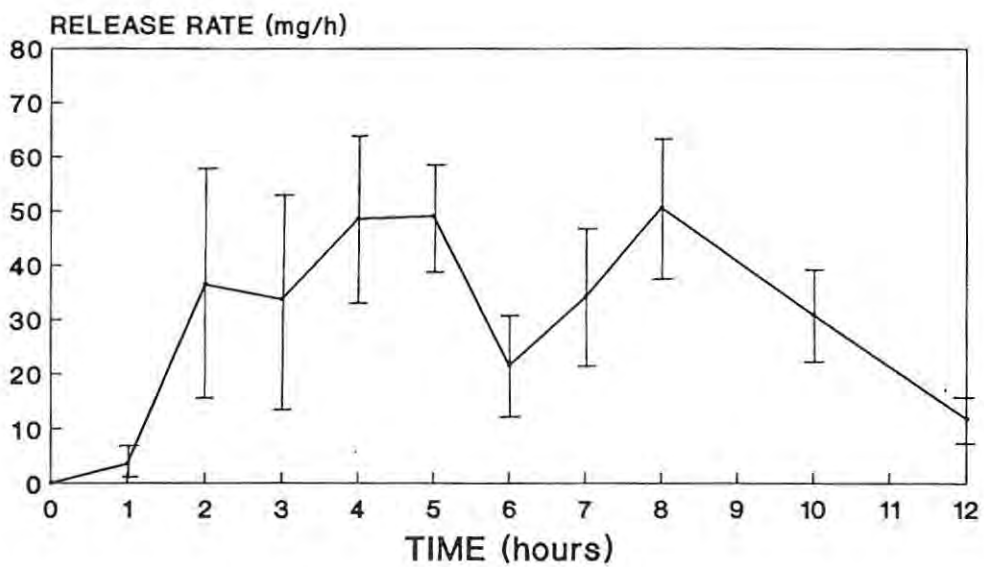
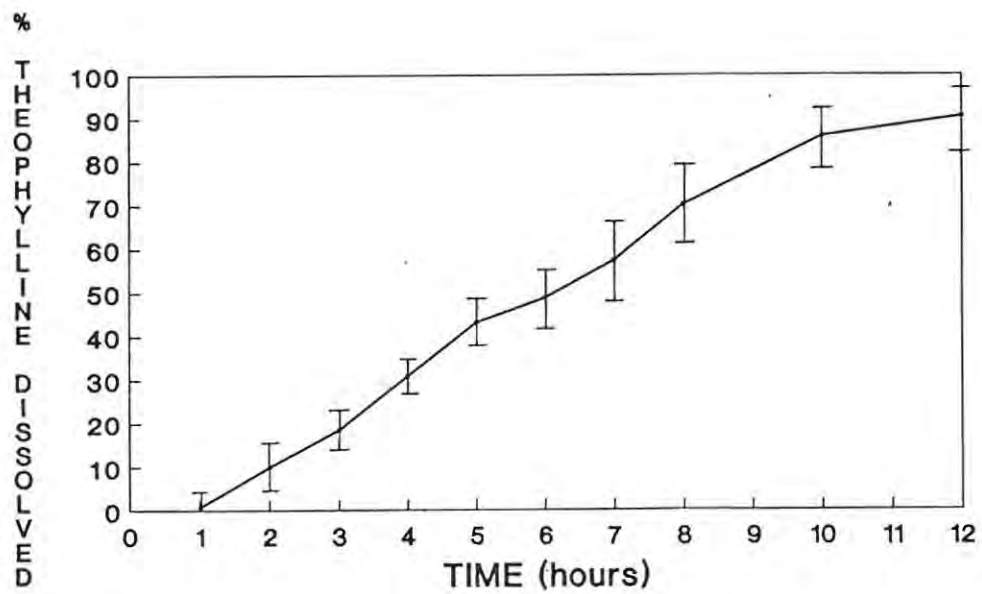


Fig. 4.12 Dissolution profiles of theophylline from mini- tablet mixture coated with ethylcellulose and PEG (2:1) in various amounts expressed as % w/w. Dissolution medium: water. Vertical bars indicate approximate S.D.

Ethylcellulose 1.7% + PEG 0.85% 2 mini-tablets

Ethylcellulose 3.3% + PEG 1.77% 4 mini-tablets

Ethylcellulose 5.0% + PEG 2.5% 4 mini-tablets

Ethylcellulose 5.0% (No PEG) 5 mini-tablets



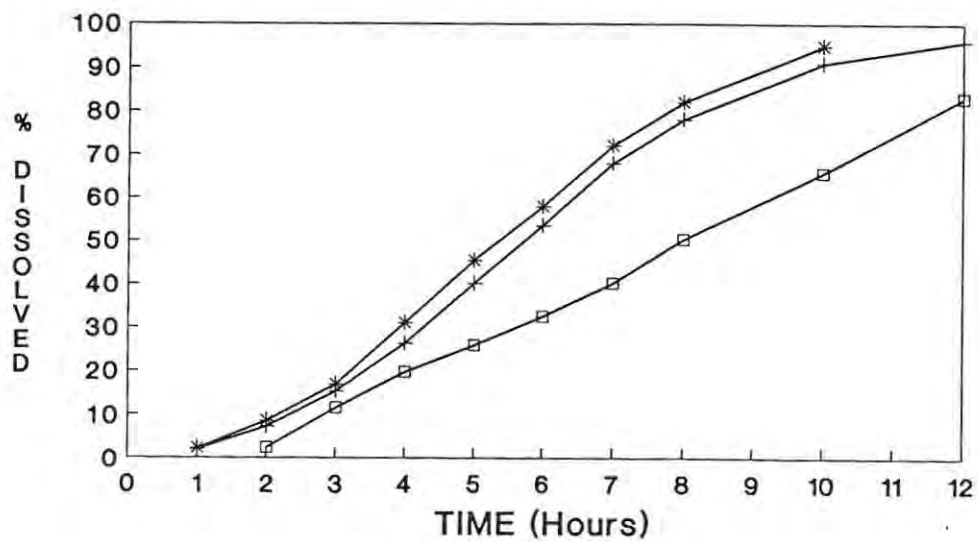


Fig. 4.13 Dissolution profiles of theophylline from mini-tablet mixtures coated with Eudragit® RS, Eudragit® RL and Eudragit® RS + Ethylcellulose (6:1) in various amounts expressed as % w/w. Dissolution medium: water.

\* { Eudragit® RL 6% 4 mini-tablets; and  
Eudragit® RS 4% 16 mini-tablets

□ { Eudragit® RS 2% + Eth.cell. 0.33% 4 mini-tablets  
Eudragit® RS 4% + Eth.cell. 0.67% 16 mini-tablets

\* { Eudragit® RL 6% 5 mini-tablets; and  
Eudragit® RS 4% 15 mini-tablets

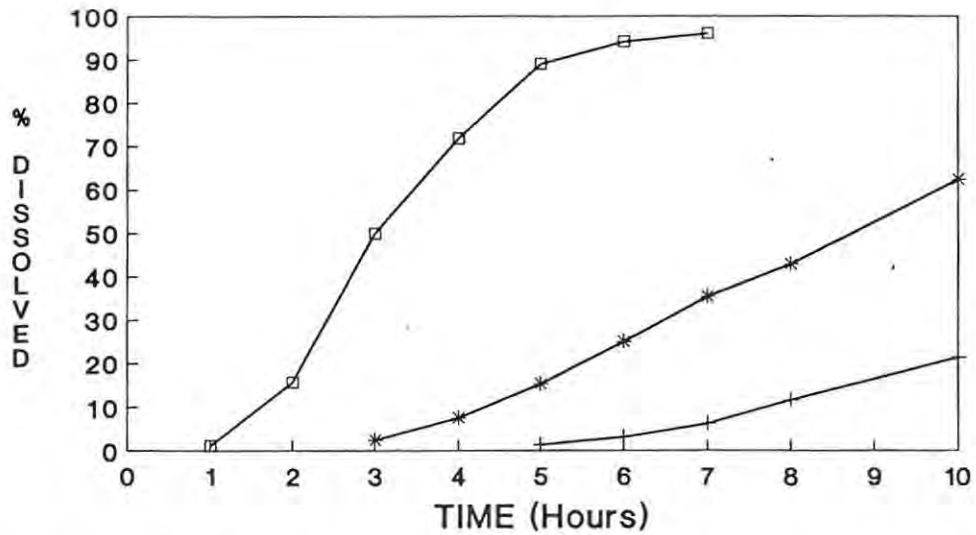


Fig. 4.14 Dissolution profiles of theophylline from mini- tablets coated with mixture of Eudragit<sup>®</sup>RS and Ethylcellulose (6:1) in various amounts expressed as % w/w. Dissolution medium: water.

- +Eudragit<sup>®</sup>RS 6% + Ethylcellulose 1%
- \*Eudragit<sup>®</sup>RS 4% + Ethylcellulose 0.67%
- Eudragit<sup>®</sup>RS 2% + Ethylcellulose 0.33%

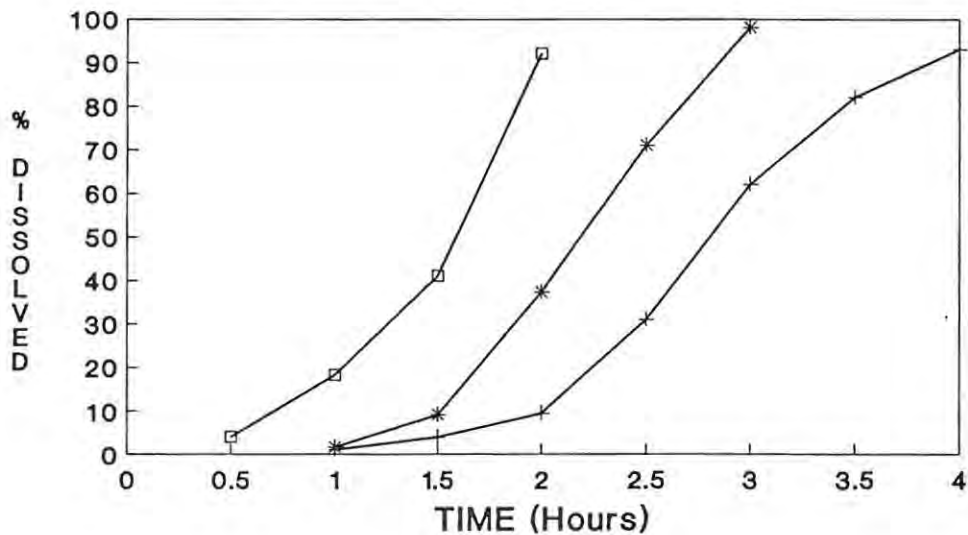


Fig. 4.15 Dissolution profiles of theophylline from mini- tablets coated with a mixture of Eudragit<sup>®</sup>RL and Ethylcellulose (3:1) in various amounts expressed as % w/w. Dissolution medium: water.

- +Eudragit<sup>®</sup>RL 6% + Ethylcellulose 2%
- \*Eudragit<sup>®</sup>RL 4% + Ethylcellulose 1.33%
- Eudragit<sup>®</sup>RL 2% + Ethylcellulose 0.67%

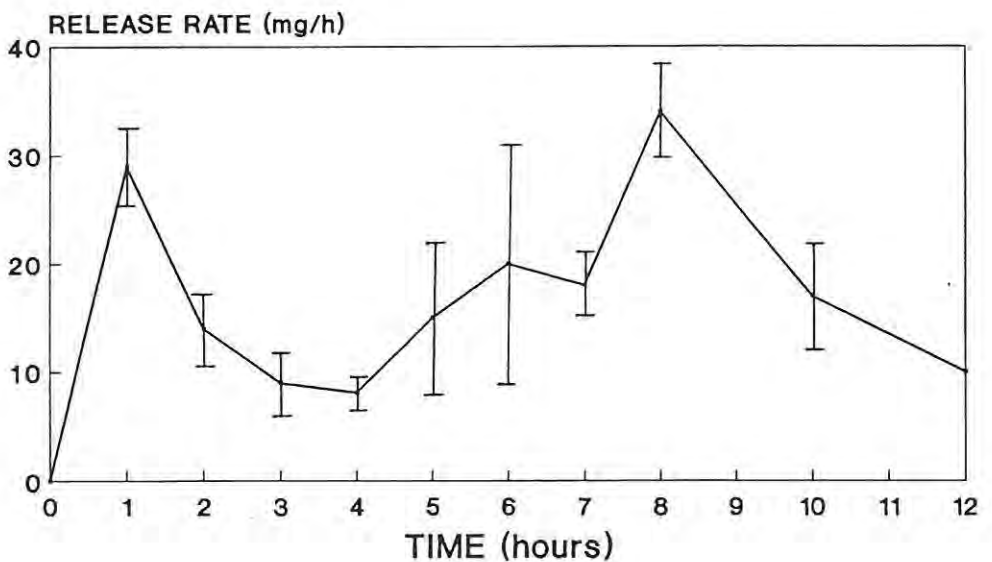
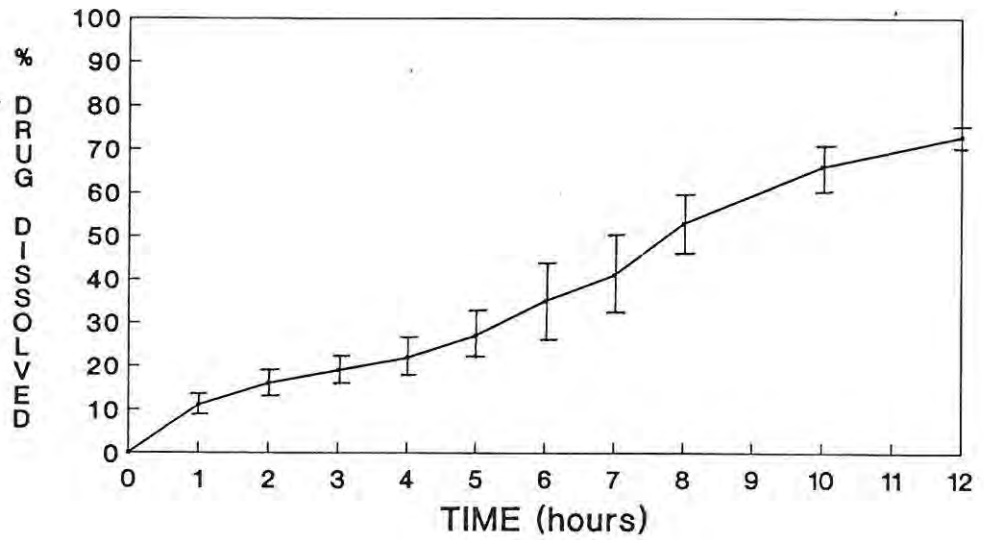


Fig. 4.16 Dissolution profiles of theophylline (% released and release rates) from Theo-Dur<sup>®</sup> 300 mg tablets. Vertical bars indicate approximate S.D. Dissolution medium: water.

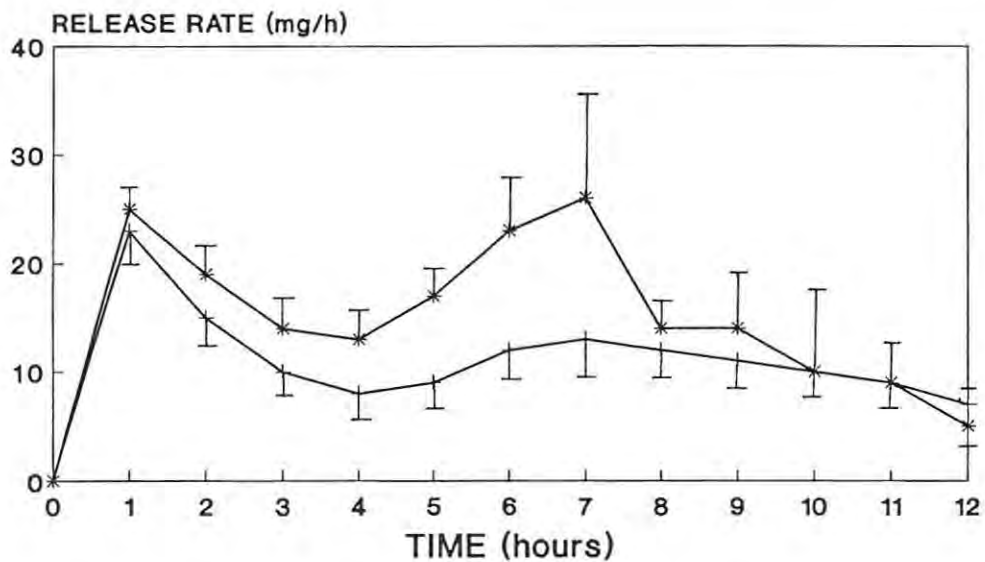
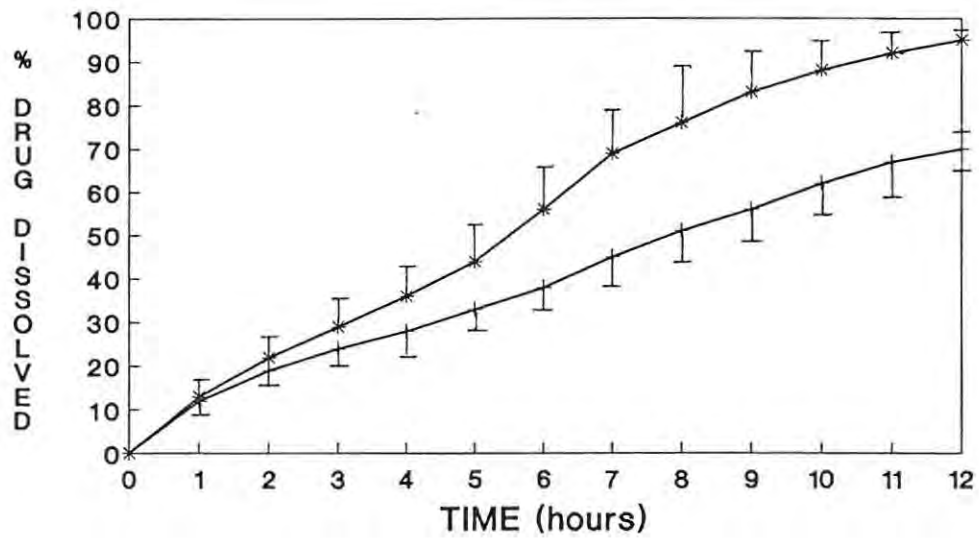


Fig. 4.17 Dissolution profiles of theophylline from Theo-Dur<sup>®</sup> 200 mg tablets. Vertical bars indicate approximate S.D.

+ Percentage drug dissolved and release rate (mg/h) using water as dissolution medium

\* Percentage drug dissolved and release rate (mg/h) using simulated intestinal fluid U.S.P. (pH 7.5) as dissolution medium.

Plain, uncoated mini-tablets were compressed to various hardnesses (25 N, 15 N and 10 N) to investigate the effect of compression force on the dissolution rate. The differences in dissolution rate were so slight that it was concluded that hardness was not a significant factor influencing the dissolution of theophylline from the mini-tablets. The dissolution curve for mini-tablets with a hardness of 25 N is shown in Fig. 4.18 .

It is expected that not every film coated mini-tablet will release the drug at exactly the same rate within a particular batch due to slight imperfections or unevenness of coating in individual mini-tablets. To assess the degree to which each mini-tablet varied in this respect, *in vitro* dissolution tests were carried out on individual mini-tablets film coated with ethylcellulose 3.3% w/w and PEG 1540 1.7% w/w and the  $t_{10\%}$  (time for 10% of drug release in minutes) of each mini-tablet was determined (see Fig. 4.19). The  $t_{10\%}$  of the most rapid releasing mini-tablet was about 90 minutes while the slowest was about 150 minutes (mean  $120.6 \pm 22$  minutes). This demonstrates significant variability between individual mini-tablets, however in a hard gelatin capsule containing 20 mini-tablets these differences may not be significant.

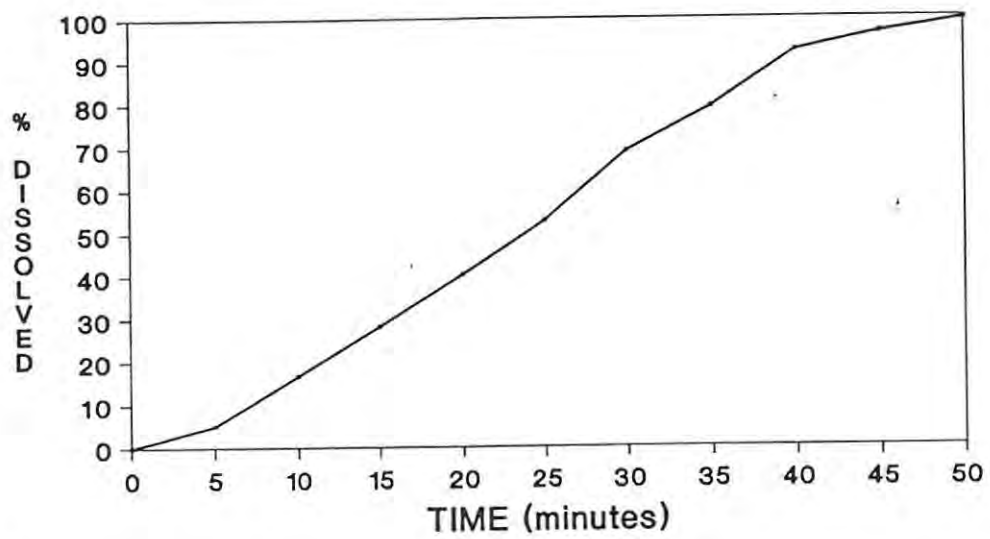


Fig. 4.18 Dissolution profile of theophylline from uncoated mini-tablets compressed to a hardness of 25 N.

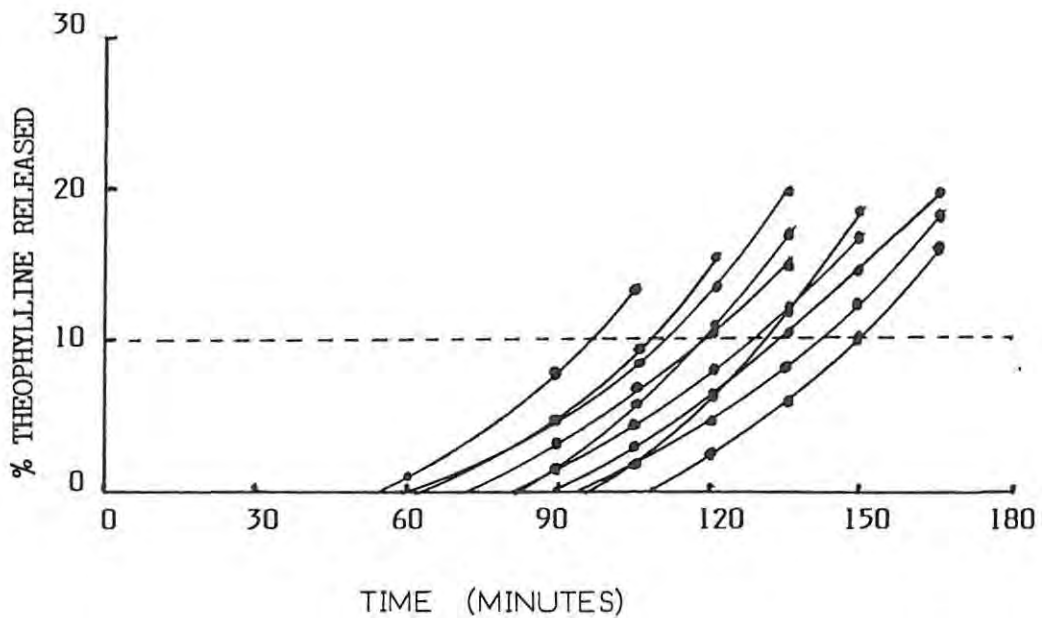


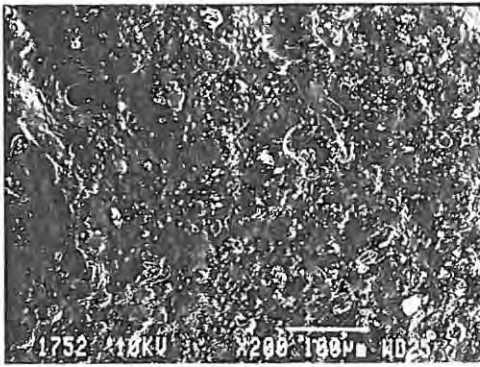
Fig. 4.19 Dissolution profiles of 10 mini-tablets coated with 3.3% w/w ethylcellulose and 1.7% w/w PEG 1540 determined individually to show the difference in the  $t_{10\%}$  (time in minutes for 10% of drug release)

### **Effects of variation in pH of dissolution medium on drug release**

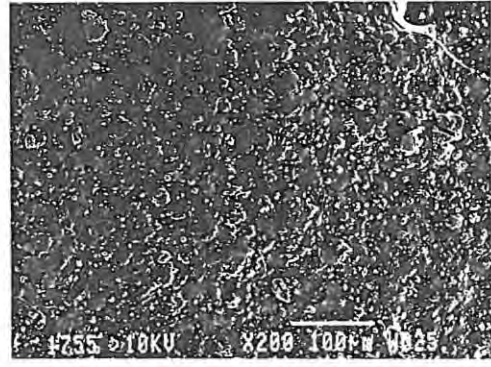
Dissolution tests carried out show the importance of the composition of the dissolution medium used. We have seen that simulated intestinal fluid pH 7.5 (no enzymes) hinders the dissolution process from film coated mini-tablets when both ethylcellulose and the Eudragits® are used as film coating material. Simulated gastric fluid (without enzymes) however allows dissolution to proceed normally. The pH of the medium itself could not be the reason for retarded release since identical tests were carried out using dilute NaOH (pH 7.4) and there was only a small difference from when water is used. Dissolution tests were also carried out using dilute HCl (pH 2.0) for the first hour, then NaOH solution added to raise the pH to 4.0 for the second hour, to pH 6.0 for the third hour, and then finally pH 7.5 from the fourth hour onwards. Once again dissolution was not significantly different from the situation when water is used as the dissolution medium.

Further electronmicrographs (Fig. 4.20) show surface views of film coated mini-tablets at various magnifications, as well as cross sectional views of fractured mini-tablets showing clearly the uniformity of the film coating around mini-tablets.

This work has demonstrated the importance of slight variation in coating composition on drug release from film coated tablets.



A Eth.cell. 5% coating  
(surface view x 200)



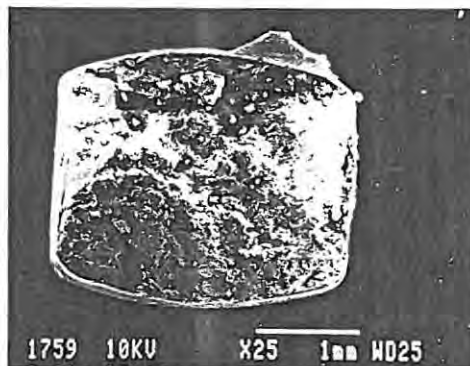
B Eudragit®RS 6% coating  
(surface view x 200)



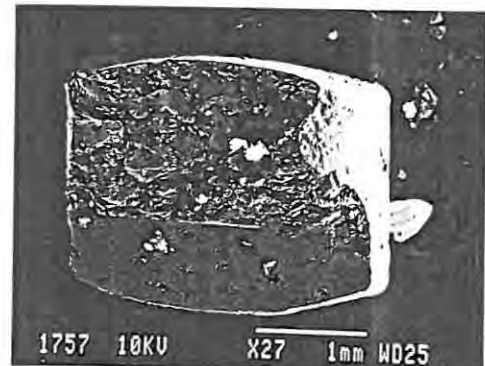
C Eth.cell. 5% coating  
(surface view x 27)



D Eudragit®RS 4% coating  
(surface view x 25)



E Eth.cell. 5% coating  
(cross section x 25)



F Eudragit®RS 6% coating  
(cross section x 27)

Fig. 4.20 Scanning electron micrographs of mini-tablets film coated with various polymers expressed as % w/w. Both surface and cross sectional views through fractured mini-tablets are shown.



However it is important to note that release of up to 95% of total drug content is achievable by the selection of a suitable polymeric mixture to uniformly film coat individual batches of mini-tablets. By selecting definite numbers of mini-tablets and enclosing them in a hard gelatin capsule, the desired modified-release characteristics with good reproducibility may be consistently achieved.

## **CHAPTER FIVE**

## CHANGES IN DRUG RELEASE RATE: EFFECT OF STRESS STORAGE CONDITIONS ON POLYMERIC FILM COATED MINI-TABLETS

### 5.1 INTRODUCTION

The practice of coating powder, pellets, granules and tablets with a thin film of a polymeric material in order to perform a specific pharmaceutical function is becoming increasingly widespread (Rowe, 1985; Porter and Hogan, 1984). This increasing popularity is due mainly to recent advances in fluidised bed processes and to the development of both aqueous and organic solvent-based polymeric coating systems. Besides providing a protective coating to the dosage form, the film coating may be effective in controlling both the rate of drug release (controlled release preparations) and the time of release depending on the pH of the gastro-intestinal milieu (enteric coatings) (Lehmann et al., 1976; Lindholm et al., 1986; Suryakusuma and Jun, 1984; Lehmann, 1975; Källstrand and Ekman, 1983; Li et al., 1988; and Benita and Donbrow, 1982).

In controlled release systems the rate at which the drug is released through the outer film coating is often the rate limiting step for bioavailability. The dissolution profiles of these drug delivery systems are usually determined *in vitro* soon after manufacture. Pharmaceuticals normally experience a shelf life and it is necessary therefore to determine what effect changes in the ambient conditions during the shelf life will have on the ultimate release of the drug at the time of use. The two environmental variables chosen for this investigation were temperature and relative humidity (RH).

An investigation into the effect of storing film coated mini-tablets at varying temperatures and relative humidities on the rate of drug release was carried out. Previous

workers (Hoblitzell et al., 1985) demonstrated the effects of ageing by storing enteric-coated aspirin tablets at different temperatures and relative humidities. They demonstrated that there were significant differences in dissolution profiles and dissolution efficiencies depending on storage conditions, storage time and types of packages in which the enteric-coated aspirin tablets were packed. Dissolution times increased significantly and it was suggested that temperature is the primary factor causing "baking" of the coating resulting in dissolution being impeded. The tablets used by Hoblitzell et al. (1985) possessed a shellac type enteric coating.

In this study the effects of stress storage conditions for relatively short to long time periods on theophylline mini-tablets are reported. The mini-tablets were film coated with polymeric agents commonly used in the pharmaceutical industry such as ethylcellulose and polymers of methacrylic acid esters.

## **5.2 MATERIALS, METHODS AND EQUIPMENT**

### **5.2.1 Preparation of Film Coated Mini-tablets**

Theophylline anhydrous obtained from Holpro Chemical Corporation was used to prepare mini-tablets (3mm in diameter) by the methods described in the previous sections. Small batches of mini-tablets were film coated using an Aeromatic Film Coating Dryer (Switzerland) by the upward spray method. Optimum conditions were maintained to obtain smooth uniform coatings. Table 5.1 shows the compositions of the coating materials and their amounts expressed as percent w/w.

Table 5.1 Composition of the coating materials and the amount of coatings expressed as % w/w.

Coating Composition	Amount of coating (% w/w)*
Eudragit <sup>®</sup> RL	1.5 and 3.0
Ethylcellulose + PEG 1540 (2:1)	0.5 + 0.25 and 1.0 + 0.5
Ethylcellulose + Eudragit <sup>®</sup> L (2:1)	1.0 + 0.5 and 2.0 + 1.0

\*  $\pm$ S D of amount of polymer coating was always less than 0.15.

The Eudragits<sup>®</sup> were obtained from Röhm Pharma, Darmstadt, and the ethylcellulose (NF grade) 10 cps from Hercules, Wilmington. The polyethylene glycol 1540 was supplied by Riedel-De Haen AG, Seelze-Hannover. Acetone and isopropanol (analytical grade) were used as solvents in the coating process and were used as received.

### 5.2.2 *In vitro* Dissolution

The dissolution tests were conducted using apparatus II of the USP XXI. The paddles were driven by a multiple-spindle drive (Hanson Research Corporation, Northridge, Ca.) at a rotational speed of  $50 \pm 1$  rpm. Distilled water (1L) was the dissolution medium at  $37 \pm 0.5^\circ\text{C}$ . Samples consisting of ten coated mini-tablets were contained in the wire mesh basket. Samples of dissolution medium were removed at regular time intervals, diluted, and assayed for theophylline by UV spectrophotometry at 271 nm. Distilled water at  $37^\circ\text{C}$  was added in order to maintain constant volume.

### 5.2.3 Experimental Storage Conditions

Samples consisting of about 10 g of film coated mini-tablets of each coating material and thickness were contained in open petri dishes and subjected to the following experimental conditions:

1. Isothermal storage at 28°C, 35°C and 45°C with the R.H. maintained constant at between 55 - 60%.
2. Cyclic conditions:
  - (i) Samples were exposed to 45°C at 55% R.H. for 24 hours, then at 28°C and 20% R.H. for 24 hours, and then at 5°C and 10% R.H. for 24 hours after which the cycle was repeated.
  - (ii) Exposure alternating every 24 hours between 45°C and 55% R.H., and 28°C and 0% R.H.

The relative humidity was controlled within  $\pm 5\%$  by storing the samples in dessicators containing appropriate mixtures of sulphuric acid and water (In: CRC Handbook of Chemistry and Physics, 60th Edition, R.C. Weast (ed.), CRC Press, Florida, (1981) pp E46, F7). The complete absence of moisture was produced using phosphorous pentoxide. Temperature control was achieved using incubators set at 28°C, 35°C, and 45°C, and a refrigerator for 5°C. To facilitate subsequent dissolution measurements, coating and storage of samples was staggered at one week intervals.

Samples were submitted to dissolution testing 24 - 48 hours after coating (initial profile), and then dissolution profiles obtained after 21, 90 and 180 days under isothermal conditions and after 90 days of cyclical storage.

### 5.3 RESULTS AND DISCUSSION

The dissolution profiles of the mini-tablet samples exposed to stress storage conditions showing the percentage theophylline released as a function of time in hours (h) are shown in Figs. 5.1 a to l and 5.2 a to f. From each dissolution curve, the time in hours for 50% release of theophylline ( $t_{50\%}$ ) was obtained and these results are tabulated (see Table 5.2). These dissolution curves and  $t_{50\%}$  values demonstrate that a similar change in drug release pattern occurs which is irrespective of the nature of the polymeric film. The ageing process brought about by storage under stress conditions tended to impede the dissolution process.

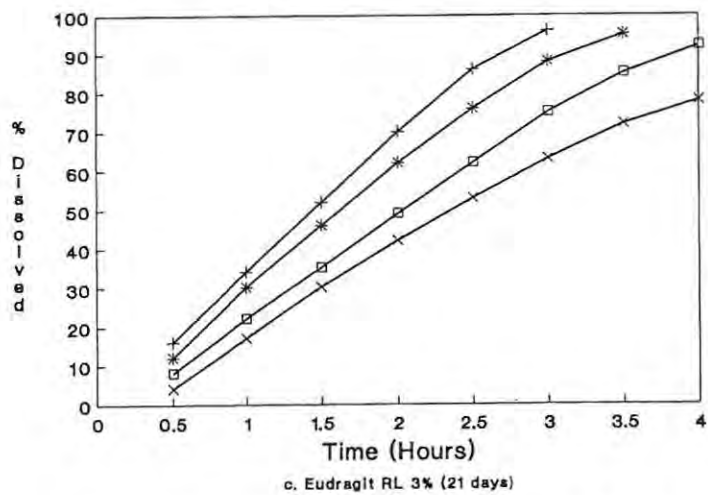
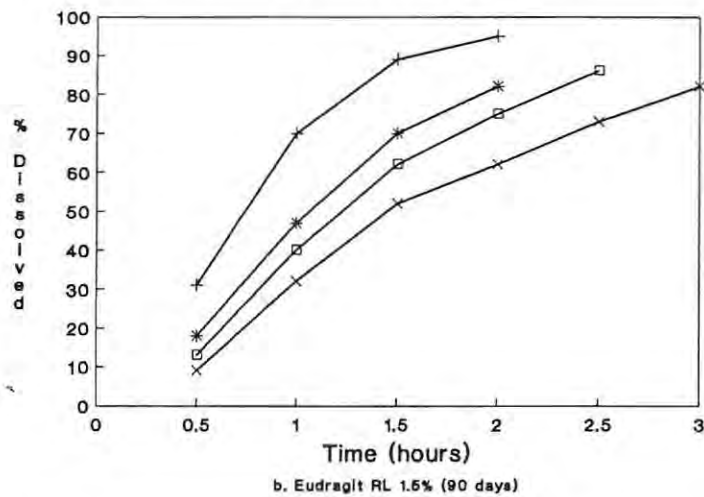
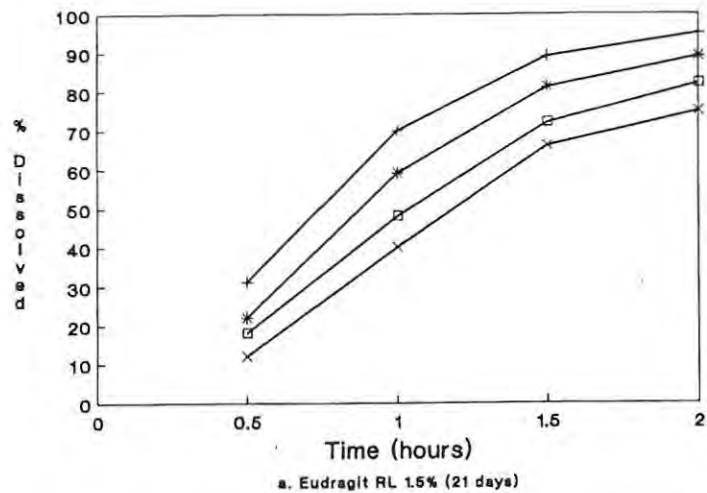
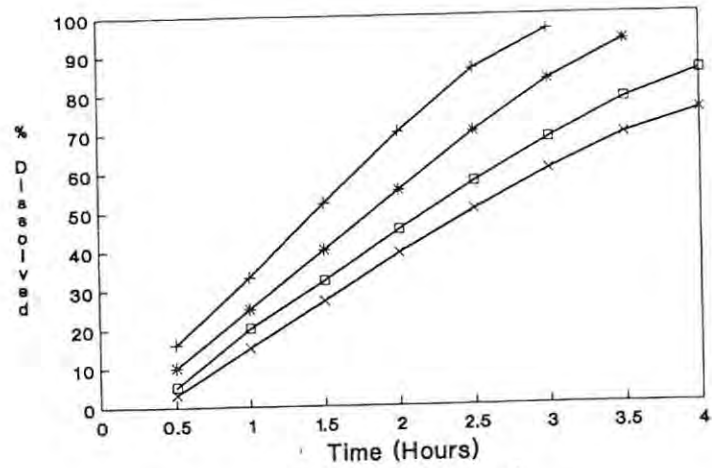


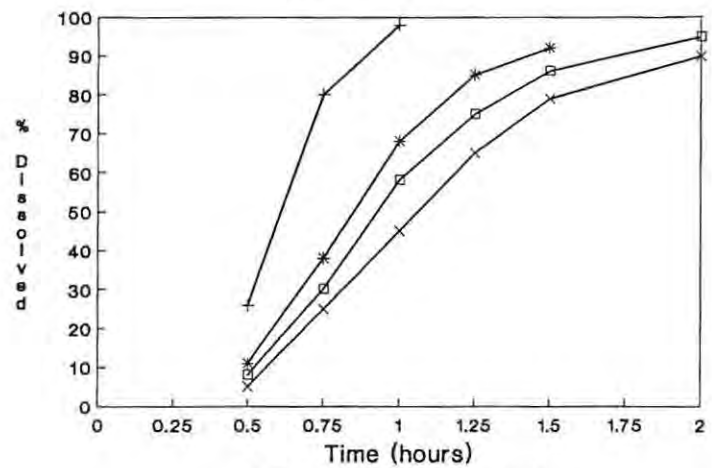
Fig. 5.1 Changes in drug release profiles resulting from the exposure of mini-tablets film coated with various polymeric materials to isothermal stress storage conditions for periods of 21 days and 90 days.

+, Initial profile 24 h after coating; \*, 28°C; □, 35°C; X, 45°C.

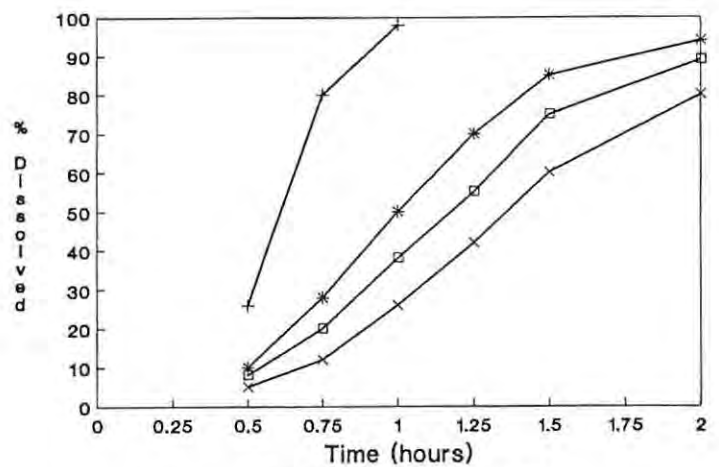




d. Eudragit RL 3% (90 days)



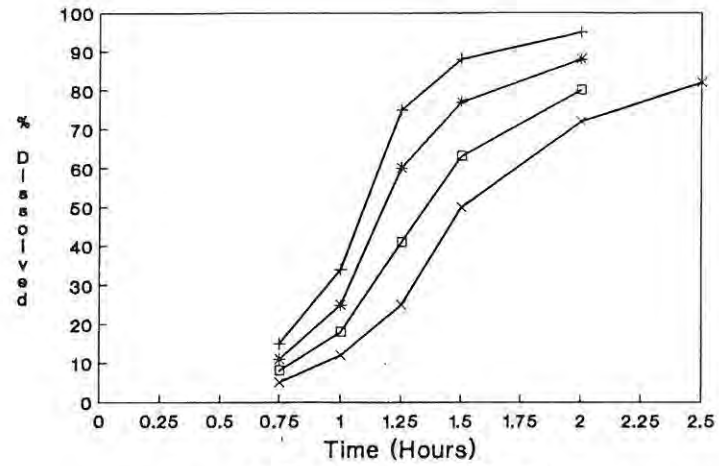
e. Eth.cell.0.5%+PEG 0.25%(21days)



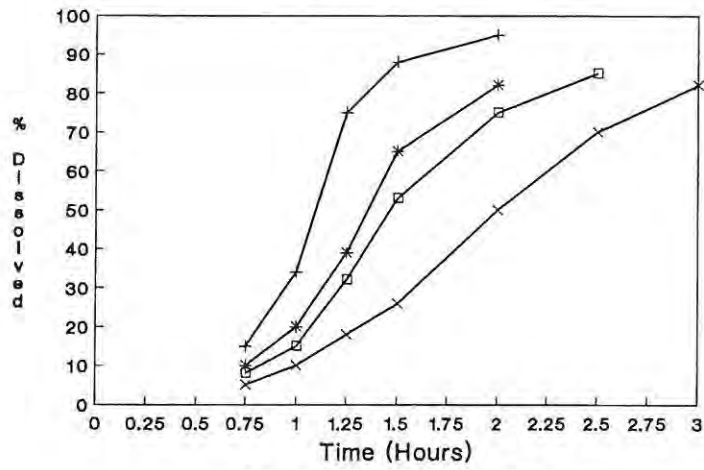
f. Eth.cell.0.5%+PEG 0.25%(90days)

Fig. 5.1 Changes in drug release profiles resulting from the exposure of mini-tablets film coated with various polymeric materials to isothermal stress storage conditions for periods of 21 days and 90 days.

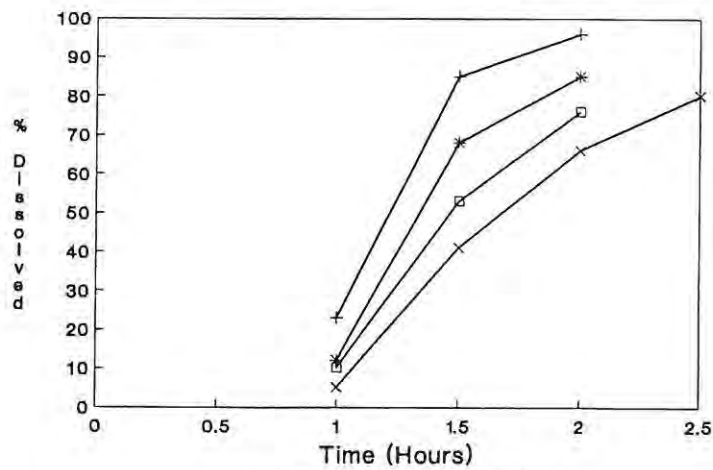
+, Initial profile 24 h after coating; \*, 28°C; □, 35°C; X, 45°C.



g. Eth.cell. 1% + PEG 0.5% (21 days)



h. Eth.cell. 1% + PEG 0.5% (90 days)



i. Eth.cell.1% + Eudragit L 0.5% (21 days)

Fig. 5.1 Changes in drug release profiles resulting from the exposure of mini-tablets film coated with various polymeric materials to isothermal stress storage conditions for periods of 21 days and 90 days. +, Initial profile 24 h after coating; \*, 28°C; □, 35°C; X, 45°C.

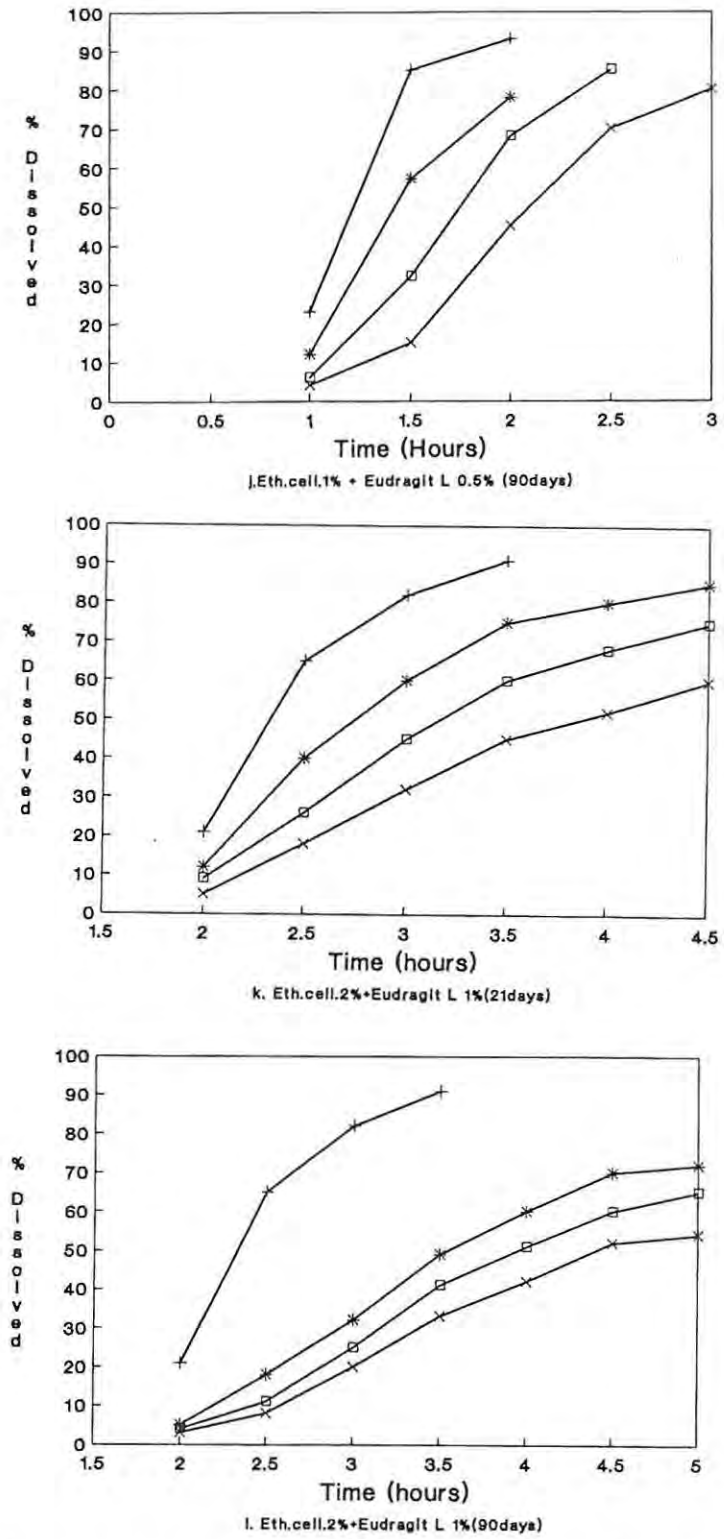
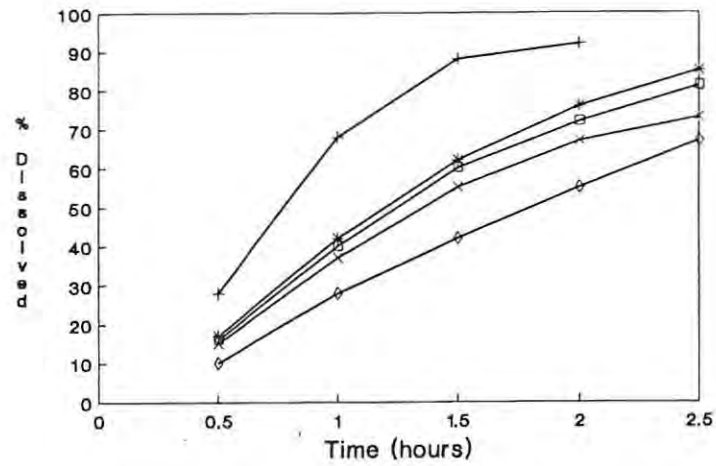
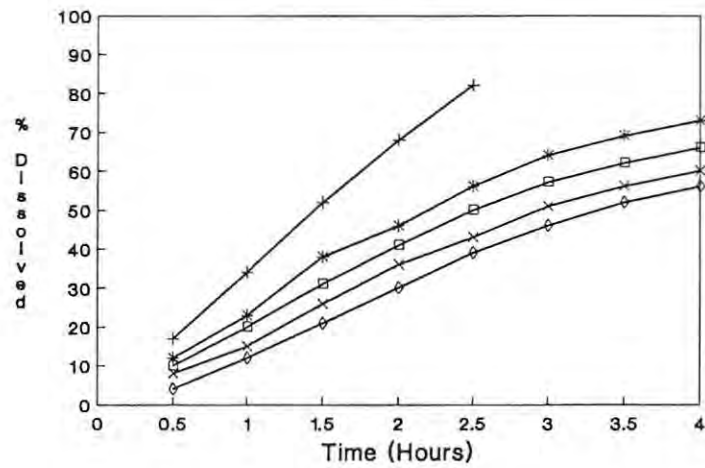


Fig. 5.1 Changes in drug release profiles resulting from the exposure of mini-tablets film coated with various polymeric materials to isothermal stress storage conditions for periods of 21 days and 90 days.

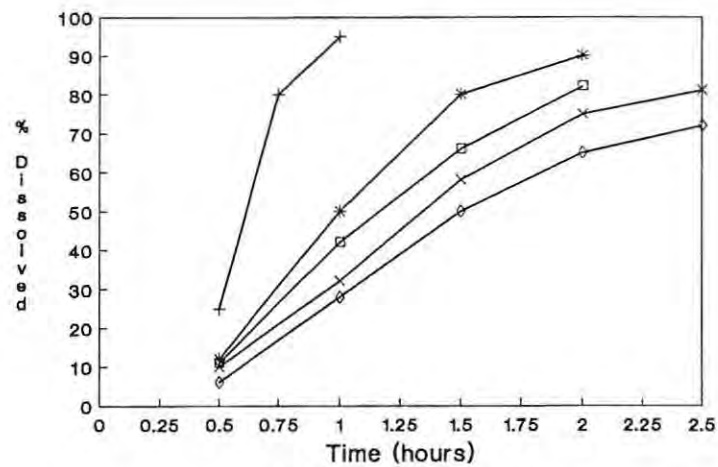
+, Initial profile 24 h after coating; \*, 28°C; □, 35°C; X, 45°C.



a. Eudragit RL 1.5%



b. Eudragit RL 3%



c. Eth.cell. 0.5% + PEG 1540 0.25%

Fig. 5.2 Changes in drug release profiles after storage of mini-tablets film coated with various polymeric materials (% w/w) under experimental conditions: +, Initial (before exposure); \*, cyclic 45°C/28°C/5°C 90 days; □, 28°C 180 days; X, 35°C 180 days; ◇, 45°C 180 days.

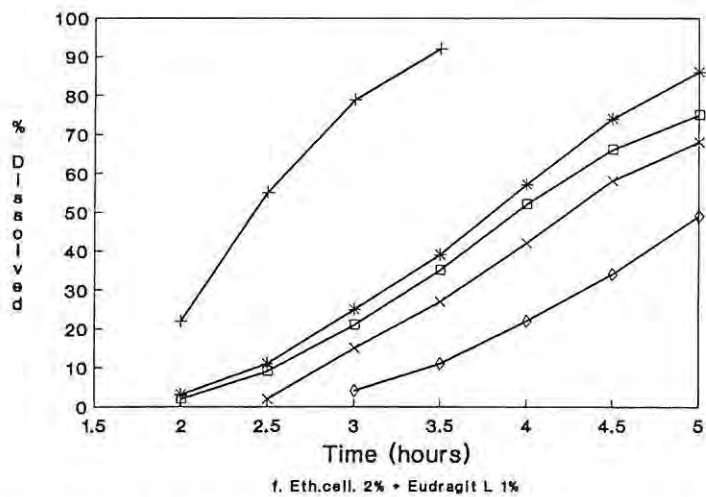
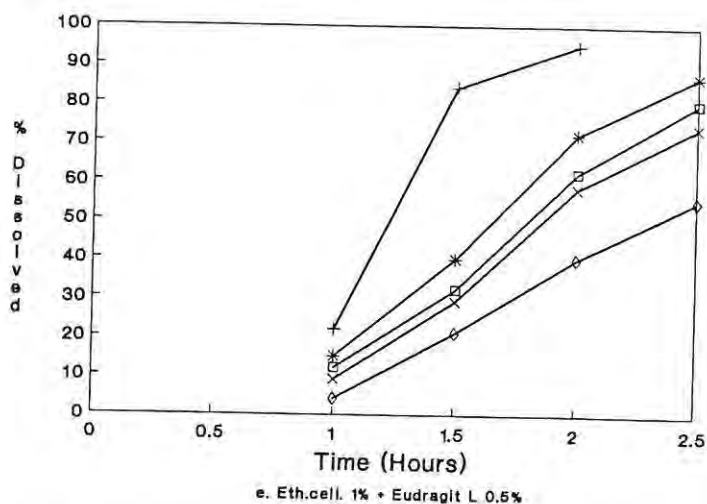
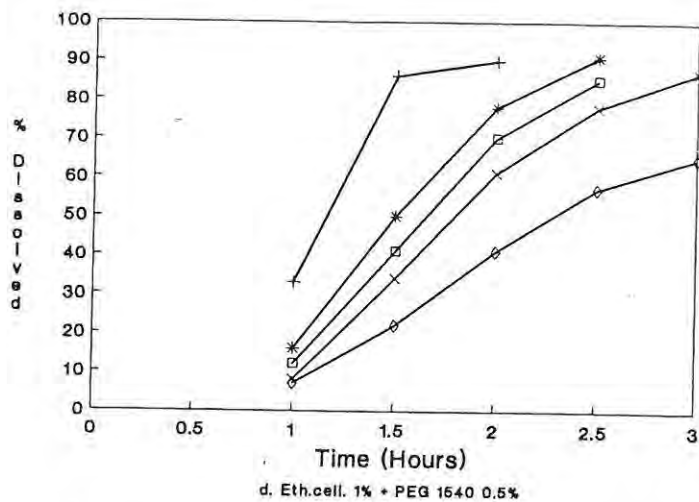


Fig. 5.2 Changes in drug release profiles after storage of mini-tablets film coated with various polymeric materials (% w/w) under experimental conditions: +, Initial (before exposure); \*, cyclic 45°C/28°C/5°C 90 days; □, 28°C 180 days; X, 35°C 180 days; ◇, 45°C 180 days.

**TABLE 5.2** The time in hours for 50% release of theophylline ( $t_{50\%}$ ) obtained from dissolution profiles of mini-tablets coated with various polymeric materials.

Coating composition of the mini-tablets	Initial value	Isothermal 28°C 55% R.H.			Isothermal 35°C 55% R.H.			Isothermal 45°C 55% R.H.			Cyclic 45°C 55% R.H. 28°C 20% R.H. 5°C 10% R.H.		Cyclic 45°C 55% R.H. 28°C 0% R.H.	
		21D	90D	180D*	21D	90D	180D*	21D	90D	180D*	90D*	90D*		
Ethylcellulose 1% + PEG 1540 0.5%	1.1	1.3	1.4	1.6	1.4	1.6	1.7	1.6	2.1	2.3	1.5	1.5		
Ethylcellulose 0.5% + PEG 1540 0.25%	0.6	0.8	1.0	1.1	1.0	1.2	1.3	1.1	1.4	1.5	1.0	1.1		
Eudragit <sup>®</sup> RL 3%	1.5	1.7	2.0	2.5	2.2	2.6	2.8	2.7	3.0	3.2	2.2	2.3		
Eudragit <sup>®</sup> RL 1.5%	0.7	0.8	1.1	1.2	1.1	1.3	1.4	1.3	1.6	1.8	1.2	1.3		
Ethylcellulose 2% + Eudragit <sup>®</sup> L 1%	2.4	2.8	3.6	3.9	3.2	4.0	4.2	4.2	5.0	5.1	3.8	3.8		
Ethylcellulose 1% + Eudragit <sup>®</sup> L 0.5%	1.2	1.5	1.6	1.7	1.6	1.7	1.8	1.8	2.0	2.3	1.6	1.7		

\*D = days

There is no evidence in the literature to suggest that these moderate storage conditions could produce any physical or chemical changes to the anhydrous theophylline which comprises the tablet core. Hence the decrease in the rate of release is therefore presumably due to the slowing in the rate of molecular diffusion of the drug across the polymeric coating material. Support for this assumption is provided by recently published work (Okhamafe and York, 1985; Okhamafe and York, 1987) in which it is suggested that the permeability of polymer systems may be significantly altered by changes in crystallinity, glass transition temperature, polarity, degree of cross-linking and the binding of drugs with some of the functional groups of the polymer. It is likely that such changes in certain of these parameters will occur in the film coatings during the experimental storage period thus causing the dissolution process to be impeded.

The intention of these tests under conditions of continual stress was to determine the integrity of the film coating. Internal stresses may build up in the film due to differences in the relative thermal expansion of the coating and the substrate. If these stresses exceed the cohesive strength of the film then cracking and loss of film integrity occurs (Rowe, 1985). This would manifest itself by a faster than expected drug release profile, or even an "immediate release" caused by the entire splitting of the coat. This can lead to toxicity or variable bioavailability. However the dissolution curves clearly demonstrate that the integrity of each of the film coatings was maintained even though there are differences in the chemical structures of the polymers used. There was no evidence of cracking or splitting even in the thinner films.

It is apparent from the  $t_{50\%}$  values in Table 5.2 that the greatest reduction in release rate occurs in the first 21 days (isothermal storage) after coating. Although there are further reductions in the release rates at 90 days and 180 days these changes appear

to become less significant upon prolonged storage. This would suggest that the mechanism responsible for impeded dissolution would eventually achieve equilibrium.

It is also clear that the mechanism responsible for reducing drug release is temperature related since the degree to which the drug was impeded became greater as the storage temperature increased. It would appear that the effect of the variable humidity was insignificant. Samples stored under cyclic conditions for 90 days tended to release the drug faster than those samples stored isothermally at 28°C, although it is probable that this release rate would have been slower than that for 28°C had the samples been stored for 180 days.

There was only a slight difference between the release rates determined for both storage procedures under cyclic conditions. This demonstrates that temperature has a significant effect on the retardation of release as the dissolution profiles obtained for samples stored under cyclic conditions corresponded approximately to the average temperature during storage.

It is assumed that any change in *in vitro* dissolution rate will also produce a corresponding change in drug release *in vivo*. Therefore it is considered important that film coated oral dosage systems, which release the drug by diffusion through a polymeric membrane, should undergo *in vitro* dissolution testing after programmed storage periods (simulating the shelf life) so that a more realistic assessment of release may be achieved.



## **CHAPTER SIX**

# DISSOLUTION OF THEOPHYLLINE FROM FILM COATED SLOW RELEASE MINI-TABLETS IN VARIOUS DISSOLUTION MEDIA AND AN IN VIVO COMPARISON USING AN ANIMAL MODEL

## 6.1 INTRODUCTION

Modern pharmaceutical technology allows the design of oral dosage forms that modify the bioavailability of a drug by retarding the rate of dissolution so that this becomes the rate-limiting step. pH is a major variable affecting this but dissolution test data are also influenced by mechanical, chemical and physical factors associated with either the apparatus itself or its environment (Prasad et al., 1982; Mazuel et al., 1983). Although dissolution testing has not replaced *in vivo* bioavailability assessment it can be a valuable tool to predict *in vivo* performance of a dosage form. If bioavailability problems exist with a drug, this commonly reflects continued absorption for only a limited time after ingestion. This places an upper time limit on the dissolution process in the gut, if the total amount of drug absorbed is to be maximised. Attempts to correlate *in vivo/in vitro* performance for tablets commonly involve either the time for a specified fraction (usually 50%) of drug content to dissolve, or the amount of the total dose content which dissolves in a specified time. During the dosage form design programme for the development of a multiple unit mini-tablet controlled release system an investigation of the effect of various recommended dissolution media (USP XXI) on the release profiles of those tablets was initiated. An animal model was also employed together with the *in vitro* studies, to assess the *in vivo* performance of the dosage forms.

## 6.2 MATERIALS AND METHOD

Theophylline (anhydrous) BP quality was used. Ethylcellulose was obtained from the Hercules Company, UK, and PEG 1540 and magnesium stearate were from BDH Chemicals Ltd. Isopropanol and acetone were reagent grade, and sodium carboxymethylcellulose (Holpro Chemical Corporation) was used as a binder. A series of B.S. sieves and a mechanical sieve shaker were used for particle size selection. A Manesty Type F3 tableting machine with 3 mm diameter concave punches was used for compression. Breaking strength was measured on an Erweka testing machine. An Aeromatic fluidized bed (Size 1, laboratory unit, capacity 1 - 2 kg) was used for coating. The USP XXI dissolution apparatus (paddle method) used was from Hanson Research Corp., Northridge, Ca. Male, white New Zealand rabbits, 2.8 - 3.5 kg were used for *in vivo* studies.

### 6.2.1 Solution properties

The solubility of theophylline in various solvents was determined by adding excess drug to the solvent. The solutions were mixed overnight at  $25 \pm 0.5^\circ\text{C}$  to achieve saturation, then filtered through a  $0.22\ \mu\text{m}$  filter and measured spectrophotometrically at 271 nm. Solubilities were (mol/L): 0.0458 (water, pH 5.8), 0.0469 (HCl, pH 6), 0.0455 (HCl, pH 1.2), 0.0462 and 0.0468 (phosphate buffers pH 5.4 and 7.4, respectively). Kinematic viscosities of the dissolution media were measured at  $25 \pm 0.2^\circ\text{C}$  by the standard capillary-tube Ostwald viscometer. Values were ( $\times 10^{-6}\ \text{m}^2\text{s}$ ): 0.892 (HCl, pH 1.2), 0.889 and 0.888 (phosphate buffers pH 5.4 and 7.4). Density was determined by weighing a known volume of the solution at  $25 \pm 0.2^\circ\text{C}$ .

### 6.2.2 Preparation of tablets

Sodium carboxymethylcellulose (5% w/v) in water was added to the theophylline powder in a Turbula mixer, and blended for 7 min; the wet mass was then passed through a 16 mesh (1.0 mm) screen sieve in an oscillating granulator and dried. The granules were sieved and the fraction finer than 200  $\mu\text{m}$  was lubricated in the cube mixer with 0.5% w/w magnesium stearate for 5 min. Bi-convex mini-tablets weighing  $22 \pm 1$  mg (3 mm diameter x 2 mm thick) having an average breaking strength of 26 N, and containing approximately 20 mg of drug, were produced by compressing the granules. Tablets were coated by fluid bed technology using an ethylcellulose-PEG mixture in equal parts of acetone and isopropanol as a coating solution. The conditions for optimum film coating and thickness are given in Table 6.1.

Table 6.1 The process conditions for optimum film coating

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Bed weight	60 g
* Coating solution	Film former in isopropanol acetone 1:1
Solution delivery rate	8 - 10 mL/min
Atomizing air pressure to spray	2 kg/cm <sup>2</sup>
Rated value drying temperature	55°C
Drying temperature	60°C
Outlet air temperature	45°C
Fluidizing air flow rate	100 - 120 m <sup>3</sup> /h

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\* The film former used in this study was 5% w/v ethylcellulose and 2% w/v PEG 1540 in the given solvent system.

### **6.2.3 Preparation of solvent-cast membranes**

The solution of ethylcellulose (5% w/v) and PEG 1540 (2% w/v) in equal proportions of isopropanol-acetone was prepared and the required amounts were cast on clean glass plates and allowed to dry. The hardened membranes were removed and cut into round (20 mm) disks. The thicknesses were recorded and selected samples exposed to the various dissolution media.

### **6.2.4 Dissolution studies**

The dissolution tests were conducted using the USP paddle method (apparatus II) at 50 rpm, and 900 mL of dissolution fluid at  $37 \pm 0.2^\circ\text{C}$ . Five coated tablets were tested individually in dissolution media at pH 1.2 (HCl). Further dissolution studies were made in phosphate buffers at pH 5.4 and 7.4. Dissolution rate measurements were carried out by passing filtered dissolution medium through a spectrophotometer cell and monitoring absorbance at 271 nm. Samples of the medium (5 mL) were removed at 1 h intervals for 12 h, and filtered through a  $0.22 \mu\text{m}$  Millipore filter. The volume was restored by adding fresh dissolution medium at  $37^\circ\text{C}$ . The pH of the dissolution medium was checked at the end of each hour during the dissolution run. No significant change in the pH of the test medium occurred when phosphate buffers were used. The hydrochloric acid medium increased from an initial pH 1.2 to a final pH 2.1.

### **6.2.5 Administration and blood sampling**

Rabbits fasted overnight with water freely available. One theophylline coated tablet was administered to the rabbit via a plastic catheter sufficiently far into the oropharynx

to avoid ejection (Venho & Eriksson, 1986). Blood samples (2.0 to 3.0 mL) were drawn from the marginal ear vein at suitable time intervals. The serum was separated and stored at -18°C before theophylline concentrations were measured by fluorescence polarization immunoassay (TDX-analyser system, Abbott Laboratories).

### 6.3 RESULTS AND DISCUSSION

For drugs formulated as modified-release dosage forms, it is appropriate to assess the extent to which pH of the dissolution medium affects release, and whether such effects are significant.

Drug release profiles from the coated mini-tablets in various dissolution media over a period of 12 h, under identical hydrodynamic conditions, are shown in Fig. 6.1. The rate of dissolution of theophylline at pH 1.2 is substantially greater than the rate of dissolution in phosphate buffers. Theophylline solubility is pH-independent and its  $pK_a$  is 8.6 (Cohen, 1975) so pH-dependent release of the drug was not expected in the pH range studied. Although a lag period of 15 to 25 min to commencement of dissolution was observed in all the dissolution media, drug release into media containing phosphate ions (pH 5.4 and 7.4) was slow over the entire range of sampling times (Fig. 6.1). The maximum amount of drug released after 12 h was approximately 20 and 30% of total drug content of the tablet in pH 5.4 and 7.4, respectively. When quality control limits are defined for a finished product specification, these should normally ensure that at least 80% of the active content is released within a narrow "release window" (Cartwright, 1987).

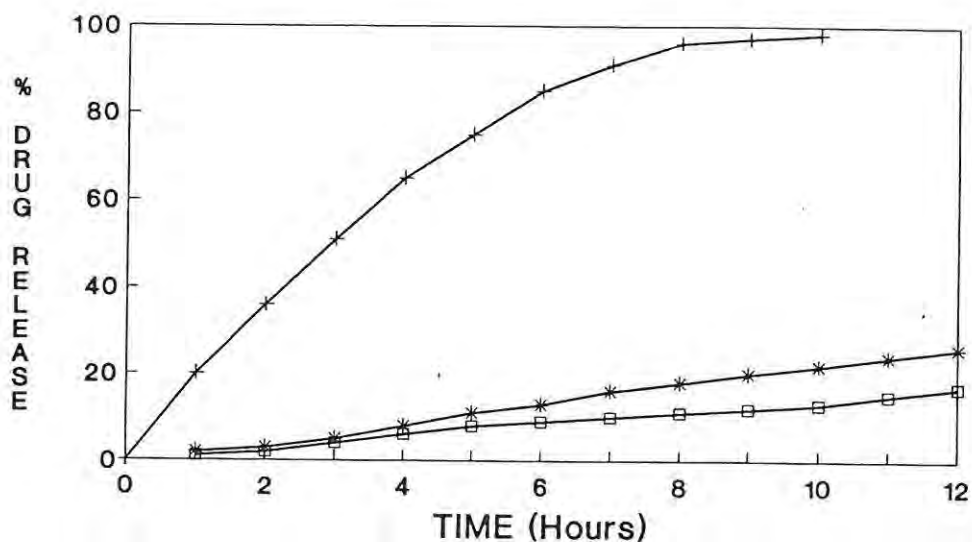


Fig. 6.1 Release profiles of slow-release theophylline mini-tablets coated with ethylcellulose-PEG in hydrochloric acid pH 1.2 (+), phosphate buffers pH 7.4 (\*), and pH 5.4 (□), respectively. Each value represents the mean  $\pm$  s.e.m. (n = 5)

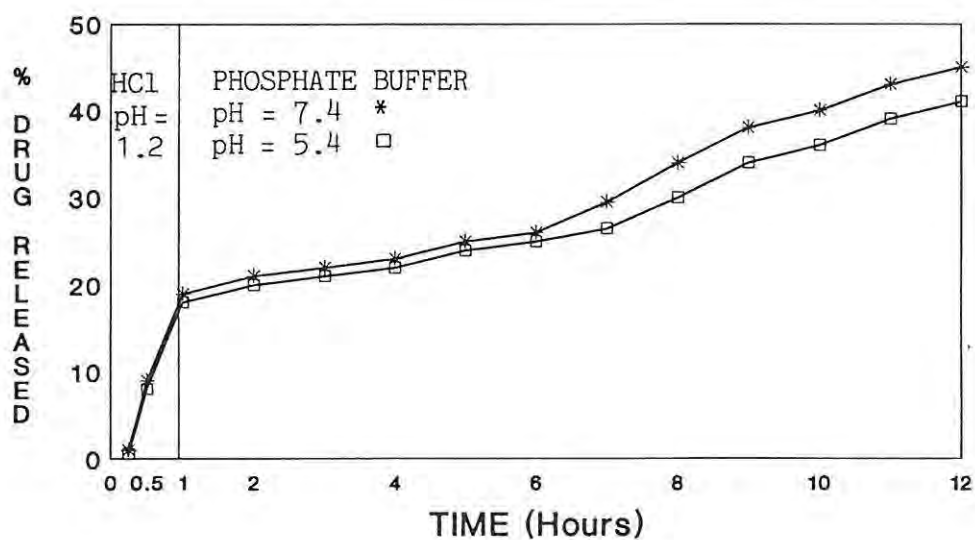


Fig. 6.2 Dissolution profiles of film coated slow release theophylline mini-tablets in hydrochloric acid dissolution medium (first hour) and in phosphate buffers (second hour and thereafter). Data are expressed as mean  $\pm$  s.e.m. (n = 5).

The results of the present investigation with film coated mini- tablets provide further evidence of the substantial effect that different dissolution media may have on both the rate and the extent of dissolution (Fig. 6.1)

While retarded drug dissolution is intended for the controlled release tablets, too slow a release process may result in poor bioavailability. Fig. 6.2 shows the results of an attempt to simulate an initial 1 h exposure of the tablet to gastric fluid (pH 1.2), followed by exposure to intestinal fluid of pH 5.4 and pH 7.4. Both buffers inhibited the release process in comparison with media containing hydrochloric acid. Dissolution studies were also performed using water and dilute hydrochloric acid (pH 6) to evaluate the influence of pH on the dissolution rate in the absence of phosphate ions. The release profiles obtained were within 5% of data obtained for dissolution rates at pH 1.2 (hydrochloric acid), with no change being observed in the pH of the dissolution medium during the test. In an attempt to establish that the cause of inhibition in the release process was not a lack of channel formation, solvent-cast films of the coating solution were prepared. Scanning electron micrographs confirmed that pores were formed in the coating film on exposure to the various dissolution media investigated and that pore formation was not affected by phosphate ions. The size and size distribution of channels formed in the membranes exposed to both dilute hydrochloric acid (pH 1.2) and phosphate buffers (pH 5.4 and 7.4) were similar. Thus retardation of dissolution in phosphate buffer apparently cannot be ascribed to an effect of phosphate ions on the coating film.

An investigation was initiated to establish the *in vivo* bioavailability and the influence of gastrointestinal fluid on drug delivery and absorption, using the rabbit as an animal



model. Fig. 6.3 shows the serum concentration-time profile of theophylline administered as a slow-release, coated mini-tablet. Comparison of the area under this curve with data following intravenous infusion demonstrated that the orally administered dose was 95% bioavailable. This clearly indicates that phosphate buffered media are not suitable dissolution fluids for the *in vitro* screening of release profiles of coated theophylline tablets. It appears that the rate-determining step for theophylline release is a transport step, since water channels were formed in the film by each of the various dissolution media and the solubility of theophylline was not significantly affected by the medium used (see solution properties). This may involve an interaction of phosphate ions with theophylline molecules at the core-coat interface resulting in an insoluble complex or large molecular structure in comparison with that arising in the presence of chloride ion. This is depicted in Fig. 6.4, showing that the dissolution rate may be controlled by a surface reaction.

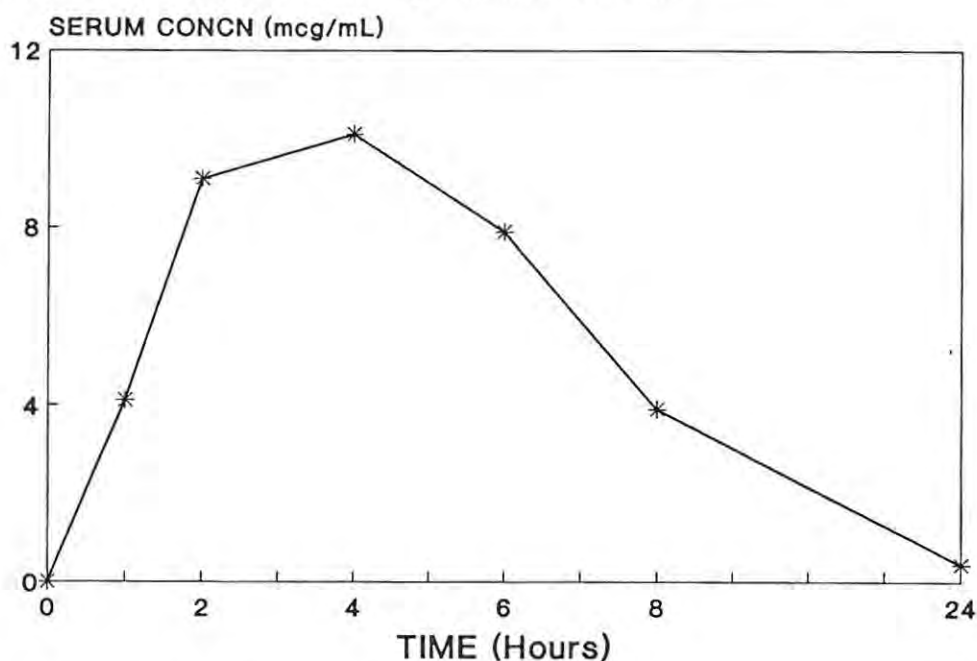


Fig. 6.3 Theophylline serum concentration versus time profile following oral administration of 20 mg slow release coated mini-tablet to a rabbit.

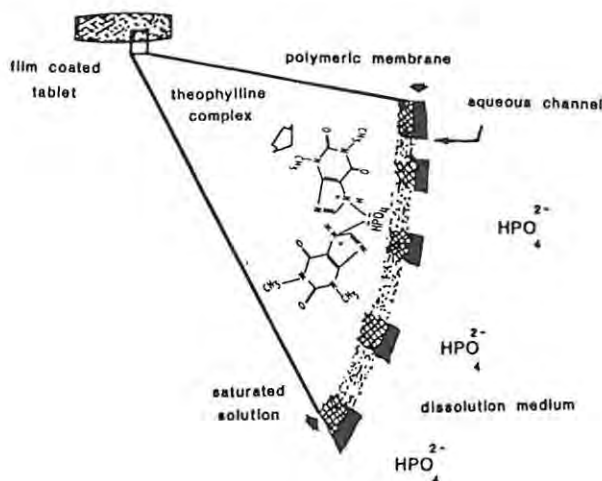
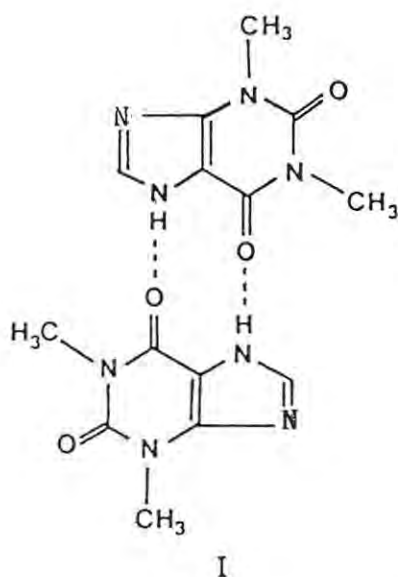


Fig. 6.4 Schematic representation of proposed interaction of phosphate ions with theophylline at the core-coat interface influencing the mass transport phenomenon.

The classical theory describing dissolution rate in relation to pH and  $pK_a$ , based on the Noyes-Whitney equation, suggests that the dissolution rate per unit area of a weak acid is controlled by its solubility, diffusion coefficient and Nernst diffusion layer thickness. On this basis, Higuchi et al., (1958, 1964) developed a theory describing the dissolution rate as a combined process of simultaneous chemical reaction and diffusion. When the concentration of drug in the film pores approaches saturation the reverse process should also be taken into account, that is the simultaneous deposition of solid drug (Kallay and Senjkovic, 1987). Conversion of anhydrous theophylline into the less soluble hydrated form, and crystallization on the surface of the undissolved anhydrous theophylline as a direct surface reaction, may also occur (Shefter and Higuchi, 1963; De Smidt et al., 1987). These processes, as well as decreased fluid shear rate over the dissolving surface within the pores, may influence mass transport causing less efficient removal of dissolved solute from the vicinity of the dissolving surface. This would result in a concentration build-up at the core-coat

interface within the pores, conducive to self-association of theophylline molecules (I), (Thakkar et al., 1971).



Consequently partial supersaturation within the diffusion boundary layer, and changes in kinematic viscosity, pH gradient, and hydrodynamic conditions with respect to pore size and diameter, may alter the rate of dissolution and diffusivity of drug molecules in the system investigated. The rate limiting step may alternatively be attributable to an activated complexation, the stoichiometry of which would depend to a large extent on the physiochemical properties of the drug and tablet constituents at the core-coat interface. These results emphasise the importance of screening and selection of dissolution media in dissolution testing. *In vitro* dissolution tests do not necessarily give reliable information about the absorption properties of drugs, and an animal model thereof is useful for the evaluation of *in vivo* drug release and subsequent bioabsorption during the development of modified-release dosage forms.

## **CHAPTER SEVEN**

## **IN VIVO EVALUATION OF A THEOPHYLLINE ORAL CONTROLLED RELEASE CAPSULE CONTAINING FILM COATED MINI-TABLETS IN BEAGLE DOGS**

### **7.1 INTRODUCTION**

Sustained release oral dosage forms of theophylline should provide release properties such that peak-trough fluctuations are minimised. The bronchodilating effect is closely related to the plasma concentration (Mitenko and Ogilvie, 1973) and concentrations between 10 and 20  $\mu\text{g/mL}$  are considered best for both therapeutic efficacy and freedom from toxicity (Jacobs et al, 1976). However its pharmacokinetic characteristics are such that plasma levels within the desired range are difficult to maintain. There is great inter- individual and age dependant variability in elimination rates (Ellis, et al., 1976; Paifsky and Ogilvie, 1975; Jenne et al., 1972) depending upon factors such as age, smoking history, diet, disease and concurrent use of other drugs (Lefebvre et al., 1988; Ogilvie, 1978). Numerous single-unit and multiple-unit oral controlled release dosage forms have been developed (Gangadharan et al., 1987; Lippold and Förster, 1984; de Haan and Lerck, 1986).

The production and *in vitro* release of theophylline from mini-tablets film coated with polymers were described in chapter four. Hard gelatin capsules containing a certain number of mini-tablets film coated with Eudragit<sup>®</sup> RL and RS 2% w/w were subjected to *in vivo* evaluation in Beagle dogs using both single dose and multiple dose studies. The various pharmacokinetic parameters were calculated such as area under the curve (AUC), extent of bioavailability (EBA), peak concentrations ( $C_{\text{max}}$ ), time to peak ( $t_{\text{max}}$ ), dosage form index (DI) and the constancy of serum concentrations. A comparison was made with parallel studies using a commercial oral controlled release

preparation (Theo-Dur<sup>®</sup>) as well as administration of theophylline anhydrous powder enclosed in a hard gelatin capsule. Section 7.2 of this chapter describes a single dose bioavailability study of the test capsule, while Section 7.3 describes a multiple dose study to steady state conditions. The protocols of these studies were approved by the Director of the Provincial Animal Centre, Kuils River, Cape Town.

## **7.2 SINGLE DOSE BIOAVAILABILITY STUDY**

### **7.2.1 MATERIALS AND METHODS**

#### **Products tested**

Hard gelatin capsules containing a certain number of film coated mini-tablets (3 mm diameter,  $15 \pm 0.5$  mg each) of theophylline manufactured by a process described in Chapter four.

**Test unit A:** Capsules (size 1) each containing 20 mini-tablets (300 mg theophylline) of which 10 were uncoated (immediate release 150 mg) and 10 were coated with Eudragit<sup>®</sup> RS 2% (sustained release 150 mg).

**Test unit B:** Capsules similar to test unit A but the sustained release component was film coated with Eudragit<sup>®</sup> RL 2% w/w.

#### **Parallel Studies**

**Test Unit C:** Capsule (size 1) containing 300 mg theophylline anhydrous powder B.P.

Tablets of a standard marketed controlled release theophylline product (Theo-Dur<sup>®</sup> 300 mg).

### **Dosing and Blood Sampling**

Four Beagle dogs (1 male and 3 female) weighing 12 - 15 kg ( $13.78 \pm 1.72$  kg) were used in this cross-over design single dose study on each test unit after a suitable wash-out period (14 days). The dogs were fasted for 24 h before administration of the first test dose with water ad libitum. A test unit was administered between 06h00 and 07h00 on the day of the study.

Oral administration of the unit was achieved by opening the mouth of the dog, depressing the tongue, placing the unit in the throat region with subsequent administration of about 100 mL water, and firmly closing the mouth and blowing air through the dog's nose in order to facilitate swallowing (Gangadharan et al., 1987). The dogs received their normal food (commercial brand of dog chunks) on the day of study.

Blood samples were drawn at 0, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after dosing. About 3 - 5 mL of blood were drawn each time from the jugular vein via a teflon 16 G cannula. The projecting end of the cannula was sutured to the skin to prevent it from being pulled out. The neck of the animal was bandaged to prevent interference. During sampling the bandage was removed to facilitate blood withdrawal after which the cannula was flushed with heparinised normal saline. The blood samples were allowed to stand for one hour, centrifuged and the serum kept frozen ( $-20^{\circ}\text{C}$ ) until analysis.

### **Assay of theophylline in serum**

Theophylline concentrations in serum were determined using a fluorescence immunoassay system (TDX Analyser, Abbott).

### **Pharmacokinetic Analysis**

The pharmacokinetic parameters relevant to this single dose study include area under the curve ( $AUC^{0 \rightarrow \infty}$ ), peak concentration, time to peak and time for which blood levels remain above  $7 \mu\text{g/mL}$ . The  $AUC^{0 \rightarrow \infty}$  was calculated in each case using the linear trapezoidal rule.

### **Dissolution Studies**

The *in vitro* dissolution of theophylline from the encapsulated mini-tablets and the Theo-Dur 300 tablets was determined by the USP XXI paddle method. The dissolution medium was distilled water (1L) at  $37^\circ\text{C}$  at a paddle speed of 50 rpm (influence of pH was not significant on release profiles as has been described in Chapter 6). The concentrations of theophylline were assayed by UV spectrophotometry at 271 nm.

## **7.2.2 RESULTS**

### ***In vitro* dissolution studies**

The dissolution profiles of theophylline from test units A and B and also from Theo-Dur<sup>®</sup> 300 mg tablets are shown in Fig. 7.1 a and b. The mini-tablets from test units A and B released the drug in excess of 90% over periods of 4 h and 2 h, respectively.



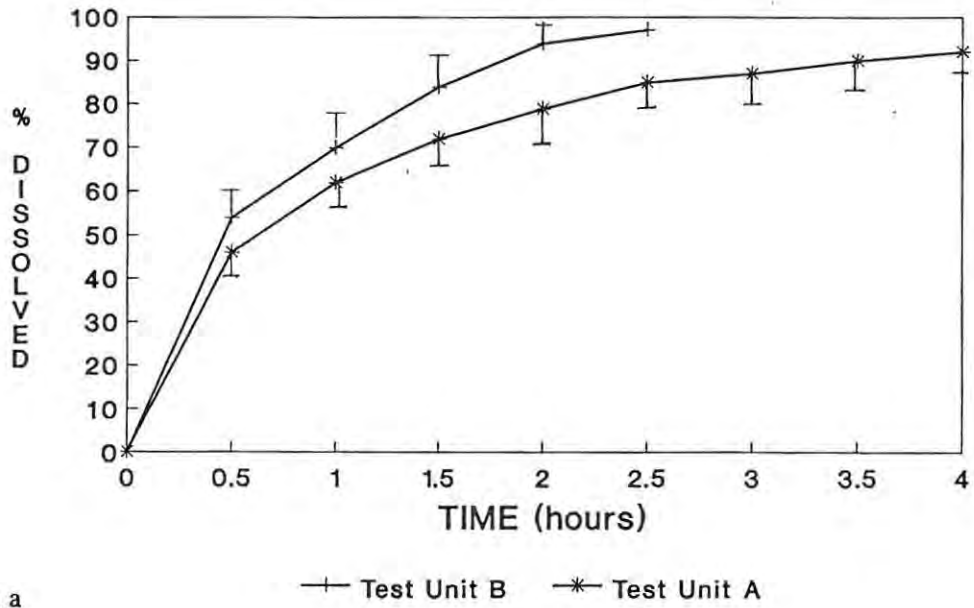


Fig. 7.1 a

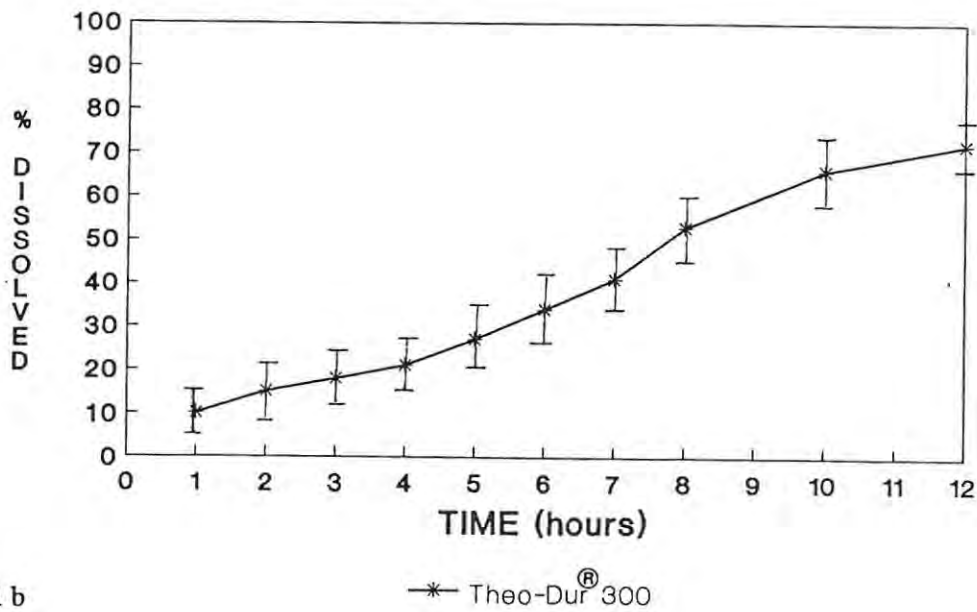


Fig. 7.1 b

Fig. 7.1 a and b. Percent theophylline dissolved *in vitro* from test units A and B and also from Theo-Dur<sup>®</sup> 300 mg tablets.

The maximum amount of theophylline released *in vitro* from the Theo-Dur<sup>®</sup> 300 tablets was about 70% of the amount stated on the label over 12 hours.

### Bioavailability studies

The mean serum theophylline concentrations ( $\mu\text{g/mL}$ ) as a function of time in hours for each test unit is shown in Fig. 7.2 a and b. Table 7.1 shows the relevant pharmacokinetic parameters after single dosing with each test unit.

TABLE 7.1 Pharmacokinetic parameters calculated ( $\pm$ S.D.) from the data from four dogs after a single oral dose of the test products.

PARAMETER	PRODUCT			
	Test unit A	Test unit B	Test unit C	Theo-Dur <sup>®</sup> 300
AUC $0 \rightarrow \infty$ ( $\mu\text{g/mL.h}$ )	88.2 ( $\pm$ 19.3)	175.2 ( $\pm$ 26.3)	166.4	118.9 ( $\pm$ 22.4)
EBA (test unit C as standard)	0.53	1.05	1.0	0.71
C <sub>max</sub> ( $\mu\text{g/mL}$ )	8.2 ( $\pm$ 2.6)	10.7 ( $\pm$ 3.8)	20.0	11.9 ( $\pm$ 3.6)
t <sub>max</sub> (h)	3.0 ( $\pm$ 0.6)	5.0 ( $\pm$ 0.6)	2.0	6.0 ( $\pm$ 1.4)
Duration above 7 $\mu\text{g/mL}$ (h)	2.2 ( $\pm$ 1.2)	9.3 ( $\pm$ 1.7)	6.2	7.9 ( $\pm$ 1.1)

Test unit A - mini-tablets uncoated and coated with Eudragit<sup>®</sup> RS 2%

Test unit B - mini-tablets uncoated and coated with Eudragit<sup>®</sup> RL 2%

Test unit C - anhydrous theophylline (300 mg)

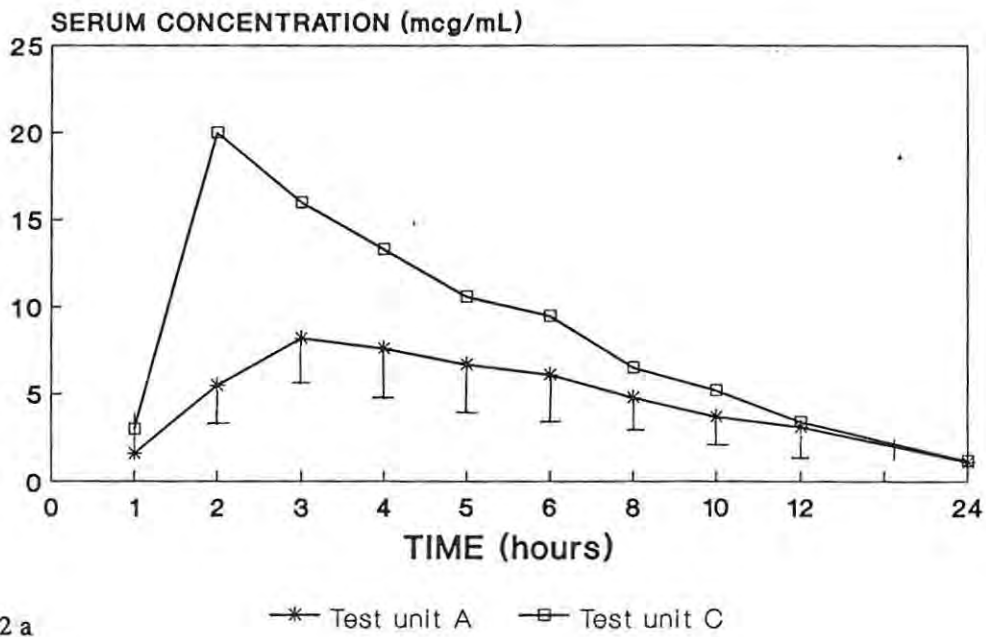


Fig. 7.2 a

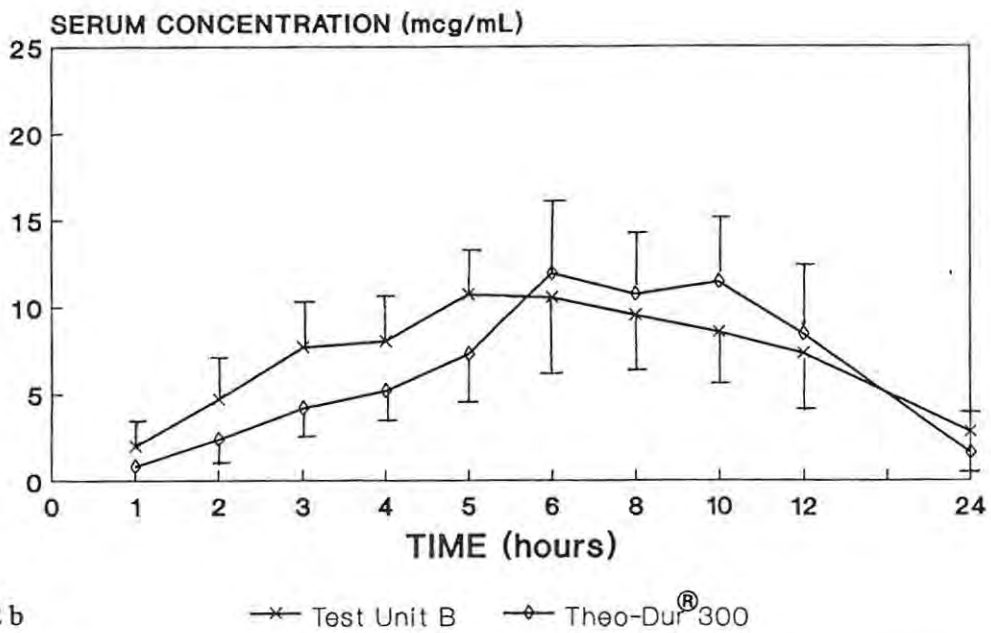


Fig. 7.2 b

Fig. 7.2 a and b. Mean theophylline concentrations as a function of time in serum following peroral administration of 1 unit of each of the test units A, B and C and Theo-Dur<sup>®</sup>300. (n = 4 except for C which is the mean of duplicate studies). The composition of the test units are described in the text.

### 7.2.3 DISCUSSION

The pharmacokinetic parameters and serum concentration profile shows that test unit B compares favourably with that of the commercially available controlled release product (Theo-Dur<sup>®</sup>300 mg). The AUC of the test unit B (175.2  $\mu\text{g}/\text{mL}\cdot\text{h}$ ) was significantly greater than that of Theo-Dur<sup>®</sup> (118.9  $\mu\text{g}/\text{mL}\cdot\text{h}$ ). The time to peak ( $t_{\text{max}}$ ) was smaller for test unit B (5h) than Theo-Dur<sup>®</sup> (6 h) which means that the onset of action for the test unit was faster. Although the  $C_{\text{max}}$  value for Theo-Dur<sup>®</sup> was greater than that for test unit B (11.9  $\mu\text{g}/\text{mL}$  and 10.7  $\mu\text{g}/\text{mL}$  respectively), the test unit over the time period 2 to 10 h produced more constant serum concentrations with a range of 4.7 - 10.7  $\mu\text{g}/\text{mL}$  while the range for Theo-Dur<sup>®</sup> was 2.4 - 11.9  $\mu\text{g}/\text{mL}$ . In addition the time period over which the serum levels remained above 7  $\mu\text{g}/\text{mL}$  (assumed level above which the drug will produce a therapeutic effect) was longer for the test unit B compared to Theo-Dur<sup>®</sup> (9.3 h and 7.9 h respectively).

The faster onset of action by test unit B was probably achieved by the uncoated mini-tablets in the capsule which provided the immediate release component. This immediate rise in blood levels occurred over the first 3 hours after dosing and it is worthy of note that a similar rise occurred with test unit A in which the immediate release component was identical.

Test unit A contained mini-tablets coated with Eudragit<sup>®</sup> RS 2% combined with an immediate release component of uncoated mini-tablets. The immediate release portion caused the serum level to rise to 8  $\mu\text{g}/\text{mL}$  within 3 hours but thereafter levels dropped steadily to just above 3  $\mu\text{g}/\text{mL}$  after 12 hours. The  $\text{AUC}^{0 \rightarrow \infty}$  for this test unit

was 88.2  $\mu\text{g/mL}\cdot\text{h}$  which was lower than that for Theo-Dur<sup>®</sup> which in turn was significantly lower than the AUC for test unit B.

By virtue of the content of quaternary ammonium groups it contains, Eudragit RL<sup>®</sup> films are, in contrast to Eudragit RS<sup>®</sup>, freely permeable to water and dissolved drugs so that theophylline release is relatively modestly retarded. The *in vitro* dissolution profile for mini-tablets coated with Eudragit RL 2% w/w<sup>®</sup> confirms this fact (Fig. 7.1). Although test unit B (mini-tablets film coated with Eudragit RL 2%<sup>®</sup>) released theophylline *in vitro* to the extent that over 90% was released in 2 hours the release profile *in vivo* was much slower and test unit B produced serum concentrations within the therapeutic range over a period of about 9 hours. There is a distinct lack of *in vitro* - *in vivo* correlation data and these findings are in general agreement with the conclusions drawn in Chapter 6. The parallel study using theophylline anhydrous powder 300 mg (test unit C) produced a  $C_{\max}$  of 20  $\mu\text{g/mL}$  and a  $t_{\max}$  of 2 hours. After peak concentration serum levels dropped rapidly to 3.4  $\mu\text{g/mL}$  after 12 hours. The  $\text{AUC}^{0 \rightarrow \infty}$  was 166.4  $\mu\text{g/mL}\cdot\text{h}$  and by comparison with the AUC for test unit B (175.2  $\mu\text{g/mL}\cdot\text{h}$ ) there is no significant difference between test units B and C. (EBA is close to 1). Therefore the degree of theophylline absorption from test unit B is similar to that from capsules containing 300 mg of anhydrous theophylline powder. However the extent of bioavailability (EBA) of test unit B (1.47) is significantly higher compared to the commercial marketed product (Theo-Dur<sup>®</sup>). This indicates that test unit B liberates the total amount of its theophylline content and is more bioavailable compared with Theo-Dur 300<sup>®</sup> (which only releases 70% of its theophylline content in 12 h). In summary this study has shown that the test unit B, a capsule containing uncoated mini-tablets and mini-tablets film coated with Eudragit RL 2% w/w<sup>®</sup> (each

providing 150 mg theophylline as immediate release and controlled release respectively), can offer advantages over the commercially available product.

### **7.3 MULTIPLE DOSE BIOAVAILABILITY STUDY**

#### **7.3.1 MATERIALS AND METHODS**

This multiple dose study was conducted over 4 days (96 h) in four Beagle dogs which had not been used in any other test over the previous 14 days. The dogs (1 male and 3 females) weighed 12 - 15 kg ( $13.78 \pm 1.72$  kg). The dogs were fasted for 24 h prior to administration of the first dose. The dosage units consisted of capsules each containing 14 film coated mini-tablets providing a dose of  $200 \pm 5$  mg of theophylline (this dose provided blood levels within the therapeutic range after 4 half lives). Each capsule (size 1) contained 7 uncoated mini-tablets (0.3 cm in diameter,  $15 \pm 0.5$  mg in weight) and providing 100 mg of drug as an immediate release component. The other 7 mini-tablets of similar dimensions were film coated with an amount of Eudragit<sup>®</sup> RL 2% w/w, the methods of manufacture and coating, as well as the dissolution profiles, are described in chapter four. The dissolution profile of the dosage unit was identical to the profile for test unit B given in Fig. 7.1 a. The film coated mini-tablets comprised the 100 mg of controlled release drug.

The first dose unit was administered between 06h00 and 06h45 on the first day of the study. Dosing of each dog was staggered at 15 minute intervals so as to facilitate subsequent blood sampling. Oral administration of the unit was achieved by opening the mouth of the dog, depressing the tongue, placing the capsule in the throat region with subsequent administration of about 100 mL of water. The mouth was firmly closed and, when necessary, air was blown through the dog's nose in order to facilitate

swallowing (Gangadharan et al., 1987). The second, third, fourth, fifth, sixth and seventh doses were administered in the same manner every 12 hours after the first administration, corresponding to 12, 24, 36, 48, 60 and 72 h. Normal feeding was resumed after the first dose until 72 h when food was again discontinued for a period of 24 h. Blood samples were drawn at 0, 2, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 74, 76, 78, 80, 82, 84, 87 and 96 hours. About 3 - 5 mL of blood were drawn each time from the cephalic veins in the forelegs of the dogs. The blood samples were allowed to stand for one hour, centrifuged and the serum kept frozen until analysis.

#### **Determination of Extent of Bioavailability (EBA)**

Parallel studies were carried out using the same four dogs (after a wash-out period of 14 days) and a further two dogs. These were single dose studies involving the oral administration of theophylline anhydrous powder (200 mg) enclosed in a hard gelatin capsule to two dogs, another two received orally a commercial controlled release theophylline tablet (Theo-Dur<sup>®</sup> 200 mg), while the third pair received the test capsule (200 mg). In these parallel studies blood was sampled every hour until 12 h and then at 24 h. In this case blood was drawn each time from the jugular vein via a teflon 16 G cannula and flushed with heparinised normal saline. The parallel studies were performed so that the extent of bioavailability (EBA) of the test unit may be calculated.

#### **Theophylline Determination in Serum**

The concentrations of theophylline in serum were determined using a fluorescence immunoassay system (TDX Analyser, Abbott). The area under the curve (AUC) was calculated in each case by the linear trapezoidal rule.

### 7.3.2 RESULTS

Serum levels of theophylline ( $\mu\text{g/mL}$ ) following the first and seventh doses of the dose unit are shown individually for the four dogs in Fig. 7.3. The area under the curve ( $\text{AUC}^{0 \rightarrow \infty}$ ) for each dog after single dose treatment, the  $\text{AUC}^{\tau_n \rightarrow \tau_n + 1}$  (the AUC during one dosing interval at steady state) after multiple dosing, and the dosage form index (DI) are shown in Table 7.2. The DI is defined as the ratio of the maximum to minimum concentrations of the drug in serum within each inter-dose interval (in h),  $\tau$ , during repetitive administration of the dosage form in the quasi-steady state (Theeuwes and Bayne, 1977). Fig. 7.4 shows the mean serum theophylline concentration  $\pm$  S.D. versus time following the first and seventh doses to the dogs ( $n = 4$ ). Table 7.3 shows the mean  $\text{AUC}^{0 \rightarrow \infty}$  determined during the parallel studies after single dose p.o. treatment with theophylline powder and the commercial product (Theo-Dur<sup>®</sup>). The relative bioavailability (EBA) is calculated with reference to both the Theo-Dur<sup>®</sup> and the theophylline powder.



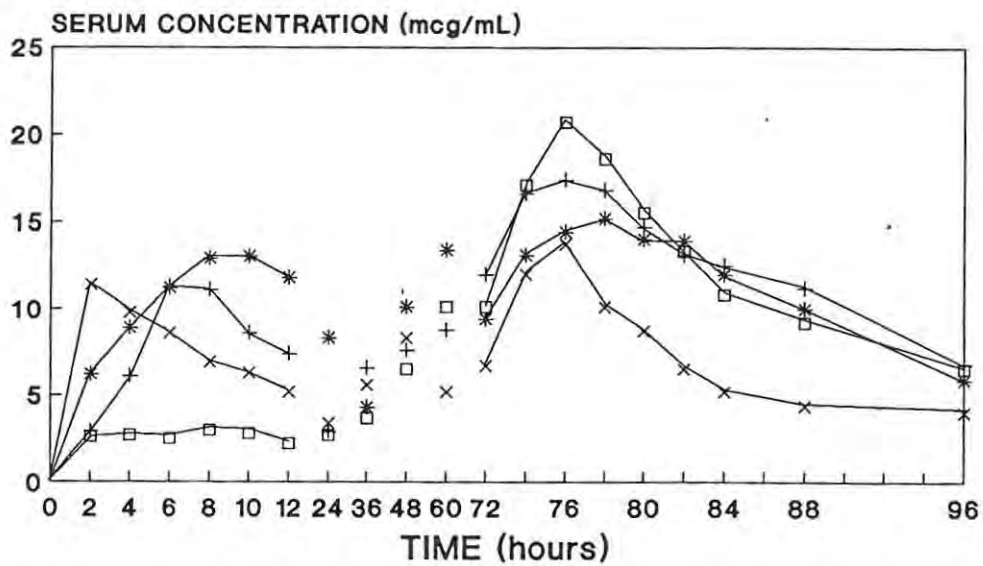


Fig. 7.3 Individual theophylline concentrations as a function of time in serum following peroral administration of 1 unit (200 mg) of experimental controlled release dosage form every 12 h in 4 Beagle dogs.

+ Dog A   \* Dog B   □ Dog C   × Dog D

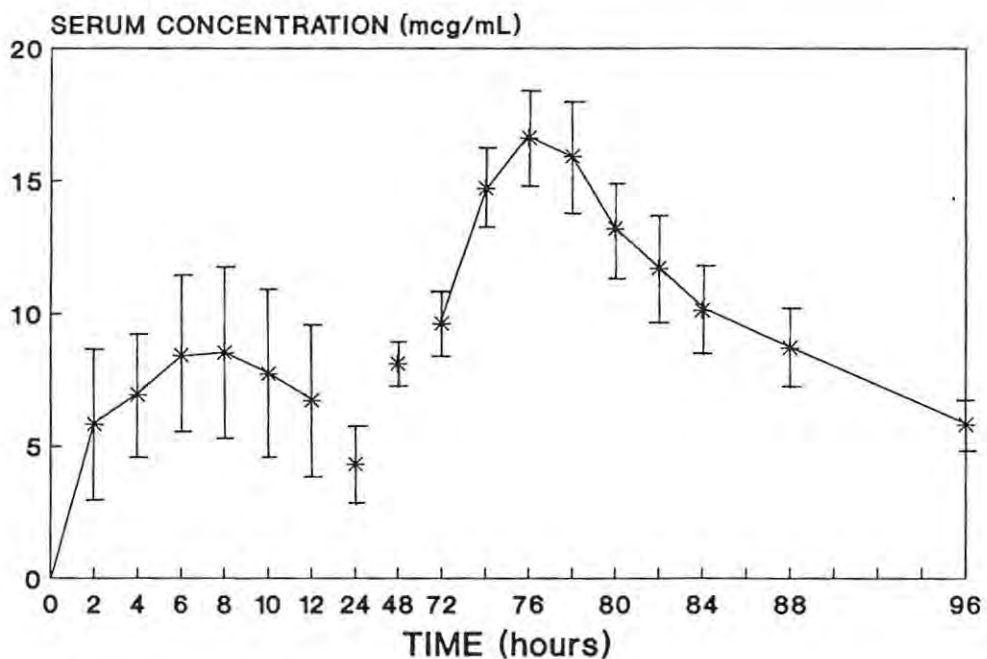


Fig. 7.4 Mean theophylline concentrations  $\pm$ S.D. as a function of time in serum following peroral administration of 1 unit (200 mg) of experimental controlled release dosage form every 12 h in Beagle dogs ( $n = 4$ ).

**TABLE 7.2 Pharmacokinetic parameters after single and multiple dose administration of capsule dosage unit (200 mg) to Beagle dogs.**

Dog	Single Dose		Multiple Dose		D.I.
	$\beta$	$AUC^{0 \rightarrow \infty}$ [( $\mu\text{g/mL}$ )h]	$AUC^{\tau_n \rightarrow \tau_n + 1}$ [( $\mu\text{g/mL}$ )h]	$\frac{AUC^{0 \rightarrow \infty}}{AUC^{\tau_n \rightarrow \tau_n + 1}}$	
A	0.041	154.30	181.7	0.85	1.45
B	0.037	236.52	162.6	1.45	1.62
C	0.047	51.52	191.3	0.27	2.04
D	0.040	141.21	113.9	1.24	2.63
Mean	0.041	145.89	162.38	0.95	1.73
S.D.	0.00419	75.75	34.45	0.52	0.53
S.E.M.	0.00296	53.56	24.36	0.37	0.37
C.V.	10.22	51.92	21.22	54.74	30.64

C.V. = coefficient of variation

**TABLE 7.3 The extent of bioavailability for the capsule dosage unit containing mini-tablets, Theo-Dur<sup>®</sup> and theophylline powder.**

	Test Unit (mini-tablets)	Theo-Dur <sup>®</sup>	Theophylline powder
Mean $AUC^{0 \rightarrow \infty}$	145.89	98.55	133.14
EBA (Theophylline powder as standard)	1.09	0.74	1.0
EBA (Theo-Dur <sup>®</sup> as standard)	1.48	1.0	1.35

### 7.3.3 DISCUSSION

The theophylline serum concentration as a function of time for each dog following oral administration of 7 dose units of the experimental product over 96 h are shown

in Fig. 7.3. There is considerable variation in serum levels from dog to dog, particularly in the case of Dog C where in the first 12 h the serum level never exceeded  $3.0 \mu\text{g/mL}$  compared to Dog B where the concentration reached as high as  $13.0 \mu\text{g/mL}$  after 10 hours. Even at steady state conditions (after 72 h and seventh dose) this variability persisted although to a smaller extent.

With two dogs (B and D) there was a relatively small difference between peak concentrations ( $C_{\text{max}}$ ) during the first 12 h compared with that during the last dosage interval, whereas with the other two (dogs A and C in particular) the higher  $C_{\text{max}}$  during the last dosage intervals was significant. It is also noteworthy that the time to peak ( $t_{\text{max}}$ ) during the first 12 h varied considerably (2 h to 10 h). On the other hand the serum concentration curves from 72 h to 96 h show that the  $t_{\text{max}}$  was reasonably consistent (at 76 h) although the  $C_{\text{max}}$  value itself was variable. In one case (dog C) the  $C_{\text{max}}$  at 76 h exceeded  $20 \mu\text{g/mL}$  but no noticeable signs of theophylline toxicity occurred.

Higher peak concentrations after the seventh dose was expected since multiple dosing with equal dose sizes at equal dosing intervals can produce accumulation in certain individuals.

However it is apparent that dose dependency is absent (ie. no enzyme induction or inhibition occurs) since Table 7.2 shows that the mean AUC during any dosing interval on multiple dosing ( $\text{AUC}^{\tau_n \rightarrow \tau_n + 1}$ ) at steady state is almost the same as the mean AUC after single dose administration ( $\text{AUC}^{0 \rightarrow \infty}$ ). The ratio of the mean  $\text{AUC}^{0 \rightarrow \infty} / \text{AUC}^{\tau_n \rightarrow \tau_n + 1}$  is approximately 1 ( $0.95 \pm 0.52$ ). This ratio in individual dogs

does vary however (Table 7.2). For Dogs A and D this ratio is close to 1 (0.85 and 1.24 respectively) whereas Dog B and C are significantly different.

The mean DI for the experimental dosage unit was calculated to be  $1.73 \pm 0.53$  (obtained from the ratio of  $C_{\max}^{ss}$  to  $C_{\min}^{ss}$ ) which is small enough to ensure that maintenance of blood concentrations in the therapeutic range over a 12 h dosage interval is possible.

The determination of the EBA and the  $AUC^{0 \rightarrow \infty}$  was obtained after single dose cross-over parallel studies (Table 7.3). As shown in Table 7.3 there is little difference between the AUC for the test dosage unit and the theophylline powder indicating that there is as much absorption of theophylline from the test capsule (mini-tablets) as there is from the capsule containing theophylline powder. The EBA of the commercial product is only about 70% of that for the test dose unit and hence the controlled release capsule containing film coated mini-tablets has a distinct advantage over Theo-Dur<sup>®</sup> in that it has greater bioavailability. This is consistent with *in vitro* dissolution studies carried out in earlier work which showed that about 70% of the drug was released in 12 h from Theo-Dur<sup>®</sup> compared with over 95% release from mini-tablets film coated with Eudragit<sup>®</sup> RL 2%.

From the data presented in this chapter it appears that the mini-tablet formulation demonstrates complete release of theophylline and offers the advantage in that precise dosage adjustment can be made.

## **CHAPTER EIGHT**

## CONCLUSIONS

Theophylline is still an important drug used in asthma therapy. Its mechanism of action is complex and there is much which needs to be more precisely understood (Barnes, 1989). One of the problems associated with its use is the 'rather small therapeutic range made more difficult by the fact that the same dose causes considerable variation in plasma concentrations in different patients. Conventional oral dosage forms of theophylline would have to be administered at short frequent time intervals in small doses in order to maintain therapeutic concentrations. This would be greatly inconvenient to the user and produce poor patient compliance. The introduction of oral sustained release theophylline preparations has brought about a radical change to the extent that the risk of high peaks and low trough values has been substantially reduced. However the cost of manufacturing many of the recently developed novel sustained release drug delivery systems is relatively high. In times when health service costs are escalating, the development of simple inexpensive, yet effective, dosage forms are of great economic importance.

Although theophylline is by no means a new drug candidate, preformulation studies were carried out to generate certain physicochemical parameters of theophylline anhydrous which could provide a basis for the design and development of an appropriate controlled release dosage form of the drug. Information relating to the solubility and dissolution rate of the drug was considered most important for this type of dosage form. Theophylline is only slightly soluble in water yet it is rapidly and completely absorbed from uncoated tablets, but absorption is slower and may be incomplete from sustained release preparations. Studies showed that there were significant differences in the dissolution rate depending on the shape and size of the

individual drug particles. However in slow release dosage forms these differences would have little significance over 12 h time periods. The dissolution rate could be greatly reduced in the presence of water-insoluble polymers. The slowly dissolving drug could be completely absorbed at a controlled rate.

Initially granules of theophylline were produced by wet granulation techniques. The binder which provided sufficient adhesive strength to produce a hard granule at a relatively low concentration was sodium carboxymethylcellulose. The granules were film coated using the upward spray method. This method was utilised because the granule bed weight was small and to ensure that the atomising spray nozzle remained in immediate contact with the fluidising bed. The coating conditions were carefully optimised so as to ensure that the coating process was reproducible. Subsequent *in vitro* dissolution studies demonstrated that the drug release rate could be regulated by inclusion of a water-soluble polymer (PEG 1540) in the insoluble coating material (ethylcellulose), and also by varying the amount of coating material on the granules. It has been shown that almost constant release can be achieved from selected quantities of granules coated with varying amounts of polymer enclosed in hard gelatin capsules. However substantial proportions of the drug remained unreleased from the granules, due probably to their highly irregular shape and consequent non-uniform coating thickness.

Mini-tablets were manufactured in order to overcome the problems of drug retention and irregular release resulting from the non-uniformity of the granule shape and coating thickness. By contrast these mini-tablets are each identical in size, shape and

weight. However the amount of coating around each mini-tablet would only be uniform if optimal and reproducible coating conditions were maintained during the upward spray fluidised bed coating process. A diagrammatic comparison of the appearance of a coated granule and mini-tablet in cross sectional view is shown in Fig. 8.1.

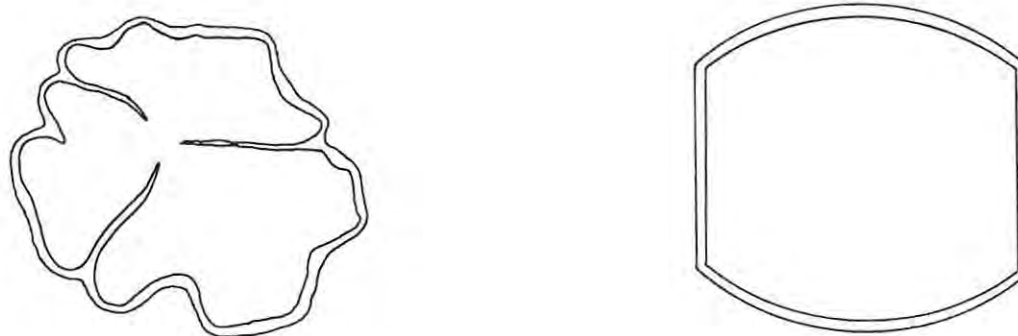


Fig. 8.1 Pores and crevices of a granule which may be filled over with coating material. Uneven coating results in irregular release.

Smooth and regular shaped mini-tablet more evenly coated. Drug release is reasonably consistent.

The mini-tablets film coated with Eudragit<sup>®</sup> RL2% consistently released up to 95% of their total theophylline content both *in vitro* and *in vivo*. In contrast to the granule, the more evenly coated mini-tablet is less likely to possess patches of thinner coating through which more rapid release would readily take place. It was found therefore that less coating material was required for the mini-tablet to provide the same release rate as that obtained from granules. This effect was so marked that mini-tablets coated with ethylcellulose required the inclusion of a water-soluble channelising agent to promote release. Dissolution profiles could be varied at will by careful adjustment of the proportionate number of encapsulated mini-tablets with various amounts of polymeric coating.



Storage of film coated mini-tablets in environments where they will be exposed to different temperatures and relative humidities for prolonged time periods was carried out to specifically establish whether the film coatings would retain their integrity under conditions of stress. It is a possibility that coatings could crack or split producing significantly faster drug release rates. The studies demonstrated that film integrity was maintained for periods even up to 180 days. However drug release was significantly impeded presumably due to some physicochemical changes taking place in the polymeric coating material. The nature and extent of these changes is not precisely known and further work could be undertaken to investigate the mechanisms producing inhibition of release. However, preliminary investigations carried out involving thermogravimetric analysis has shown that moisture loss is not responsible for retarded release. Although *in vitro* drug release is significantly impeded after storage, it is not known at this stage whether *in vivo* release would be similarly affected particularly in view of the poor *in vitro/in vivo* correlations demonstrated in this work for film coated mini-tablets.

In addition it has been shown that certain *in vitro* dissolution media recommended for use in the USP dissolution testing method cannot be relied upon to predict actual *in vivo* absorption of theophylline from film coated mini-tablets. The transport of theophylline through the coating membrane is drastically reduced if the dissolution medium is buffered with phosphate ions. Therefore it is reasonable to assume that the transport mechanisms of other drugs from this, as well as other different formulations, may be also affected producing either inhibition or even enhancement of drug release depending on the composition and nature of the dissolution medium. It is vitally important therefore, when comparing dissolution profiles of the same dosage

form, to pay particular attention to the precise conditions under which the *in vitro* dissolutions tests were conducted. *In vitro* dissolution tests do not necessarily give reliable information about absorption properties of drugs, and an animal model therefore is useful for the evaluation of *in vivo* drug release and bioabsorption during the development of modified-release dosage forms.

The *in vivo* evaluation of the capsules containing uncoated and film coated mini-tablets (Eudragit<sup>®</sup> RL 2%) in Beagle dogs demonstrates that satisfactory release of the drug is provided. Moreover precise dosage titration may be achieved for a particular individual by selecting and adjusting the exact number of mini-tablets in the capsule. There was however poor correlation between *in vitro* and *in vivo* release of theophylline from the film coated mini-tablets and prediction of *in vivo* release could not be made from *in vitro* dissolution data.

The controlled release capsules containing film coated theophylline mini-tablets (Eudragit<sup>®</sup> RL 2%) are easily produced utilising standard equipment. The film coating material was homogenous and filling machines can simply deliver a definite number of mini-tablets into the open capsule body. Production costs would hence be relatively low. This work has demonstrated the bioavailability of this mini-tablet capsule dosage form in Beagle dogs but further work could be directed at evaluating this dosage form in human volunteers.

## BIBLIOGRAPHY

Alhaique, F., Marchetti, M., Ricciari, F.M. and Santucci, E., A polymeric film responding in diffusion properties to environmental pH stimuli: a model for a self-regulating drug delivery system. *J. Pharm. Pharmacol.*, 33 (1981) 413 - 418.

Alkan, M.H., Groves, M.J., Roland, C.L., Teng, C.D., Dwyer, E.M. and Patel, M.C., Small-Scale Film Coating of Tablets, Pellets and Granules. *Pharm. Tech.*, June (1988) 98 - 104.

Alpar, H.O. and Walters, V., Prolongation of the in vitro dissolution of a soluble drug (Phenethicillin potassium) by microencapsulation with ethyl-cellulose. *J. Pharm. Pharmacol.*, 33 (1981) 419 - 422.

Bala, K. and Vasudevan, P., pH-Sensitive Microcapsules for Drug Release. *J. Pharm. Sci.*, 71 (1982) 960 - 962.

Banakar, U.V., Drug Delivery Systems of the 90's. Innovations in Controlled Release. *Am. Pharm.*, NS27 (1987) 39 - 48.

Barnes, P.J., A New Approach to the Treatment of Asthma. *N. Engl. J. Med.*, 321 (1989) 1517 - 1527.

Baveja, S.K., Ranga Rao, K.V. and Padmalatha Devi, K., Zero-order release hydrophilic matrix tablets of  $\beta$ -adrenergic blockers. *Int. J. Pharm.*, 39 (1987) 39 - 45.

Baveja, S.K., Ranga Rao, K.V., Singh, A. and Gombar, V.K., Release characteristics of some bronchodilators from compressed hydrophilic polymer matrices and their correlation with molecular geometry. *Int. J. Pharm.*, 41 (1988) 55 - 62.

Bechgaard, H., Critical factors influencing gastro-intestinal absorption. What is the role of pellets? *Acta Pharm. Technol.*, 28 (1982) 149 - 157.

Bechard, S. and McMullen, J.N., Diffusional release of a solute from a porous polymeric matrix. *Int. J. Pharm.*, 32 (1986) 71 - 77.

Beckett, A.H., Important formulation factors influencing drug absorption; in "Drug Absorption" Prescott, Nimmo (Eds.), Adis press, N.Y., (1981) 133 - 143.

Beckett, A.H., Behrendt, W.A. and Hadzija, B.W., Some aspects on the bioavailability of a controlled release clonidine formulation in man. *Int. J. Pharm.*, 52 (1989) 37 - 45.

Benita, S. and Donbrow, M., Release kinetics of sparingly soluble drugs from ethylcellulose-walled microcapsules: theophylline microcapsules. *J. Pharm. Pharmacol.*, 34 (1982) 77 - 82.

Benita, S., Hoffman, A. and Donbrow, M., Microencapsulation of paracetamol using polyacrylate resins (Eudragit<sup>®</sup> Retard), kinetics of drug release and evaluation of kinetic model. *J. Pharm. Pharmacol.*, 37 (1985) 391 - 395.

Beyger, J.W. and Nairn, J.G., Some factors affecting the microencapsulation of pharmaceuticals with cellulose acetate phthalate. *J. Pharm. Sci.*, 75 (1986) 573 - 578.

British Pharmacopoeia 1980 Vol. 1 H.M.S.O., University Press, Cambridge, p 449.

British Pharmacopoeia 1980 Vol. 2 H.M.S.O., University Press, Cambridge, p 731.

Buckton, G., Ganderton, D. and Shah, R., In vitro dissolution of some commercially available sustained-release theophylline preparations. *Int. J. Pharm.*, 42 (1988) 35 - 39.

Calanchi, M., in : *Microencapsulation*, Nixon, J.R. (ed), Marcel Dekker, Inc, New York, (1976) p 93.

Cameron, C.G. and McGinity, J.W. , Controlled Release Theophylline Tablet Formulations containing Acrylic Resins. Part 2. Combination Resin Formulations. *Drug Dev. Ind. Pharm.*, 13 (1987a) 1409 - 1427.

Cameron, C.G. and McGinity, J.W., Controlled-Release Theophylline Tablet Formulations containing Acrylic Resins. Part 3. Influence of Filler Excipient. *Drug Dev. Ind. Pharm.* 13 (1987b) 303 - 318.

Cartwright, A.C., Controlled release: A regulatory dilemma. *Manuf. Chem.*, March (1987) pp 33, 36, 42.

Chang, R-K. and Hsiao, C., Eudragit<sup>®</sup> RL and RS Pseudolatices: Properties and Performance in Pharmaceutical Coating as a Controlled Release Membrane for Theophylline Pellets. *Drug Dev. Ind. Pharm.*, 15 (1989) 187 - 196.

Chemtob, C., Chaumeil, J.C. and N'Dongo, M., Microencapsulation by ethylcellulose phase separation: microcapsule characteristics. *Int. J. Pharm.*, 29 (1986a) 1 - 7.

Chemtob, C., Chaumeil, J.C. and N'Dongo, M., Tablets of metronidazole microcapsules: Release characteristics. *Int. J. Pharm.*, 29 (1986b) 83 - 92.

Chien, Y.W., Controlled drug release from polymeric delivery systems: biomedical applications and physiochemical principles. In: Juliano, R.L. (ed.) Drug delivery systems. Oxford University Press, Oxford, (1980) p 11 - 93.

Chien, Y.W., Novel drug delivery systems: fundamentals, developmental concepts and biomedical assessments. Marcel Dekker, New York. (1982) p 465 - 573.

Chien, Y.W., Potential Developments and New Approaches in Oral Controlled-Release Drug Delivery Systems. Drug Dev. Ind. Pharm., 9 (1983) 1291 - 1330.

Chien, Y.W., The use of biocompatible polymers in rate-controlled drug delivery systems. Pharm. Tech., May (1985) 50 - 66.

Chien, Y.W., Lambert, H.J. and Grant, D.E., Controlled drug release from polymeric devices 1: Technique for rapid in vitro release studies. J. Pharm. Sci., 63 (1974) 365 - 369.

Chiou, W.L. and Riegelman, S., Pharmaceutical Applications of Solid Dispersion Systems. J. Pharm. Sci., 60 (1971) 1281 - 1302.

Chung, B-H. and Shim, C-K., Dissolution of Theophylline from Sustained-Release Dosage Forms and Correlation with Saliva Bioavailability Parameters. J. Pharm. Sci., 76 (1987) 784 -787.

Ch'ng, H.S., Park, H., Kelly, P. and Robinson, J.R., Bioadhesive polymers as platforms for oral controlled drug delivery II: Synthesis and evaluation of some swelling, water-insoluble bioadhesive polymers. J. Pharm. Sci., 74 (1985) 399 - 405.

Cohen, J.L., In: Analytical Profiles of Drug Substances, Vol. 4, K. Florey (ed.), Academic Press, New York. (1975) pp 466 - 493.

Crank, J., The Mathematics of Diffusion. Clarendon Press, Oxford, (1956) 42 - 61.

Crombeen, J.P. and De Blaey, C.J., In vitro testing of controlled release theophylline preparations: Theolair<sup>®</sup>, Theograd<sup>®</sup> and Theolin<sup>®</sup>. Pharm. Weekbl. Sci. Ed. 5 (1983) 65 - 69.

Dahlinder, L-E, Graffner, C. and Sjögren, J., Strength of the insoluble residues of plastic matrix slow release tablets (Duretter<sup>®</sup>) in vitro and in vivo. Acta Pharm. Suec., 10 (1973) 323 - 332.

Dakkuri, A., Schroeder, H.G. and DeLuca, P.P., Sustained Release from Inert Wax Matrixes II: Effect of Surfactants on Tripeleminamine Hydrochloride Release. J. Pharm. Sci., 67 (1978) 354 - 357.

Daly, P.B., Davis, S.S. and Kennerley, J.W., The effect of anionic surfactants on the release of chlorpheniramine from a polymer matrix tablet. Int. J. Pharm., 18 (1984) 201 - 205.

Davis, S.S., Hardy, J.G. and Fara, J.W., Transit of pharmaceutical dosage forms through the small intestine. Gut, 27 (1986) 886 - 892.

Davis, S.S., Khosla, R., Wilson, C.G. and Washington, N., Gastrointestinal transit of a controlled-release pellet formulation of tiaprofenic acid and the effect of food. Int. J. Pharm., 35 (1987) 253 - 258.

Deasy, P.B., Regina Brophy, M., Ecanow, B. and Joy, M.M., Effect of ethylcellulose grade and sealant treatments on the production and in vitro release of microencapsulated sodium salicylate. *J. Pharm. Pharmacol.*, 32 (1980) 15 - 20.

de Haan, P. and Lerk, C.F., The megaloporous system: a novel principle for zero-order drug delivery I. In vitro and in vivo performance. *Int. J. Pharm.*, 31 (1986) 15 - 24.

Desai, S.J., Simonelli, A.P. and Higuchi, W.I., Investigation of factors influencing release of solid drug dispersed in inert matrices. *J. Pharm. Sci.*, 54 (1965) 1459 - 1464.

Desai, S.J., Singh, P., Simonelli, A.P. and Higuchi, W.I., Investigation of factors influencing release of solid drug dispersed in inert matrices IV. *J. Pharm. Sci.*, 55 (1966) 1235 - 1239..

de Smidt, J.H., Offringa, J.C.A. and Crommelin, D.J.A., Dissolution kinetics of griseofulvin in sodium dodecylsulphate solutions. *J. Pharm. Sci.*, 76 (1987) 711 - 714.

Donbrow, M. and Friedman, M., Enhancement of permeability of ethylcellulose films for drug penetration. *J. Pharm. Pharmacol.*, 27 (1975) 633 - 646.

Dubois, J-L. and Ford, J.L., Similarities in the release rates of different drugs from polyethylene glycol 6000 solid dispersions. *J. Pharm. Pharmacol.*, 37 (1985) 494 - 496.

Eddine, A., Droin, A., Taverdet, J.L. and Vergnaud, J.M., Effect of pH on drug release between sodium salicylate-Eudragit<sup>®</sup> compound and gastric liquid: modelling of the process. *Int. J. Pharm.*, 32 (1986) 143 - 150.



Ellis, E.F., Koysooko, R. and Levy, G., Pharmacokinetics of theophylline in children with asthma. *Pediatrics*, 58 (1976) 542 - 547.

Emori, H., Takafumi, I. and Koishi, M., Effects of Acrylic Acid Polymer and its Arrangement on Drug Release from a Wax Matrix. *J. Pharm. Sci.*, 73 (1984) 910 - 915.

Eskilson, C., Controlled Release by Microencapsulation. *Manuf. Chem.*, March (1985) 33, 36, 39.

Fagerstrom, P.O. and Heintz, L., Absorption of sustained-release theophylline tablets. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, 21 (1983) 359 - 362.

Fassihi, A.R., Biopharmaceutical aspects of drug formulations. *S.A. Pharm. J.*, 57 (1990) 151 - 156.

Fassihi, A.R., Kinetics of drug release from solid matrices: effect of compaction pressure. *Int. J. Pharm.*, 37 (1987) 119 - 125.

Fassihi, A.R., Parker, M.S. and Pourkavoos, N., Solid dispersion controlled release: effect of particle size, compression force and temperature. *Drug Dev. Ind. Pharm.*, II (2 and 3) (1985) 523 - 535.

Feely, L.C. and Davis, S.S., The influence of polymeric excipients on drug release from hydroxypropylmethylcellulose matrices. *Int. J. Pharm.*, 44 (1988a) 131 - 139.

Feely, L.C. and Davis, S.S., Influence of surfactants on drug release from hydroxypropylmethylcellulose matrices. *Int. J. Pharm.*, 41 (1988b) 83 - 90.

Fessi, H., Marty, J.P., Puisieux, F. and Carstensen, J.T., Square root of time dependence of matrix formulations with low drug content. *J. Pharm. Sci.*, 71 (1982) 749 - 752.

Fessi, H., Marty, J.P., Puisieux, F. and Carstensen, J.T., The Higuchi square-root equation applied to matrices with high content of soluble drug substance. *Int. J. Pharm.*, 1 (1978) 265 - 274.

Flynn, G.L., Yalkowsky, S.H. and Roseman, T.J. Mass transport phenomena and models: theoretical concepts. *J. Pharm. Sci.*, 63 (1974) 479 - 510.

Ford, J.L., The Current Status of Solid Dispersions. *Pharm. Acta Helv.* 61 (1986) 69 - 88.

Ford, J.L., Rubinstein, M.H. and Hogan, J.E., Propranolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropylmethylcellulose. *Int. J. Pharm.*, 24 (1985a) 339 - 350.

Ford, J.L., Rubinstein, M.H. and Hogan, J.E., Formulation of sustained release promethazine hydrochloride tablets using hydroxypropylmethylcellulose matrices. *Int. J. Pharm.*, 24 (1985b) 327 - 338.

Ford, J.L., Rubinstein, M.H., McCaul, F., Hogan, J.E. and Edgar, P.J., Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. *Int. J. Pharm.*, 40 (1987) 223 - 234.

Gal, P., Jusko, W.J., Yurichak, A.M. and Franklin, B.A., Theophylline disposition in obesity. *Clin. Pharmacol. Ther.*, 23 (1978) 438 - 444.

Gamlen, M.J., Pellet manufacture for controlled release. *Manuf. Chem.*, June (1985) 55, 57, 59.

Ganderton, D., Sustained release for oral administration. *Manuf. Chem.*, March (1985) 27 - 28, 31.

Gangadharan, B., Ritschel, W.A. and Hussain, S.A., In vivo Evaluation of a Theophylline Oral Controlled-release Unit Dosage Form. *Arzneim. Forsch.* 37 (II) (1987) 1256 - 1257.

Goodhart, F.W., McCoy, R.H. and Ninger, F.C., Release of a Water-Soluble Drug from a Wax Matrix Timed-Release Tablet. *J. Pharm. Sci.*, 63 (1974) 1748 - 1751.

Gregoriadis, G., Targeting of drugs: implications in medicine. *Lancet*, 2 (1981) 241 - 247.

Haleblian, J. and McCrone, W., Pharmaceutical Applications of Polymorphism. *J. Pharm. Sci.*, 58 (1969) 911 - 929.

Hecquet, B., Fournier, C., Depadt, G. and Cappelaere, P., Preparation and release kinetics of microencapsulated cisplatin with ethylcellulose. *J. Pharm. Pharmacol.*, 36 (1984) 803 - 807.

Heller, J. and Trescony, P.V., Controlled Drug Release by Polymer Dissolution II: Enzyme-Mediated Delivery Device. *J. Pharm. Sci.*, 68 (1979) 919 - 921.

Hendeles, L., Weinberger, M., Milavetz, G., Hill, M. and Vaughan, L., Food-Induced "Dose-Dumping" from a Once-a-Day Theophylline Product as a Cause of Theophylline Toxicity. *Chest*, 87 (1985) 758 - 765.

Hendeles, L., Weinberger, M. and Bighley, L., Absolute bioavailability of oral theophylline. *Am. J. Hosp. Pharm.*, 34 (1977) 525 - 527.

Hendeles, L., Weinberger, M. and Wyatt, R. Guide to oral theophylline therapy for the treatment of chronic asthma. *Am. J. Dis. Child.*, 132 (1978) 876 - 880.

Herman, J., Remon, J.P., Lefebvre, R., Bogaert, M., Klinger, G.H. and Schwartz, J.B., The Dissolution Rate and Bioavailability of Hydrochlorothiazide in Pellet Formulations. *J. Pharm. Pharmacol.*, 40 (1988) 157 - 160.

Higuchi, T., Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci.*, 50 (1961) 874 - 875.

Higuchi, T., Mechanisms of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.*, 52 (1963) 1145 - 1149.

Higuchi, W.I., Analysis of data on the medicament release from ointments. *J. Pharm. Sci.*, 51 (1962) 802 - 804.

Higuchi, W.I., Nelson, E. and Wagner, J.G., Solubility and dissolution rate in reactive media. *J. Pharm. Sci.*, 53 (1964) 333 - 335.

Higuchi, W.I., Parrot, E., Wurster, D. and Higuchi, T., Investigation of drug release from solids II. *J. Am. Pharm. Assoc. Sci. Ed.*, 47 (1958) 376 - 383.

Hoblitzell, J.R., Thakker, K.D. and Rhodes, C.T., Effects of Moderate Stress Storage Conditions on the Dissolution Profile of Enteric-coated Aspirin Tablets. *Pharm. Acta Helv.*, 60 (1985) 28 - 32.

Hsieh, D.S.T., Rhine, W.D. and Langer, R., Zero-Order Controlled-Release Polymer Matrices for Micro-and Macromolecules. *J. Pharm. Sci.*, 72 (1983) 17 - 22.

Huber, H.F. and Christenson, G.I., Utilization of hydrophilic gums for the control of drug substance release from tablet formulations II. Influence of tablet hardness and density on dissolution behaviour. *J. Pharm. Sci.*, 57 (1968) 164 - 166.

Huber, H.E., Dale, L.B. and Christenson, G.L., Utilisation of hydrophilic gums for the control of drug release from tablet formulations I. Disintegration and dissolution behaviour. *J. Pharm. Sci.*, 55 (1966) 974 - 976.

Jacobs, M.H., Senior, R.M. and Kessler, G., Clinical experience with theophylline: relationship between dosage, serum concentration, and toxicity. *J.A.M.A.*, 235 (1976) 1983 - 1986.

Jain, N.K. and Naik, S.U., Design of a Slow-Release Capsule Using Laser Drilling. *J. Pharm. Sci.*, 73 (1984) 1806 -1811.

Jalsenjak, I., Nicolaidou, C.F. and Nixon, J.R., The in vitro dissolution of phenobarbitone sodium from ethylcellulose microcapsules. *J. Pharm. Pharmacol.*, 28 (1976) 912 - 914.

Jalsenjak, I., Nixon, J.R., Senjkovic, R. and Stivic, I., Sustained-release dosage forms of microencapsulated isoniazid. *J. Pharm. Pharmacol.*, 32 (1980) 678 - 680.

Jenne, J.W., Wyze, E., Rood, E.S. and MacDonald, F.M., Pharmacokinetics of theophylline. Application to adjustment of the clinical dose of aminophylline. *Clin. Pharmacol. Ther.*, 13 (1972) 349 - 360.

Jonkman, J.H.G., Shoenmaker, R., Grimberg, N. and de Zeeuw, R.A., A new in vitro dissolution test for controlled release theophylline tablets. *Int. J. Pharm.*, 8 (1981) 153 - 156.

Jonkman, J.H.G., Steijnans, V.W., Beier, W., Yska, J.P., Kerkhof, F.A., de Noord, O.E. and Grasmeyer, G., Sustained release properties of the once daily theophylline capsule Euphylong<sup>®</sup> as compared with Theo-Dur<sup>®</sup> tablets. *Int. J. Pharm.* 43 (1988) 139 - 143.

Juslin, M., Turakka, L. and Puumalainen., Controlled Release Tablets Part 1: The use of pellets coated with retarding acrylate plastic in tableting. *Pharm. Ind.*, 42 (1980) 829 - 832.

Kallay, N. and Senjkovic, R., Kinetics of drug dissolution from tablets and capsules at high saturation. *Pharm. Acta Helv.*, 62 (1987) 337 - 340.

Källstrand, G. and Ekman, B., Membrane-Coated Tablets: A System for the Controlled Release of Drugs. *J. Pharm. Sci.*, 72 (1983) 772 - 775.

Kawashima, Y., Handa, T., Kasai, A., Takenaka, H., Lin, S.Y. and Ando, Y., Novel Method for the Preparation of Controlled-Release Theophylline Granules Coated with a Polyelectrolyte Complex of Sodium Polyphosphate - Chitosan. *J. Pharm. Sci.*, 74 (1985) 264 - 268.

Kim, S.W., Petersen, R.V. and Feyen, J., Polymeric drug delivery systems. In: Ariëns, E.J. (ed), *Drug Design*. Academic Press, London, 10 (1980) 193 - 250.

Kohri, N., Iwasa, K., Kurihara, J., Miyazaki, K. and Arita, T., Inter-subject variation in oral absorption of ketoprofen from controlled-release granules in rabbits. *Int. J. Pharm.*, 49 (1989) 213 - 221.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A., Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm.*, 15 (1983) 25 - 35.

Korsmeyer, R.W. and Peppas, N.A., Swelling-controlled delivery systems for pharmaceutical applications: Macro-molecular and modelling considerations. In S.Z. Mansdorf and T.J. Roseman (Eds), *Control Release Delivery Systems*, Dekker, New York, 1983, pp. 77 - 90.

Kotzan, J.A., Vallner, J.V., Stewart, J.T., Honigberg, I.L. and Brown, W.T., An in vivo single-and multiple-dose study of several marketed brands of conventional and controlled-release theophylline. *Drug Intell. Clin. Pharm.*, 18 (1984) 147 - 153.

Lagas, M. and Jonkman, J.H.G., Studies on the delivery mechanisms of Theophylline from a sustained release tablet. *Drug Dev. Ind. Pharm.*, 12 (1986) 489 - 506.

Lagas, M. and Jonkman, J.H.G., Greatly enhanced bioavailability of theophylline on postprandial administration of a sustained release tablet. *Eur. J. Clin. Pharmacol.*, 24 (1983) 761 - 767.

Laghoueg, N., Paulet, J., Taverdet, J.L. and Vergnaud, J.M., Oral polymer-drug devices with a core and an erodible shell for constant drug delivery. *Int. J. Pharm.*, 50 (1989) 133 - 139.

Lapidus, H. and Lordi, N.G., Some factors affecting the release of a water-soluble drug from compressed hydrophilic matrices. *J. Pharm. Sci.*, 55 (1966) 840 - 843.

Lapidus, H. and Lordi, N.G., Drug release from compressed hydrophilic matrices. *J. Pharm. Sci.*, 57 (1968) 1292 - 1301.

Law, T.K., Florence, A.T. and Whateley, T.L., Some chemically modified poloxamer hydrogels: controlled release of prostaglandin-E<sub>2</sub> and testosterone. *Int. J. Pharm.*, 33 (1986) 65 - 69.

Lazarus, J., Pagliery, M. and Lachman, L., Factors influencing the release of a drug from a prolonged-action matrix. *J. Pharm. Sci.*, 53 (1964) 798 - 802.

Lee, V.H-L. and Robinson, J.R., Methods to achieve sustained drug delivery. The Physical Approach: Oral and Parenteral Dosage Forms. In: Sustained and Controlled Release Drug Delivery Systems. Robinson, J.R. (ed.), Dekker, New York, (1978) p 143.

Leeds, N.H., Gal, P., Purohit, A.A. and Walter, J.B., Effect of food on the bioavailability and pattern of release of a sustained-release theophylline tablet. *J. Clin. Pharmacol.*, 22 (1982) 196 - 200.

Lefebvre, R.A., Belpaire, F.M. and Bogaert, M.G., Influence of food on steady state serum concentrations of theophylline from two controlled-release preparations. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, 26 (1988) 375 - 379.

Lehmann, K., Enteric and Retard Coatings of Pharmaceutical Preparations with Aqueous Acrylic Resin Dispersions. *Acta Pharm. Technol.*, 21 (1975) 255 - 260.

Lehmann, K., Bossler, H.M. and Dreher, D., Controlled Drug Release from Small Particles Encapsulated with Acrylic Resins. *Acta Pharm. Suec.*, 13 (1976) supp. page 37.



Li, S.P., Mehta, G.N., Buehler, J.D., Grim, W.M. and Harwood, R.J., A Method of Coating Non-Uniform Granular Particles. *Drug Dev. Ind. Pharm.*, 14 (1988) 573 - 585.

Lindholm, T., Lindholm, B-A., Niskanen, M. and Koskiniemi, J., Polysorbate 20 as a drug release regulator in ethyl cellulose film coatings. *J. Pharm. Pharmacol.*, 38 (1986) 686 - 688.

Lippold, Von B.C., Förster, H., Entwicklung, Herstellung und In- vitro-Testung von peroralen Depotarzneiformen mit konstanter Wirkstoffliberation am Beispiel des Theophyllins. *Pharm. Ind.*, 44 (1982) 735 - 740.

Lippold, Von B.C. and Förster, H., In-vivo-Profung einer peroralen Theophyllin-Depotarzneiform mit Freisetzung nach nullter Ordnung. *Arzneim. Forsch.* 34 (II) (1984) 824 - 829.

Liu, J.C., Farber, M. and Chien, Y.W., Comparative Release of Phenylpropanolamine HCl from Long-Acting Appetite-Suppressant Products: Acutrim<sup>®</sup> v. Dexatrim<sup>®</sup>. *Drug Dev. Ind. Pharm.*, 10 (1984) 1639 - 1661.

Luzzi, L.A. Microencapsulation. *J. Pharm. Sci.*, 59 (1970) 1367 - 1376.

Luzzi, L.A., Zoglio, M.A. and Maulding, H.V., Preparation and evaluation of the prolonged release properties of nylon microcapsules. *J. Pharm. Sci.*, 59 (1970) 338 - 341.

Macheras, P., Koupparis, M. and Apostolelli, E., Dissolution of 4 controlled-release theophylline formulations in milk. *Int. J. Pharm.*, 36 (1987) 73 - 79.

Maysinger, D. and Jalsenjak, I., In situ absorption and in vitro release of microencapsulated cimetidine. *Int. J. Pharm.*, 17 (1983) 129 - 134.

Mazuel, G., Cohen, E.M. and Bastide, M., Standardization of in vitro dissolution assays. *Int. J. Pharm.*, 16 (1983) 97 - 103.

McGinity, J.W., Cameron, C.G. and Cuff, G.W., Controlled Release Theophylline Tablet Formulations containing Acrylic Resins. 1. Dissolution Properties of Tablets. *Drug Dev. Ind. Pharm.*, 9 (1983) 57 - 68.

Mehta, A.M., Scale-up considerations in the fluid-bed process for controlled-release products. *Pharm. Tech.*, February (1988) 46 - 47, 50 - 52.

Mehta, A.M., Valazza, M.J. and Abele, S.E., Evaluation of fluid-bed processes for enteric coating systems. *Pharm. Tech.*, April (1986) 46 - 56.

Mehta, A.M. and Jones, D.M., Coated pellets under the microscope. *Pharm. Tech.*, June (1985) 52 - 60.

Melander, A., Brante, G., Jogansson, O., Lindberg, T. and Wahlin-Boll, E., Influence of food on the absorption of phenytoin in man. *Eur. J. Clin. Pharmacol.*, 15 (1979) 269 - 274.

Miller, R.E., Fanger, G.O. and McNiff, R.G., Republic of South Africa. Pat., (1967), 4211 - 4266.

Mitenko, P.A. and Ogilvie, R.I., Rational intravenous doses of theophylline. *N. Engl. J. Med.*, 289 (1973) 600 - 603.

Motycka, S., Newth, C.J.L. and Nairn, J.G., Preparation and Evaluation of Microencapsulated and Coated Ion-Exchange Resin Beads Containing Theophylline. *J. Pharm. Sci.*, 74 (1985) 643 - 646.

Nakano, M., Ohmori, N., Ogata, A., Sugimoto, K., Tobino, Y., Iwaoku, R. and Juni, K., Sustained Release of Theophylline from Hydroxypropylcellulose Tablets. *J. Pharm. Sci.*, 72 (1983) 378 - 380.

Nicklasson, M., Brodin, A. and Graffner, C., Studies on a rotating disc method to determine drug dissolution rates from inert PVC matrices. *Acta Pharm. Suec.*, 19 (1982) 211 - 222.

Nicklasson, M. and Magnusson, A-B., Program for Evaluating Drug Dissolution Kinetics in Preformulation. *Pharm. Res.*, 6 (1985) 262 - 266.

Nimmo, W.S., Gastric emptying and drug absorption. In: Prescott, L.F., Nimmo, W. (eds) *Drug Absorption*. Adis Press, New York, (1981) p 11 - 18.

Nyqvist, H., Preformulation studies of drug substances for solid dosage forms. *Drug Dev. Ind. Pharm.*, 12 (7) (1986) 953 - 968.

Ogilvie, R.I., Clinical pharmacokinetics of theophylline. *Clin. Pharmacokinet.*, 3 (1978) 267 - 293.

Okhamafe, A.O. and York, P., Interaction Phenomena in some Aqueous-Based Tablet Coating Polymer Systems. *Pharm. Res.*, 1 (1985) 19 - 23.

Okhamafe, A.O. and York, P., Interaction Phenomena in Pharmaceutical Film Coatings and Testing Methods. *Int. J. Pharm.*, 39 (1987) 1 - 21.

Paifsky, K.M. and Ogilvie, R.I., Dosage of theophylline in bronchial asthma. *N. Engl. J. Med.*, 292 (1975) 1218 - 1222.

Parab, P.V., Oh, C.K. and Ritschel, W.A., Sustained Release from Precirol (Glycerol Palmito-Stearate) Matrix. Effect of Mannitol and Hydroxypropylmethylcellulose on the Release of Theophylline. *Drug Dev. Ind. Pharm.*, 12 (1986) 1309 - 1327.

Park, K. and Robinson, J.R., Bioadhesive polymers as platforms for oral-controlled drug delivery: method to study bioadhesion. *Int. J. Pharm.*, 19 (1984) 107 - 127.

Parsons, R.L. and Kaye, C.M., Plasma propranolol and practolol in adult cardiac disease. *Br. J. Clin. Pharmacol.*, 1 (1974) 348 P.

Paul, D.R., Modelling of solute release from laminated matrices. *J. Membr. Sci.*, 23 (1985) 221 - 235.

Pedersen, S., Delay in the absorption rate of theophylline from a sustained release theophylline preparation caused by food. *Br. J. Clin. Pharmacol.*, 12 (1981) 904 - 905.

Pedersen, S. and Moller-Petersen, J., Erratic absorption of a slow release theophylline sprinkle product. *Pediatrics*, 74 (1984) 534 - 538.

Peppas, N.A., Analysis of Fickian and non-Fickian drug release from polymers. *Pharm. Acta Helv.*, 60 (1985) 110 - 111.

Pitt, C.G., Gratzl, M.M. Jeffcoat, A.R., Zweidinger, R. and Schindler, A., Sustained Drug Delivery Systems II: Factors Affecting Release Rates from Poly(E-caprolactone) and Related Biodegradable Polyesters. *J. Pharm. Sci.*, 68 (1979) 1534 - 1538.

Prasad, V.K., Rapaka, R.S., Knight, P.W. and Cabana, B.E., Dissolution medium a critical parameter to identify bioavailability problem of frusemide tablets. *Int. J. Pharm.*, 11 (1982) 81 - 90.

Porter, S.C. and Hogan, J.E., Tablet film-coating. *Pharm. Int.*, 5 (1984) 122 - 127.

Raghunathan, Y., Amsel, L., Hinsvark, O. and Bryant, W., Sustained-Release Drug Delivery System I: Coated Ion-Exchange Resin System for Phenylpropanolamine and Other Drugs. *J. Pharm. Sci.*, 70 (1981) 379 - 384.

Rall, T.W. in: Gilman, A.G., Goodman, L.S., Gilman, A. (eds) *The Pharmacological Basis of Therapeutics*, 6th edn, Macmillan, New York, (1980) pp 592 - 607.

Ranga Rao, K.V. and Padmalatha Devi, K., Swelling controlled- release systems: recent developments and applications. *Int. J. Pharm.*, 48 (1988) 1 - 13.

Roseman, T.J. Controlled release from matrix systems. *J. Pharm. Sci.*, 64 (1975) 1731 - 1732.

Roseman, T.J. and Higuchi, W.I., Release of medroxyprogesterone acetate from a silicone polymer. *J. Pharm. Sci.*, 59 (1970) 353 - 357.

Rotstein, J., Estrin, I., Cunningham, C., Gilbert, M., Jordan, A., Lamstein, J., Safrin, M., Wimer, E. and Silson, J., The use of a sustained-release aspirin preparation in the management of rheumatoid arthritis and osteoarthritis. *J. Clin. Pharmacol.*, 7 (1967) 97.

Rowe, R.C., Film-coating - the ideal process for the production of modified-release oral dosage forms. *Pharm.Int.*, January (1985) 14 - 17.

Rowe, R.C., The effect of the molecular weight of ethylcellulose on the drug release properties of mixed films of ethylcellulose and hydroxypropylmethylcellulose. *Int. J. Pharm.*, 29 (1986) 37 - 41.

Saini, T.R., Gour, H.S. and Sharma, S.N., Microcapsules - how to design a dosage form. *Manuf. Chem.*, July (1989) 40 - 41.

Salib, N.N., El-Menshawly, M.A. and Ismail, A.A., Utilization of Sodium Alginate in Drug Microencapsulation. *Pharm. Ind.*, 40 (1978) 1230 - 1234.

Samuelov, Y., Donbrow, M. and Friedman, M., Sustained Release of Drugs from Ethylcellulose-Polyethylene Glycol Films and Kinetics of Drug Release. *J. Pharm. Sci.*, 68 (1979) 325 - 329.

Schwartz, J.B. Simonelli, A.P. and Higuchi, W.I., Drug Release from Wax Matrixes I. *J. Pharm. Sci.*, 57 (1968) 274 - 277.

Shah, N.B. and Sheth, B.B., A method for study of timed-release films. *J. Pharm. Sci.*, 61 (1972) 412 - 416.

Shami, E.G., Dudzinski, J.R. and Lantz, R.J. in "The Theory and Practice of Industrial Pharmacy" (Lachman, L., Lieberman, H.A. and Kanig, J.L., ed.), Lea & Febiger, Philadelphia, (1976) pp 1 - 31.

Shaw, J.E. and Chandrasekaran, S.K., Controlled topical delivery of drugs for systemic action. *Drug Metab. Rev.*, 8 (1978) 223 - 233.

Shefter, E. and Higuchi, T., Dissolution behaviour of crystalline solvated and non-solvated form of some pharmaceuticals. *J. Pharm. Sci.*, 52 (1963) 781 - 791.

Simonelli, A.P., Mehta, S.C. and Higuchi, W.I., Dissolution Rates of High Energy Polyvinylpyrrolidone (PVP) - Sulfathiazole Coprecipitates. *J. Pharm. Sci.*, 58 (1969) 538 - 549.

Simons, K.J., Simons, F.E.R., Plett, K.D. and Scerbo, C., Dissolution Studies of Some Sustained-Release Theophylline Dosage Forms. *J. Pharm. Sci.*, 73 (1984) 939 - 941.

Singhvi, S.M., McKinstry, D.N., Shaw, J.M., Willard, D.A. and Migdalof, B.H., Effect of food on the bioavailability of captopril in healthy subjects. *J. Clin. Pharmacol.*, 22 (1982) 135 - 140.

Sips, A.P., Edelbroek, P.M., Kulstad, S., De Wolff, F.A. and Dijkman, J.H., Food does not effect bioavailability of theophylline from Theolin<sup>®</sup> retard. *Eur. J. Clin. Pharmacol.*, 26 (1984) 405 - 407.

Sjögren, J., Controlled release oral formulation technology. In: Prescott, L.F. and Nimmo, W.S. (eds), *Rate Control in Drug Therapy*. Churchill Livingstone, N.Y. (1985), p 39.

Sjögren, J., Drug formulation to minimise gastrointestinal toxicity. In: Prescott, L.F., Nimmo, W.S. (eds). *Drug Absorption*. Adis Press, New York. (1981) p 205 - 216.

Sjögren, J., Studies on a sustained release principle based on an inert plastic matrix. *Acta Pharm. Suec.* 8 (1971) 153 - 168.

Spangler, D.L., Kalof, D.D., Bloom, F.L. and Wittig, H.J., Theophylline bioavailability following oral administration of six sustained-release preparations. *Ann. Allergy*, 40 (1978) 6.

Staniforth, J.N., in *Pharmaceutics: The Science of Dosage Form Design* (Ed. Aulton, M.E.), Churchill Livingstone, N.Y., (1988) p 564.

Summers, R.S., Summers, B. and Rawnsley, S., The bioavailability, absorption characteristics and formulation of four commercially-available controlled-release theophylline products. *Int. J. Pharm.*, 30 (1986) 83 - 88.

Suryakusuma, H. and Jun, H.W., Encapsulated hydrophilic polymer beads containing indomethacin as controlled release drug delivery system. *J. Pharm. Pharmacol.*, 36 (1984) 497 - 501.

Suzuki, K. and Price, J.C., Microencapsulation and Dissolution Properties of a Neuroleptic in a Biodegradable Polymer, Poly(D,L-lactide). *J. Pharm. Sci.*, 74 (1985) 21 - 24.

Thakkar, A.L., Tensmeyer, L.G. and Wilham, W.L., NMR evidence for self-association of theophylline in aqueous solution. *J. Pharm. Sci.*, 60 (1971) 1267 - 1269.

"The Merck Index" 10th edn., (1983) Windholly, M. (Ed.) Merck: Rahway N.J., p 1328.

The United States Pharmacopeia XXIst et Revision, Mack Easton, Pa. (1985) p 1243 - 1244.

Theeuwes, F., Elementary Osmotic Pump. *J. Pharm. Sci.*, 64 (1975) 1987 - 1991.

Theeuwes, F., Novel drug delivery systems. In: Prescott, L.F., Nimmo, W.S. (eds) *Drug absorption*. Adis Press, New York, (1981) p 157 - 176.

Theeuwes, F., Oros Osmotic System Development. *Drug Dev. Ind. Pharm.*, 9 (1983) 1331 - 1357.



Theeuwes, F. and Bayne, W., Dosage Form Index: An Objective Criterion for Evaluation of Controlled-Release Drug Delivery Systems. *J. Pharm. Sci.*, 66 (1977) 1388 - 1392.

Theeuwes, F., Swanson, D., Wong, P., Bensen, P., Place, V., Heimlich, K. and Kwan, K.C., Elementary osmotic pump for indomethacin. *J. Pharm. Sci.*, 72 (1983) 253 - 258.

Thiel, W.J. and Nguyen, L.T., Fluidised bed film coating of an ordered powder mixture to produce microencapsulated ordered units. *J. Pharm. Pharmacol.*, 36 (1984) 145 - 152.

Thompson, P.J., Skypala, I., Dauson, S., McAllister, W.A.C. and Turner Warwick, M., The effect of diet upon serum concentrations of theophylline. *Br. J. Clin. Pharmacol.*, 16 (1983) 267 - 270.

Tojo, K., Intrinsic Release Rate from Matrix-Type Drug Delivery Systems. *J. Pharm. Sci.* 74 (1985) 685 - 687.

Touitou, E. and Donbrow, M., Drug release from non- disintegrating hydrophilic matrices: sodium salicylate as a model drug. *Int. J. Pharm.*, 11 (1982) 355 - 364.

Turnberg, L.A., Gastrointestinal drug absorption - anatomical and physiological considerations. In: Prescott, L.F., Nimmo, W.S. (eds) *Drug Absorption*. Adis Press, New York, (1981) p 6 - 10.

Urtti, A., Juslin, M. and Munalainen, O., Pilocarpine release from hydroxypropylcellulose-polyvinylpyrrolidone matrices. *Int. J. Pharm.*, 25 (1985) 165 - 178.

Upton, R.A., Thiercelin, J-F., Guentert, T.W., Sansom, L., Powell, J.R., Coates, P.E. and Riegelman, S., Evaluation of the absorption from some commercial sustained-release theophylline products. *I. Pharmacokinet. Biopharm.*, 8 (1980) 131.

Vashi, V.I. and Meyer, M.C., Effect of pH on the In Vitro Dissolution and In Vivo Absorption of Controlled-Release Theophylline in Dogs. *J. Pharm. Sci.*, 77 (1988) 760 - 764.

Venho, V.M.K. and Eriksson, H., The rabbit: an animal model for comparative bioavailability studies of drug. *Int. J. Pharm.*, 30 (1986) 91 - 94.

Weinberger, M.M., Hendeles, L. and Bighley, L., The relation of product formulation to absorption of oral theophylline. *N. Engl. J. Med.*, 299 (1978) 852 - 857.

Weinberger, M.M., Hendeles, L. and Wong, L., Relationship of formulation and dosing interval to fluctuation of serum theophylline concentration in children with chronic asthma. *J. Pediatr.*, 99 (1981) 145 - 152.

Wilson, C.G. and Hardy, J.G., Gastrointestinal transit of an osmotic tablet drug delivery system. *J. Pharm. Pharmacol.*, 37 (1985) 573 - 575.

Wilson, C.G. and Washington, N., Physiological factors in novel drug delivery. *Manuf. Chem.*, February (1985) 37, 39.

Wood, J.H., Syarto, J.E. and Letterman, H., Improved Holder for Intrinsic Dissolution Rate Studies. *J. Pharm. Sci.*, 54 (1965) 1068.

Zuidema, J., Physical and chemical properties of xanthine derivatives; in Sustained Release Theophylline. A biopharmaceutical challenge to a clinical need. Merkus, Hendeles (Eds.), Excerpta Medica, Amsterdam, (1983) 11 - 25.

Zwillich, C.W., Sutton, F.D., Neff, T.A., Cohn, W.M., Matthay, R. and Weinberger, M., Theophylline induced seizures in adults; correlation with serum concentrations. Ann. Intern. Med., 82 (1975) 784 - 787.