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INVESTIGATION OF CELLULOSE ETHER POLYMERS IN CONTROLLED DRUG DELIVERY

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INVESTIGATION OF CELLULOSE ETHER POLYMERS IN CONTROLLED DRUG DELIVERY

by

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Dedication

To my Father and my Mother,

Mr. Prasit and Mrs. Poolsuk Mahaguna

To my Family

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INVESTIGATION OF CELLULOSE ETHER POLYMERS IN CONTROLLED DRUG DELIVERY

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Cellulose ethers are widely used in a variety of pharmaceutical applications. The purpose of this research was to investigate the use of cellulose ether polymers to formulate different oral pharmaceutical dosage forms, and to control the release of active ingredient from the specific drug delivery system over an extended period of time. In this study, applications of the cellulose ether polymer in matrix tablets and multiparticulate dosage forms, were investigated. Specifically, ethylcellulose (EC) used in aqueous polymeric coating, and hydroxypropyl methylcellulose (HPMC) used in hydrophilic matrix tablets, were investigated in this study. Formulations and processing parameters were developed and optimized in order to achieve the desirable rate of drug release from each drug delivery system.

For the matrix tablet system, an efficient method to achieve complete recovery of alprazolam from powder blends and tablets containing HPMC was developed and qualified. Formulation parameters, including tablet size, polymer levels, excipient type and level, molecular weight type of HPMC, and dissolution media, were investigated and optimized during development of the drug delivery systems. Finally, two oral controlled release tablet formulations (containing different molecular weight types of HPMC) with equivalent dissolution profiles were developed and used for *in vivo* bioequivalence study. Molecular weight types of HPMC did not influence *in vitro* or *in vivo* performance of controlled release tablets and provided bioequivalent results in both fed and fasted states.

For the multiparticulate system, the amount of drug release from EC coated matrix beads was influenced by drug type, plasticization, water-soluble additive, and curing condition. Optimum curing conditions were determined in order to ensure complete film coalescence without disrupting film integrity. Additionally, the amount of theophylline released from EC coated beads was manipulated by the inclusion of different types and levels of water-soluble additives.

As found for both controlled release drug delivery systems, formulation and processing parameters must be investigated and optimized in order to achieve desirable release profiles and stabilize the amount of drug released throughout the shelf-life of the product.

This research study provided useful information on preformulation and formulation optimization during development of controlled drug delivery systems containing cellulose ether polymers.

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CHAPTER 1

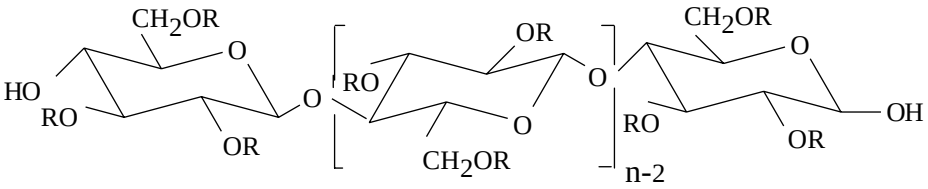
INTRODUCTION

1.1 HISTORICAL REVIEW OF CELLULOSE AND CELLULOSE ETHERS

Cellulose has been the primary component of the human diet since the early human history and it is the most abundant natural polymeric raw material (i.e. wood source) available. Cellulose is also a primary source for all cellulose derivatives that are considered safe and acceptable for use in food, pharmaceutical, medical, cosmetic, and agricultural applications [Nevell and Zeronian, 1985]. Structurally, cellulose consists of repeating units of anhydro ß-D glucopyranose, bonded together by ß-1,4-glycosidic linkage, non-reducing end unit on one side, determined number-average degree of polymerization, and reducing end unit on another side of the cellulose chain, exhibited the chemical properties similar to those of the glucose molecule. Due to a high degree of polymerization, physicochemical properties of cellulose, determined by the intermediate backbone, are high crystallinity, high cohesive density, are water insoluble, but are water absorbable. Cellulose structure can be chemically modified and classified by methods of preparation into four groups of cellulose derivatives - hydrocellulose (hydrolysis method), cellulose esters (esterification method; non-enteric and enteric subgroups), cellulose ethers (etherification or nucleophilic substitution method), and oxycellulose (oxidation method). Cellulose ethers currently described in the USP/NF, such as methylcellulose

(MC), hydroxypropyl methylcellulose (HPMC), ethylcellulose (EC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), sodium carboxymethylcellulose (NaCMC), and calcium carboxymethylcellulose (CaCMC), are most widely used in a variety of pharmaceutical applications, including solid dosage forms (i.e. tablets, pellets, microparticles), liquid or semi-solid dosage forms (i.e. solution, gel, emulsion, suspension), and taste or odor masking. As shown in Figure 1.1, different types of cellulose ethers are commonly prepared by a nucleoophilic substitution method. Except for EC polymer, which is soluble in a variety of organic solvents (e.g. esters, aromatic hydrocarbons, alcohols, chlorinated solvents), other cellulose ethers are water soluble and the viscosity of aqueous solutions depends on polymer concentration, molecular weight, and temperature. Hydration rates of each type of cellulose ether depend on the nature of the substitution unit present, degree of substitution (i.e. moles of substitution), pH and temperature of dissolution media, and particle size. For example, the hydroxypropoxyl group is more hydrophilic than the methoxyl group; therefore, HPMC is more readily hydrated than MC. Cellulose ethers serve multiple functions in pharmaceutical dosage forms. MC (Methocel A, The Dow Chemical Company) can be used as a binder and thickening agent. EC powder (Aqualon®, Hercules Inc., Ethocel, The Dow Chemical Company) can be used for solvent granulation for water sensitive drugs, tablet coatings, microencapsulation, taste masking, controlled release matrix tablets, and binder, whereas EC aqueous colloidal dispersion (Aquacoat® ECD, FMC Corporation; Surelease®, Colorcon) can be used for coating, granulation, and taste masking.

HEC (Natrosol®, Hercules Inc.), HPC (Klucel®, Hercules Inc.), and NaCMC (Aqualon™ Cellulose Gum, Hercules Inc.) function as thickening agents, protective colloidal agents, suspending agents, and emulsion stabilizers. The crossed-link form of NaCMC or croscarmellose sodium type A (Ac-Di-Sol, FMC Corporation) can be used as a dissolution aid or as a disintegrant in tablets or capsules. HPMC (Methocel E, F, K, J, The Dow Chemical Company) is used as a binder, coatings, and controlled release polymer [Kumar and Banker, 1993]. In this study, applications of the cellulose ether polymers in two types of controlled release solid dosage forms, including single unit system and multiparticulate system, were investigated. Specifically, EC, a water insoluble cellulose ether, which is widely used in aqueous polymeric coating, and HPMC, a water soluble cellulose ether, which is commonly used in hydrophilic matrix drug delivery systems, were used in this study.



Cellulose Ether Type	**Substitution Unit**
Methylcellulose (MC)	R = -H, $-CH_3$
Ethylcellulose (EC)	R = -H, $-C_2H_5$
Hydroxyethylcellulose (HEC)	R = -H, $-CH_2CH_2OH$, $-(CH_2)_2O(CH_2)_2OH$
Hydroxypropylcellulose (HPC)	R = -H, $-CH_2CH(OH)CH_3$
Hydroxypropyl methylcellulose (HPMC)	R = -H, $-CH_3$, $-CH_2CH(OH)CH_3$
Sodium carboxymethylcellulose (NaCMC)	R = -H, $-CH_2COONa$

Figure 1.1 Structure of cellulose ethers

1.2 CELLULOSE ETHERS IN CONTROLLED RELEASE DRUG DELIVERY

Novel drug delivery devices available today are administered by oral, buccal, transdermal, parenteral, ocular, implantable, intravaginal, or intrauterine. These devices are constructed from two types of controlled release drug delivery systems: capsule-type drug delivery systems and matrix-type drug delivery systems [Chien, 1982]. Controlled release solid dosage forms become important for the oral administration of many drug substances because they provide more consistency in blood levels [Pather et al., 1998]. Oral controlled release solid dosage forms can also be classified into two systems as follow:

- Single unit system (i.e. film coated tablets, matrix tablets, film coated hard and soft gelatin capsules)

- Multiparticulate system (i.e. film coated beads)

In this research study, the use of cellulose ether polymers in both systems, including matrix tablets (HPMC polymer) and film coated matrix beads (EC polymer), was investigated.

1.2.1 Single Unit System (Matrix Tablets)

Hydrophilic matrix drug delivery systems consist of a hydrophilic polymer, drug, and other excipients distributed throughout the matrix. This system is dependent on polymer wetting, polymer hydration, and polymer dissolution for the controlled release of drug. At the same time, other soluble excipients or drug substances comprising the tablet will also become wet, dissolve, and diffuse out of the matrix, while insoluble excipients or drug

substances will be held in place until the surrounding polymer/excipient/drug complex erodes or dissolves away (Figure 1.2) [The Dow Chemical Company, 2000].

Hydrophilic matrix drug delivery systems are widely used to control drug release due to their major advantages over other delivery systems, including [Vazquez et al., 1992; Alderman, 1984]:

- Desirable drug release profile can be obtained due to high flexibility of the system.

- Reproducible drug release profiles can be obtained by properly controlling the formulation parameters. Variability is slightly lower than coated dosage forms.

- Risk of dose dumping can be minimized since the drug release is controlled by diffusion through the hydrophilic gel layers or polymer erosion.

- Cost effectiveness is considered low since most products can be manufactured using inexpensive gelling agents with broad FDA acceptance and by using direct compression.

- Wide range of drug loading can be incorporated into the system and large doses of active drug substances can be delivered.

HPMC, one of the commercially available hydrophilic polymers, is commonly used to prepare hydrophilic drug delivery systems.

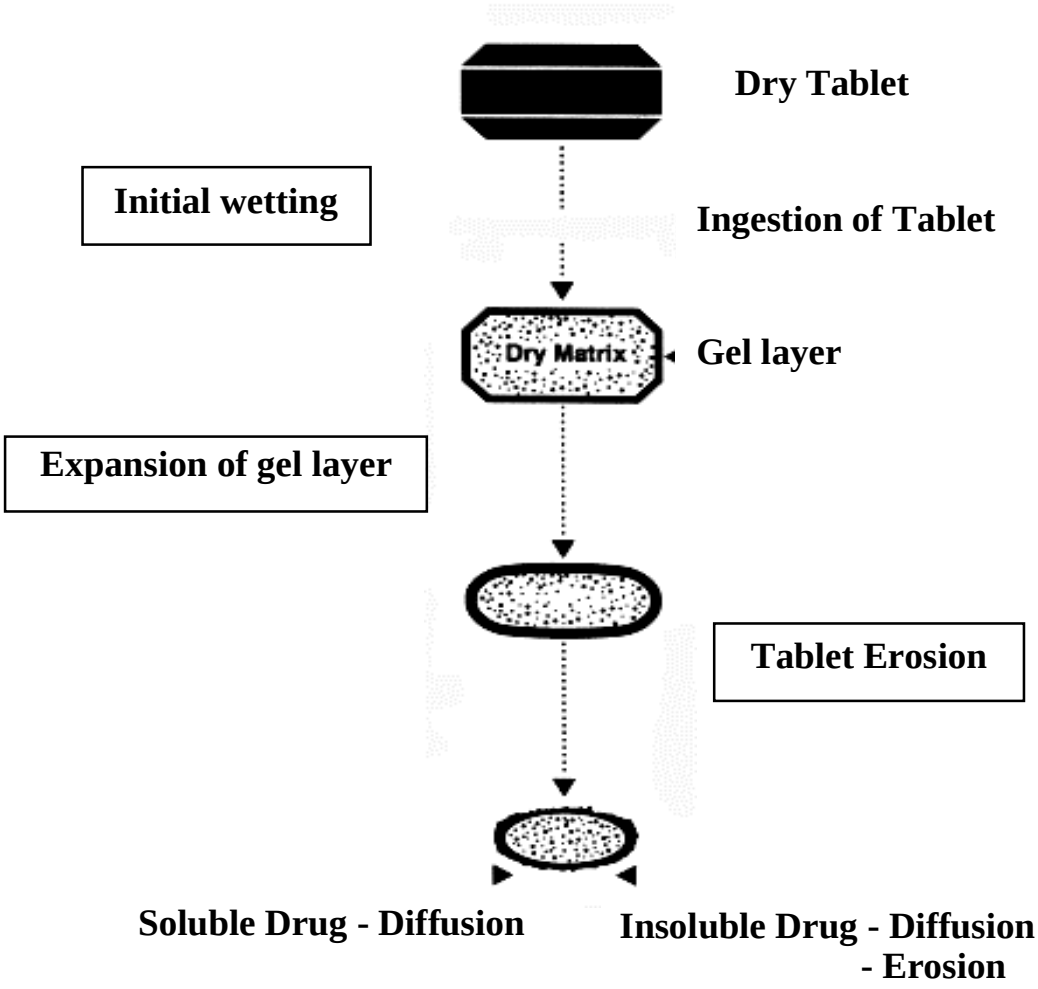


Figure 1.2 Hydrophilic matrix system [Alderman, 1984]

Hydroxypropyl Methylcellulose (HPMC) Polymer

HPMC, a non-ionic cellulose ether, is a mixed alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropoxyl groups. The hydration rate of HPMC depends on the nature of these substituents, such as the molecular structure and the degree of substitution. Specifically, the hydration rate of HPMC increases with an increase in the hydroxypropoxyl content [The Dow Chemical Company, 1995]. The gelation temperature of HPMC ranges between 58-90˚C, depending on the hydroxypropoxyl and methoxyl contents [The Dow Company, 1988]. The solubility of HPMC is pH independent [Alderman, 1984]. HPMC can be slowly dissolved in cold water to form a viscous solution, but is not very soluble in hot water. Additionally, it can be dissolved in most polar organic solvents or binary systems of methylene chloride or chloroform and alcohol [Budavari et al., 1996; Kumar and Banker, 1993; Archer, 1992]. It is practically insoluble in pure chloroform, ethanol and ether [Kibbe, 2000]. Therefore, the recommended method to prepare HPMC aqueous solutions is to first thoroughly disperse and hydrate the powder in a portion of hot water (about one-third of the total volume) heated above 90˚C with vigorous stirring to prevent lumping. Complete solubilization is then accomplished by adding the remaining cold water (two-thirds of the total volume) to lower the temperature of the dispersion. As the temperature is lowered, a point is reached where HPMC becomes water soluble, resulting in increased viscosity ("hot/cold" techniques) [The Dow Chemical Company, 1988]. The viscosity of the aqueous solution can be increased by

increasing the molecular weight distribution of the polymer, the concentration of the polymer or decreasing the temperature of the solution.

According to the USP Official Monograph, HPMC polymer is classified into four types based on percent of methoxyl and hydroxypropoxyl substitution groups. They include HPMC substitution types 1828, 2208, 2906, and 2910. Percent of each substitution group for each HPMC type is shown in Table 1.1 [United States Pharmacopeial Convention, 1999]. Examples of commercially available cellulose ether products, under the tradename of Methocel, from the Dow Chemical Company (Midland, MI, USA), that corresponds to each USP type, are also included in Table 1.1. For Methocel products, each letter identifies the type of cellulose ether. Specifically, "A" identifies MC products, whereas "E", "F", "J", and "K" identify HPMC products. Each type of cellulose ether has a different rate of hydration due to variation of the substitution level within the molecule. The methoxyl substituent is a relatively hydrophobic component and does not contribute to the rate of hydration as greatly as the hydrophilic hydroxypropoxyl substituent does. In addition to the letter-identified type, the number that follows identifies the viscosity in millipascal-seconds (mPa.s) or centipoises (cPs) of that product measured at 2% concentration in water at 20˚C (68˚F). The letters "C" and "M" represent "100" and "1000" in designating viscosity, respectively. While the letters "P", "LV", and "CR" stand for "Premium grade" for food and pharmaceutical application, "Low Viscosity", and "Controlled Release grade", respectively. For example, Methocel K100LVP is the HPMC Premium grade product with low viscosity around 100 cPs measured at 2%

concentration in water at 20 ˚C. Methocel K4MP is the HPMC Premium grade product with viscosity around 4000 cPs measured at 2% concentration in water at 20˚C [The Dow Chemical Company, 1988; The Dow Chemical Company, 1995; Kibbe, 2000].

HPMC polymers are widely used in controlled release dosage forms due to its nontoxic nature, its capacity to accommodate high levels of drug loading, and its non-pH dependence [Helena Amaral et al., 2001]. In this study, the use of HPMC in the controlled release matrix tablet is investigated in different areas within the following sections.

Table 1.1 Type of Cellulose Ethers Specified in USP 24/NF 19 and Commercially Available Products from The Dow Chemical Company [United States Pharmacopeial Convention, 1999 ; The Dow Chemical Company, 1988 ; The Dow Chemical Company, 1995]

USP Type	Dow Chemical Product	%Methoxyl	%Hydroxypropoxyl	Relative Rate of Hydration
MC	Methocel A	27.5-31.5	0.0	Slowest
HPMC				
1828	Methocel J	16.5-20.0	23.0-32.0	Fastest
2208	Methocel K	19.0-24.0	7.0-12.0	Next Fastest
2906	Methocel F	27.0-30.0	4.0-7.5	Slower
2910	Methocel E	28.0-30.0	7.0-12.0	Slow

1.2.1.1 Drug Recovery from Hydrophilic Matrix Tablets

In tablet manufacturing, quantification of the drug substance (i.e. content uniformity or composite assay) in the drug product is a mandatory requirement for release. Typically, a content uniformity assay is performed by pulverizing a tablet into powder and extracting the drug substance using an organic solvent(s) with sonication or mechanical stirring [Dortunc et al., 1998]. However, extracting a lipophilic drug substance from gelling HPMC tablets is much more complicated due to the highly lipophilic nature of the drug substance and the gelling properties of HPMC polymer. Dortunc et al. described a content uniformity method for hydrophilic matrix tablets containing HPMC K4M or K15M and pindolol in a buccoadhesive matrix tablet. A pulverized tablet was treated with enough pH 6.8 phosphate buffer solution:methanol mixture (98:2), in which pindolol had a high solubility (222.2 µg/ml) when compared to its solubility in pH 6.8 buffer solution alone (8.2 µg/ml). However, the percent drug recovery and drug content uniformity results were not reported [Dortunc et al., 1998]. Also, quantification of acetazolamide in matrix tablets containing HPMC K4M or K15M was reported, but the quantitative assay method and drug content uniformity results were not reported [Dortunc and Gunal, 1997]. A review of the literature indicated that no specific method has been reported for quantification of a lipophilic drug substance contained in HPMC matrix tablets.

In order to develop a method to recover a lipophilic drug from controlled release matrix tablets containing HPMC, alprazolam, a benzodiazepine, was

chosen as the model drug in this study. Alprazolam is classified as a DEA controlled substance Schedule IV. It has a rapid onset of action coupled with a relatively short half-life, and is indicated for the management of anxiety or panic disorders, anxiety associated with depression, and neurosis. The exact mechanism of action for alprazolam is unknown; however, literature indicates its proposed mechanism by binding to stereospecific receptors at several sites within the central nervous system (CNS). It may interact allosterically with the $GABA_A$ receptor by modulating $GABA_A$ receptor to increase activity, increasing chloride channel activity, and potentiating GABA effects throughout nervous system. Therapeutic effect is a dose-related response. A major metabolite, α-hydroxyalprazolam, has about 50% pharmacological activity of the parent compound. Another metabolite, benzophenone, is an inactive metabolite. Drug is readily absorbed (more than 90%) after oral administration (bioavailability (F) = 0.88) and widely distributed (volume of distribution about 1 L/kg in a healthy human). Peak plasma concentrations occur 1 to 2 hours after oral administration of immediate release dosage forms, whereas the elimination half-life is about 11.2 hours (with a range of 6.3 to 26.9 hours). Alprazolam and its metabolites are excreted primarily in the urine. Some may be excreted in human milk, which is similar to other benzodiazepines. Drug absorption is delayed when alprazolam is taken after fed state than fasted state, but total absorption remains unchanged. High fat diet may have a potential for drug-food interactions and may alter drug absorption [United States Pharmacopeial Convention, 1999; FDA, 1996; Greenblatt and Wright, 1993; Charman, 2000].

Alprazolam occurs as a white to off-white crystalline powder and melts in the range of 228-229˚C [Budavari et al., 1996]. Greenblatt et al. reported the high value of the partition ratio between n-octanol and aqueous buffer at physiological pH 7.4 of alprazolam to be about 18, indicating its high degree of lipophilicity [Greenblatt et al., 1983; Garzone and Kroboth, 1989]. Also, Carelli et al. determined the partition coefficient of alprazolam between n-octanol and normal saline containing 0.035% formaldehyde (as a preservative) of the drug from their permeation study through hairless mouse skin to be about 132 [Carelli et al., 1992]. In addition, it has been reported that the partition coefficient of alprazolam between human callus (tissue) and the normal saline containing 0.035% formaldehyde determined from a permeation study through human skin in vitro was about 17.5 ml/g [Carelli et al., 1994]. Alprazolam is insoluble in water, soluble in chloroform and alcohol, and slightly soluble in acetone and ethyl acetate. The solubility and intrinsic rate of dissolution of alprazolam are pH dependent [Laihanen et al., 1996a]. The structure of alprazolam, a triazo analog of the 1,4-benzodiazepine class of compounds, is shown in Figure 1.3.

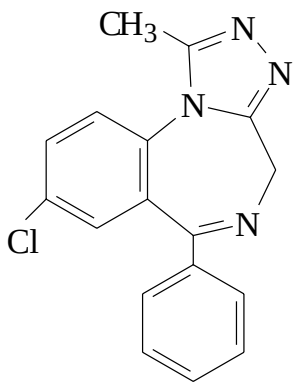


Figure 1.3 Structure of Alprazolam ($C_{17}H_{13}ClN_4$, MW 308.77)

1.2.1.2 Investigation of Formulation Parameters on Drug Release

The release of drug from a controlled release dosage form is influenced by factors relating to the physicochemical properties of the drug substance and to the dosage forms. The properties of the drug substance influencing the dissolution rate and subsequent bioavailability include solubility, particle size distribution [Ford et al., 1985a; Ford et al., 1987], and crystalline state, such as polymorphism, state of hydration, and complexation [Abdou, 1989].

The dosage form is influenced by its composition and processing parameters. Several studies have reported on the effect of formulation composition and processing parameters on the properties of the hydrophilic matrix tablets [Alderman, 1984; Vazquez et al., 1992]. Processing parameters, such as processing procedure [Alderman, 1984], compression force [Hirschorn and Kornblum, 1971; Velasco et al., 1999], and tablet characteristics (shape [Ford et al., 1987], size [Hirschorn and Kornblum, 1971], surface area [Alderman, 1984], and hardness [Huber and Christenson, 1968]), have been investigated. Factors associated with drug in the formulations, such as drug concentration [Mitchell et al., 1993a; Xu and Sunada, 1995] and drug particle size [Velasco et al., 1999], also had an impact on the drug release from tablets containing either HPMC or MC. Factors associated with polymers, such as molecular weight type (nominal viscosity) [Huber and Christenson, 1968; Harwood and Schwartz, 1982; Nakano et al., 1983; Daly et al., 1984; Ford et al., 1985b; Cheong et al., 1992; Tahara et al., 1995; Krogel and Bodmeier, 1999], concentration [Ford et al,

1985a; Ford et al, 1985b; Cheong et al., 1992; Shah et al., 1993; Xu and Sunada, 1995; Velasco et al., 1999; Helena Amaral et al., 2001], degree of substitution [Alderman, 1984; Mitchell et al., 1993b], and particle size [Alderman, 1984; Velasco et al., 1999], have been shown to have a significant influence on drug release. However, the most important factor that affects the drug release rate from HPMC matrices is the polymer concentration or drug:polymer ratio [Ford et al., 1985a; Ford et al., 1985b; Xu and Sunada, 1995; Velasco et al., 1999; Helena Amaral et al., 2001].

In this formulation investigation study, alprazolam was also selected as the model drug because it is highly lipophilic and compatible with other excipients. No drug/excipient incompatibilities have been reported between alprazolam and the excipients, lactose, microcrystalline cellulose, magnesium stearate, or dicalcium phosphate dihydrate [Laihanen and Yliruusi, 1996b].

In this research study, the influence of the excipient and the molecular weight type (nominal viscosity) of HPMC polymer on a lipophilic drug released from a matrix tablet are the main focuses. Therefore, a literature review of the previous studies on these parameters will be provided in detail within the following sections.

Excipient Type

Lapidus and Lordi showed that the replacement of HPMC (15,000 cPs) by either a soluble lactose or insoluble tricalcium phosphate similarly increased the dissolution rate of water-soluble chlorpheniramine maleate from matrix tablets [Lapidus and Lordi, 1968]. Similarly, Ford et al. reported differences in release

rates of the water-soluble drug, promethazine hydrochloride, from tablets containing either lactose or calcium phosphate in combination with HPMC polymer. However, differences in release rates occurred only when the tablets contained high levels of the diluents [Ford et al., 1987]. Also, the presence of soluble lactose or insoluble dibasic calcium phosphate did not impact the naproxen release rate from the matrix tablets containing HPMC K100M (nominal viscosity of 100000 cPs) [Helena Amaral et al., 2001]. In contrast, Alderman reported that the use of swellable, insoluble excipients (i.e. microcrystalline cellulose or cross linked carboxymethylcellulose) in tablet formulations containing 10% HPMC 2208 tended to cause expansion of the gel layer resulting in greater release of insoluble riboflavin in the early stages of dissolution (burst effect) due to their disintegrating property [Alderman, 1984]. In another study, it was found that the greater the dilution of the poorly water soluble drug, quinazolinone, with water soluble lactose, the faster the drug release since the excipient assisted the solvent to better wet and dissolve the drug within the matrix [Hirschorn and Kornblum, 1971]. In comparison between tablet formulations containing different viscosity grades of HPMC, it is found that the excipient type had more of an influence on release of chlorpheniramine maleate from tablets containing the lower viscosity grade polymer, HPMC E5 [Krogel and Bodmeier, 1999]. Additionally, the incorporation of additives such as surfactants [Daly et al., 1984], ion-exchange resins, or ionic additives to modify polymer thermal gelling temperature, and pH adjusting agents has been reported to modify the

release profiles of the active from the matrix tablet formulations [Vazquez et al., 1992].

As can be seen, no studies to date have systematically investigated the influence of excipient type and level on the release of lipophilic drugs. Additionally, results from previous studies on the influence of excipient on drug release remained unclear.

HPMC Molecular Weight Type (Nominal Viscosity)

During polymerization, each HPMC molecule may be different in terms of the degree of polymerization resulting in different molecular weight types, which is reflected in the nominal viscosity of an aqueous solution [The Dow Chemical Company, 2000]. The influence of molecular weight types or viscosity grades of HPMC polymer on the release rate of drug was investigated by several researchers. Huber and Christenson reported the slower release of a tartrazine dye from tablets containing high viscosity grade (i.e. HPMC 15000 cPs) when compared to the release from tablets containing low viscosity grade (i.e. HPMC 100 cPs or HPMC 4000 cPs) [Huber and Christenson, 1968]. Similar to the HPMC system, the release rate of theophylline was delayed when higher viscosity grades of HPC were used in the tablet formulations. By mixing between low and medium-viscosity grades of HPC, the release rate of drug can be modified. [Nakano et al., 1983]. The sustained release of drug from both systems was achieved by the polymer swelling to a gel-like consistency at the tablet periphery and forming a barrier to drug diffusion. Additionally, Daly et al. reported similar findings on the influence of the viscosity grade of HPMC 2910 USP (Methocel

E5, E15, E50, and E4M) on the release of chlorpheniramine maleate from matrix tablets. The results showed that the drug release was significantly slower when the higher viscosity grade of HPMC was used. The fastest to the slowest drug release obtained from the tablets containing increased viscosity grade of HPMC was in the following order: HPMC E5 >HPMC E15 > HPMC E50 > HPMC E4M [Daly et al., 1984]. Similar results were also reported for ophthalmic HPC matrix compression molded films. The release of pilocarpine was slower for the higher viscosity grades [Harwood and Schwartz, 1982]. Another study investigated the relationship between viscosity of HPMC 2208 USP (i.e. Metolose K4 (4380 cPs), K15 (18200 cPs), K30 (35800 cPs), K50 (44400 cPs), and K100 (100000 cPs), Shin-Etsu Chemical, Japan) and drug release from a matrix system. Results indicated that the larger the amount or the higher the viscosity grade of the HPMC present in the matrix, the greater the solution viscosity of the gel layer and the more resistant the gel layer is to diffusion. Therefore, drug release from a matrix with a diffusion-controlled release mechanism is retarded [Cheong, 1992]. In addition, viscosity of HPMC 2910 USP also had a large influence on the erosion rate of the matrix tablet. Specifically for poorly water-soluble drugs, a low viscosity grade of HPMC was desirable since the drug release rate was controlled by the rate of tablet erosion. Therefore, the tablet erosion rate can also be optimized by the choice of HPMC viscosity grade or by using the combination of different viscosity grades [Tahara et al., 1995]. In the recent development study on a multifunctional matrix drug delivery system based on HPMC-matrices

surrounded by an imperable cylinder, the lower the HPMC viscosity grade, the higher the drug release from the system [Krogel and Bodmeier, 1999].

In contrast, Ford et al. found that the formulation containing the lowest viscosity grade of HPMC (i.e. HPMC K100, 106 cPs for 2% aqueous solution) had the highest release rates at constant HPMC:drug promethazine hydrochloride ratio. While the other grades including HPMC K4M (3850 cPs), K15M (12449 cPs), and K100M (93000 cPs) showed similar release rates despite the variation in molecular size of the polymers. This may be due to HPMC K100 possessing a higher apparent diffusion coefficient for the drug promethazine HCl, while other grades possessed an equivalent apparent diffusion coefficient. The viscosities of the hydrated higher molecular weight matrices may be identical, even though they were apparently different in their viscosity grades [Ford et al., 1985b]. The main factor controlling drug release was the drug promethazine hydrochloride:HPMC ratio. When the polymer content increased, the dissolution rate of drug decreased [Ford et al., 1985a].

In Vitro Release Study

In the hydrophilic matrix tablet formulation, the release of active drug can be controlled by a partially hydrated gel layer of the tablet surface formed upon contact with aqueous gastric media following ingestion and the continuous formation of additional gel layers to control the drug release. During the manufacturing process of the hydrophilic cellulose ether polymers, variations, such as degree of chemical substitution, and molecular weight type, may cause concern as to their impact on product manufacturability, reproducibility, and

clinical performance. In some cases, these differences may not be acceptable by formulators since they have the potential to influence drug release rate from a dosage form, and consequently the bioavailability.

More recently, comparison of dissolution profiles is recommended in the release guidelines by the FDA [FDA, 1997a; FDA, 1995; FDA, 1997b; FDA, 1997c]. For the composition, equipment, batch size, manufacturing site, or process changes, a comparison of dissolution profiles between pre-change and post-change formulations is recommended as it provides a more precise measurement of product similarity using dissolution characteristics [FDA, 1995]. Dissolution profiles comparison is useful for accepting product sameness under SUPAC-related changes, waiving bioequivalence requirements for lower strengths of a dosage form, and supporting waivers for other bioequivalence requirements. Dissolution profiles may be considered similar by virtue of (1) overall profile similarity; and (2) similarity at every dissolution sample time point [FDA, 1997b]. Several methods for the comparison of dissolution profiles, including model independent and model dependent methods, were proposed [FDA, 1997b; Shah et al., 1987; Sathe et al., 1996; Moore and Flanner, 1996; Tsong et al., 1996; Chow and Ki, 1997]. However, the major drawback was the quantification of the comparison of dissolution profiles [Shah et al., 1998]. In order to statistically quantify the comparison of dissolution profiles, a simple model-independent approach using mathematical indices to define the similarity factor (f_2 factor) is widely acceptable. The similarity factor (f_2) is used to quantitate agreement between two dissolution profiles. If the f_2 value approaches

100, the two profiles are nearly identical. In general, the FDA standard for f_2 ranging between 50-100 (≤ 10% average difference) indicates similarity between two dissolution profiles [FDA, 1995; FDA, 1997b; Shah et al., 1998; Shah et al., 1999; Moore and Flanner, 1996]. Similarity factor assessment will be described in detail in the next chapter.

Bioequivalence Study

Bioequivalence can be defined as the drug substance in two or more similar dosage forms reaches the systemic circulation at the same relative rate and to the same relative extent [Abdou, 1989]. The current FDA guidelines for bioequivalence are that two formulations whose rate and extent of absorption differ by -20% to +25% or less are generally considered bioequivalent. This is based on the concept that a difference of -20% to +25% would not lead to change in therapy for a patient. Additionally, the difference in area-under-the-curve (AUC), maximal concentration (Cmax), and time of maximal concentration (Tmax) of the two formulations are within 80% to 125% of a reference standard.

The therapeutic efficacy of pharmaceutical formulations is governed by factors related to both in vitro dissolution characteristics of the drug substance and its *in vivo* bioavailability. Due to the interdependency within the drug-patient biosystem as a major concern, the in vitro/in vivo correlation studies become more important in pharmaceutical development [Abdou, 1989]. The correlation between *in vitro* dissolution tests and *in vivo* plasma drug levels as a function of time has proven to be a better assessment of bioavailability and bioequivalence [Shah et al., 1981].

In the hydrophilic matrix tablet formulation, the release of active drug can be controlled by a partially hydrated gel layer of the tablet surface formed upon contact with aqueous gastric media following ingestion and the continuous formation of additional gel layers to control the drug release. Lot-to-lot variations of the hydrophilic cellulose ether polymers such as degree of chemical substitution, molecular weight type (nominal viscosity), and particle size may cause concern as to their impact on product manufacturability, reproducibility, and clinical performance. These differences may not be acceptable by formulators since they have a potential to affect the drug release rate from a dosage form, and consequently the bioavailability.

In reality, the differences in molecular weight types of the HPMC polymer probably do not significantly influence the bioavailability of a drug substance (i.e. two different molecular weight types would be bioequivalent), but this must be investigated and confirmed in a well-controlled clinical study. This would be of great significance to pharmaceutical scientists to determine exactly what degree of variability could be allowed without influencing the *in vivo* bioequivalence. As can be seen from the investigation of hard gelatin capsules, the results from gamma scintigraphy indicated that there are no significant differences in the *in vivo* disintegration properties of the cross-linked and non cross-linked hard gelatin capsules, even though the *in vitro* dissolution data of both capsules was significantly different [Brown et al., 1998].

In addition, drug release from a matrix tablet may be influenced by the presence of food in the stomach since it may alter the stomach environment.

Previous studies showed that food prolongs the residence time of a dosage form administered during or immediately after a meal by keeping the dosage form in the upper half of the stomach [Hardy et al., 1989; Davis et al., 1990]. Long retention time of drug product in the stomach provides more time for the dosage form to have intimate contact with the stomach contents. Normally, dosage forms pass through the stomach rapidly during the fasting state and they are retained longer in the stomach during the fed state. The release of drug from the dosage form, absorption and subsequent bioavailability are varied depending on the physiological changes that occur in the gastrointestinal tract during the two states [Williams et al., 1993]. Therefore, the dosage form should not be susceptible to food present in the stomach, in order to eliminate or minimize its influence on drug release. Several studies reported that a high-fat meal caused increased absorption of drug from a bead or tablet formulation [Vaughan et al., 1984; Theobault et al., 1987; McLachlan et al., 1993; Borin et al., 1995; Paintaud et al., 1995], whereas some studies found no influence of food on the *in vivo* pharmacokinetics of drug from a formulation [DeVane et al., 1990; Kenyon et al., 1995]. Therefore, the food effect on the release of specific drug from the specific matrix tablet formulation should be investigated since the effect of food on drug release seems to be influenced by drug substance type and formulation.

1.2.2 Multiparticulate System (Film-Coated Beads)

Recently, several new developed solid dosage forms have been produced in the form of film-coated pellets or beads, either of which can be filled into hard gelatin capsules or compressed into tablets. Multiparticulate pellet systems are claimed to have numerous advantages over single unit dosage forms. The use of these systems allows for distribution of the drug over a large surface area, thus minimizing the risk of local damage caused by dose dumping of the single unit, less tendency to cause gastric irritation, less variability, more uniform drug release and less dependence on gastric transit time. They may attain more constant plasma levels, achieve a slow-release effect, extend the duration of action of a sustained release dosage form, provide highly accurate dose-to-dose reproducibility, and cause less of a decrease in bioavailability [Tapia et al., 1993; Bechgaard, 1982; Eskilson, 1985; Dechesne and Dellattre, 1987; Story, 1977].

Coating Technology [Williams III and Mahaguna, 2000]

The purpose of coating is to [Cole, 1995; Bauer et al., 1998; Mehta and Jones, 1985]:

- Enhance palatability and mask the unpleasant taste and odor of the active drug substance
- Enhance the stability of an active drug substance during exposure to light, moisture and atmospheric oxygen

- Increase the mechanical integrity of the tablet during manufacturing, packaging (i.e. reduce friction and increase the production rate during high-speed processing) and shipping
- Increase the elegance and glossy appearance of the tablet or pellet core
- Protect the patient's clothes and hands from staining due to colored or migrating active drug substance
- Modify the drug release profile, such as enteric coating, sustained release coating, osmotic pumps, etc.
- Avoid side effects caused by the active drug substance (i.e. prevention of gastric irritation by employing an enteric polymer coating)
- Avoid incompatibility of active drug substances by physical separation into the core and coat
- Use for product identification unique to each company

Types of Pharmaceutical Coating Processes

There are two major types of coating processes used in pharmaceutical applications: sugar coating and film coating. Film coating process is the main focus of this research study. Therefore, this process will be described in more details.

A. Sugar Coating

Sugar coating was developed primarily from technologies employed in the confectionery industry, which have been optimized over the years, and are still widely used today. Sugar coating processes result in approximately doubling the

weight of the original tablet core, therefore batch sizes have to be calculated based on the finished tablet weight after coating. However, the use of modern spraying systems allows a dramatic reduction in the final product weight. Moreover, the airflow velocity and processing temperature are very critical in achieving a pharmaceutically elegant finished product [Cole, 1995].

Raw materials used for sugar coating include coating formers, colorants, flavors, lubricants or glidants or antiadherents, smoothing agents, polishing agents, and suspension stabilizers.

Processing steps for sugar coating include Sealing (protective coating), Subcoating, Smoothing, Coloring and Finishing, and Polishing. In some products, printing on the high-gloss surface is performed to provide unique product identification. Sugar coating layers are built up by repetition of the processing steps of application, distribution, and drying. There are three types of sugar coating techniques used [Bauer et al., 1998]:

i). Plain sugar coating (application of syrup at room temperature)

ii). Two-component coating or lamination process (application of a syrup or binder solution first in a slight excess amount, and then dusting with a powder to bind the excess solution)

iii). Hot sugar coating (application of heated syrup)

B. Film Coating

Film coating is defined as a thin and uniform polymer based coat around 20 to 100 μm in thickness applied to the surface of substrates such as tablets,

granules, powder, capsules, multiparticulates or pellets [Porter, 1995]. Compared to sugar coating, film coating provides more flexibility to coat a variety of substrates rather than just compressed tablets [Cole, 1995].

Advantages of Film coating are as follow [Cole, 1995; Porter, 1995]:

- Enhance the elegance and glossy appearance of the dosage form
- Obtain legible logo and product identification after coating. Product information can be engraved on the tablet core
- Improve mechanical integrity and resistance of the dosage form upon handling and shipping from manufacturing site to patients
- Modify the pharmaceutical function of the dosage form, especially for enteric coating and modified release coating
- Increase flexibility in type of formulations to be coated and type of processing equipment
- Minimal weight increase (about 2-3% of tablet core weight) compared to weight increase from sugar coating (doubling the weight of tablet core)
- Significantly reduced processing time, whereas increased process efficiency and output
- Prevent dosage forms from dusting

Typical film coating formulations

Typical film coating formulations usually consist of the following components:

1. Polymers

Polymers are macromolecules with a high molecular weight range between 10,000 and several million. Polymers consist of the number of repeating units in the structure. Ideal properties for polymers used in film coating include solubility in a wide range of solvent systems in order to allow more flexible formulations, ability to produce films with excellent mechanical properties, stability against light, oxygen, hydrolysis, low toxicity, and optimum dissolution in the gastrointestinal tract [Porter, 1995]. Coating polymers can be categorized into two types: (1) non-functional or conventional film coating polymers, which can be used as a coating for improving the appearance, improving the handling, and preventing of the dusting of dosage forms; and (2) functional coating polymers, which can be used to modify the pharmaceutical function of the dosage forms, especially for enteric coating and modified release coating. Characteristics of concern for polymers used during the coating process including solubility, solution viscosity, film permeability, mechanical properties (i.e. tensile strength, elastic modulus, work of failure, strain), and so on. For the coating application, the polymer is frequently dissolved in a suitable solvent such as water or a non-aqueous organic solvent. However, some water-insoluble polymers are commercially available as an aqueous dispersion, which permit aqueous film coating, and are particularly useful for modified release coating applications.

Based on the method of preparation, polymer dispersions can be classified into two types: true latexes and pseudolatexes. Comparison of the two types of polymer dispersion is shown in Table 1.2.

2. Plasticizers

Plasticizers are low molecular weight organic solvents with high boiling points. They are used to alter the physical properties of a polymer (i.e. hard or brittle) and render it more flexible and softer to function as a film coating material. Generally, there are some similar chemical features (i.e. functional groups) between a polymer and its plasticizer. The amount of plasticizers used is normally between 15-35% based on polymer weight. Plasticizers also have a significant influence on mechanical properties of the film. Specifically, they can reduce cohesive intermolecular forces along the polymer chains, enhance flexibility by increasing strain or film elongation, and decrease tensile strength and elastic modulus of the polymer. Additionally, they influence the permeability characteristics of the film, especially to water vapor, as well as lowering the glass transition temperature (T_g) of the polymer to allow a more feasible coating process. Therefore, plasticizer efficiency can be measured by the degree of lowering T_g of that particular type of plasticizer. Plasticizers also possess solvent power to insure compatibility with the polymer. Plasticization time (i.e. mixing time of plasticizer with polymer) and plasticizer level influence polymer films [Bodmeier et al., 1997].

Table 1.2 Comparison of True Latexes and Pseudolatexes [Cole, 1995]

Type	True latex	Pseudolatex
Description	Very fine dispersion of polymer in an aqueous phase	Fine dispersion of polymer in an aqueous phase
Particle size range (nm)	10-1000	10-1000
Method of preparation	Emulsion polymerization of monomer, initiator, and catalyst	- Start from polymer, mechanical means - Free of monomer residual and traces of initiators
Examples	Acrylate polymers (Eudragit® L100-55, and Eudragit® NE30D, Röhm Pharma GmbH)	Ethylcellulose dispersion (Aquacoat® ECD, FMC Corporation; Surelease®, Colorcon, Inc.)

There are three types of plasticizer commonly used in coating processes:

2.1) Polyols (water miscible): Glycerol (glycerin), Propylene glycol (PG), Polyethylene glycol (PEG 200-6000 grades)

2.2) Organic esters:

- Water insoluble: Diethyl phthalate (DEP), Dibutyl phthalate (DBP), Dibutyl sebacate (DBS), Acetyltriethyl citrate (ATEC), Acetyltributyl citrate (ATBC), Tributyl citrate (TBC)

- Water miscible: Triethyl citrate (TEC), Triacetin (glyceryl triacetate; TA)

2.3) Oils/glycerides (water insoluble): Castor oil, Distilled acetylated monoglycerides (AMG), Fractionated coconut oil

3. Pigments or opacifiers

Pigments or opacifiers are used in film coating to:

- Enable product identification
- Protect the active ingredient against light by optimizing the opacfying properties of pigments
- Modify the permeability of a film to gases
- Decrease the risk of counterfeiting the product

However, the use of pigments and opacifiers could be omitted from the formulation if a clear coating was required.

4. Vehicles or solvents

Solvents and vehicles play an important role in carrying the coating materials to the surface of the product core. They include water, alcohols,

ketones, esters, and chlorinated hydrocarbons. The type of vehicles or solvents used during the coating process can be used to classify the type of film coating into (1) organic film coating (non-aqueous film coating), and (2) aqueous film coating. These types of coating will be discussed in later sections. Necessarily, the solvent has to intimately interact with the selected polymer in order to allow both film adhesion and mechanical strength to be optimized.

5. Other components

Other components are occasionally used in minor levels in some specific formulations as processing auxiliary substances or drug release modifiers. Flavors may be included in some oral formulations to make them more palatable. Adhesion enhancers (e.g. saccharides such as polydextrose, maltodextrin, and lactose) are used to increase the adhesion of cellulosic systems to substrate as well as improve stability towards light for unstable colors [Jordan et al., 1992]. Surfactants or dissolution enhancers (i.e. xanthan gum with Eudragit® NE30D coated theophylline granules [Li et al., 1989]), as well as pore-forming agents (e.g. sucrose or sodium chloride with ethylcellulose-coated salicylic acid tablets [Lindholm and Juslin, 1982]), can be used to enhance the dissolution of the final dosage forms. Anti-tacking agents/glidants (e.g. talc, magnesium stearate, kaolin, glyceryl monostearate) are typically used to reduce sticking during film formation. Additionally, some film coatings may contain an active ingredient, preservative (i.e. sorbic acid), antifoaming agents (i.e. dimethylpolysiloxane), stabilizing agents, and waxes.

Types of film coating

There are two major types of film coating: Organic solvent film coating system and Aqueous film coating system.

B.1) Organic solvent film coating system

An organic solvent film coating system offers the processing advantage of low heat of vaporization characteristic of the organic solvents. However, due to environmental constraints, safety precautions and health-related concerns, the use of organic-based coatings has decreased recently and the use of aqueous-based coatings has increased. Additionally, the introduction of newly developed coating equipment and the development of new film coating raw materials, which can be applied in aqueous media as solutions or dispersions, enable a more practical operation of aqueous-based coating systems. Similarly, some forms of polymer that were previously used for organic-based systems were developed by manufacturers into different forms, which allow the formulators to choose a more suitable form for aqueous-based coatings.

Disadvantages of the organic solvent system [Porter, 1995; Mehta et al., 1986] include:

- Environmental, flammable and toxicity hazards;
- Requires flameproof equipment to reduce hazardous working environment for the operator;
- Residual solvent from coating process;
- Requires solvent recovery systems;

- High cost process due to the required use of organic solvents and special safety equipment.

B.2) Aqueous film coating system

Recently, the trend in coating has favored aqueous film coating due to the high capital outlay in equipment and solvents, limitation placed on chlorinated hydrocarbons use by regulatory authorities, environmental concerns for pollution, and development of perforated coating pans and spraying systems, which allow applications of more difficult coating materials. There are two major pharmaceutical applications of aqueous film coating: immediate release and modified release applications.

B.2.1) Immediate released coatings

Pharmaceutical applications include:

- Mask the unpleasant taste and odor of drug
- Protect the active drug substance from exposure to light, moisture and atmospheric oxygen
- Enhance the elegance and glossy appearance of the dosage form
- Improve mechanical integrity of the dosage forms upon handling from manufacturing site to patients
- Prevent dosage forms from dusting

Polymers used for immediate release film coating include cellulose ether polymers (Table 1.3) and acrylic polymers (methacrylic aminoester copolymer).

Table 1.3 Cellulose Ethers Used for Immediate Release Coatings

Name	Description	Tradename	Vendor
Hydroxypropyl methylcellulose (HPMC)	- low viscosity - soluble in both aqueous and organic solvents - provides aqueously clear soluble films - colored coating with addition of pigment possible - non-tacky nature → easy processing - safe to use as a thickener and emulsifier in the food industry - 4.0-20.0 %w/w methoxyl content and 7.0-12.0 %w/w hydroxypropoxyl content (USP specification)	Methocel E5 Pharmacoat 603, 606, 615, 904 Metolose Demacol 15NP	The Dow Chemical Company Shin-Etsu Shin-Etsu ZetaPharm, Inc.
Hydroxyethyl cellulose (HEC)	-soluble in water, insoluble in organic solvents - may include some additives to ensure homogeneous dispersion of powder in water and prevent caking upon storage	Natrosol®	Aqualon Division, Hercules Inc.
Hydroxypropyl cellulose (HPC)	- soluble in both aqueous and alcoholic solvents - films tend to be tacky and weak - currently used in combination with other polymers to provide additional adhesion to the substrate - Must be less than 80.5 %w/w hydroxypropoxy content (USP specification)	Klucel®	Aqualon Division, Hercules Inc.

B.2.2) Modified release film coatings

Modified release coatings can be classified into two different applications: enteric release and sustained release coatings. In this research study, only the sustained release application is focused on.

- *Enteric released coatings*

This type of film coating provides a delayed release action of drug from a coated dosage form in the acidic environment of the stomach, but readily releases the drug once it passes into the more basic pH environment of the upper intestine (i.e. duodenum). Enteric release dosage forms avoid side effects (i.e. nausea, vomiting) caused by the gastric irritation of some active drugs to the gastric mucosa, as well as prevent the destruction of some drugs by gastric enzymes and the acidic environment of the gastric fluid. The USP has specified this type of dosage form as a "delay-released dosage form". For the mechanism of enteric coating polymers, the polymer remains intact at a low pH, but will undergo dissolution to allow release of active from the dosage form at a higher pH.

Polymers used for enteric released film coating include cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), shellac, methacrylic acid copolymers, cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate (HPMCP).

- *Sustained released coatings*

Polymers used for sustained release film coating include:

- *Cellulose ethers (Ethylcellulose, Methylcellulose)*

  - *Ethylcellulose (EC)*

The role of EC in pharmaceutical coating will be described in detail in the following section.

  - *Methylcellulose (MC)* [Schwartz, 1976]

MC is soluble in water. It is rarely used in film coating for immediate released applications since there is no commercially available low viscosity grade product. USP specified a methoxyl content of 27.5-31.5 %w/w. MC powder (Methocel A) is available from The Dow Chemical Company.

- *Methacrylate ester copolymers*

This group of polymers is neutral and insoluble over the entire physiological pH range due to the lack of free carboxylic acid groups caused by their complete esterification (i.e. pH independent polymer). However, their modified release application can be obtained based on their ability to swell and their permeability to water and dissolved substances. Some hydrophilic materials (i.e. soluble cellulose ethers, PEG) are usually incorporated with this polymer to achieve desirable release profiles.

Some commercially available products include poly(ethylacrylate, methylmethacrylate) trimethylammonioethylmethacrylate chloride (1:2:0.2, USP designated type A, Eudragit® RL, Röhm Pharma GmbH, readily permeable), poly(ethylacrylate, methylmethacrylate) trimethylammonioethylmethacrylate

chloride (1:2:0.1, USP designated type B, Eudragit® RS, Röhm Pharma GmbH, poorly permeable), and poly(ethylacrylate, methylmethacrylate) (2:1, Eudragit® NE, Röhm Pharma GmbH, expandable and permeable).

As can be seen, coatings play a multifunctional role in formulations depending on the desired properties of the dosage form. Recent advances in coating equipment, coating processes, and coating materials have enabled significant improvements in coating technology. The type of coating process chosen depends upon the type of coating that is to be applied, the durability of the tablet core, stability of the dosage form, and the economics of the process. However, recent trends in coating technology have favored aqueous film coating because of its wide application, low environmental concerns, the efficiency of the process, and the commercial availability of coating materials. In the following section, the aqueous film coating system will be described in specific details.

Aqueous Film Coating System

Recently, an aqueous polymeric latex or pseudolatex has been preferable to use for sustained release or enteric release dosage forms in order to overcome the undesirable toxicity, residual solvent problems, explosion hazards, and environmental pollution of organic solvent systems [Mehta and Jones, 1985; Mehta et al., 1986].

For an aqueous polymeric dispersion, film formation can occur when the polymer in a wet state is present as a number of discrete particles. Those particles come close to each other with the facilitated capillary action of the film of water

around the particles, which are generated as water evaporates. Then, they contact, deform, coalesce, and finally fuse together to form a discrete film. At the same time, the water must be removed [Porter, 1989]. Lechmann [Lechmann, 1992] recommended that the coating temperature or bed temperature during the application process should be about 10-20°C above the minimum film-forming temperature (MFT) in order to ensure the optimum condition suitable for film formation. MFT is the minimum temperature above which continuous film formation will occur under specific conditions. Therefore, the MFT is an important parameter to determine the appropriate bed temperature of the coating process. MFT can be lowered by increasing the level of added plasticizers [Amighi and Moes, 1996], increasing the plasticization time [Lippold et al., 1990] or increasing the amount of pore former in some cases [Gunder et al., 1995; Frohoff-Hulsmann et al., 1999]. MFT is dependent upon the temperature at which the polymer changes from a hard glassy amorphous state to a softer rubbery state. This change in state is defined as the glass transition temperature (T_g) of the polymer. The coalescence process can be dramatically affected by the T_g of the polymer. If the T_g of the polymer is higher than the product bed temperature generated during the coating process, then the free volume will be too low [Wicks, 1986] and insufficient viscous flow will occur, which will then allow complete coalescence of the latex particles. At the T_g, the polymer chain segments are increasingly moving, the free volume increases and therefore increase the flexibility and penetrability of the films [Frohoff-Hulsmann et al., 1999]. Moreover, the glass transition temperature of such a polymer can be

lowered by the incorporation of a plasticizer into the polymer solution or dispersion [Porter, 1989].

Film-coating Process

Fluidized-bed coating process became more popular during the past two decades for the coating of tablets or pellets. This was due to the major improvements of the coating, when comparing to conventional pan coating or perforated pan coating processes. Fluidized-bed process can provide a greater drying efficiency to avoid the formation of liquid bridges between two or more pellets, and high surface evaporation to avoid solvent penetration into the core. As a result, an improvement in the smoothness, continuity, and coalescence of the polymer particles over the surface of the pellets can be obtained. Bottom sprayed fluidized-bed with a Wurster column inserted appears to be superior and most widely used for coating of the pellets (Figure 1.4). The coating solution is applied from the bottom at the same time and in the same direction as the flow of the pellets through the Wurster column. Therefore, this pattern followed by the pellets is more regular than the top-spray method, resulting in further improvements in the physical characteristics and quality of the coating applied. This process also provides ideal conditions for the completeness coalescence of the polymer particles, with decreased water penetration into the core of the pellet. The droplets of the coating solution produced from this method should have a low viscosity, so when they come into contact with the substrate, they will uniformly distribute and form a continuous film. In addition, the evaporation rate of the

solvent droplets from the surface of the core should be readily fast to prevent liquid bridging between pellets [Mehta and Jones, 1985].

To achieve the coating purposes as previously described, the film coating of the dosage forms should be uniform, reproducible, and no physical imperfections. Therefore, the coating process as well as processing parameters used are very critical and should be readily optimized [Mehta and Jones, 1985]. Drug release from pellets is controlled as diffusion through a membrane, which is obtained from film coating process [Goodhart et al., 1984].

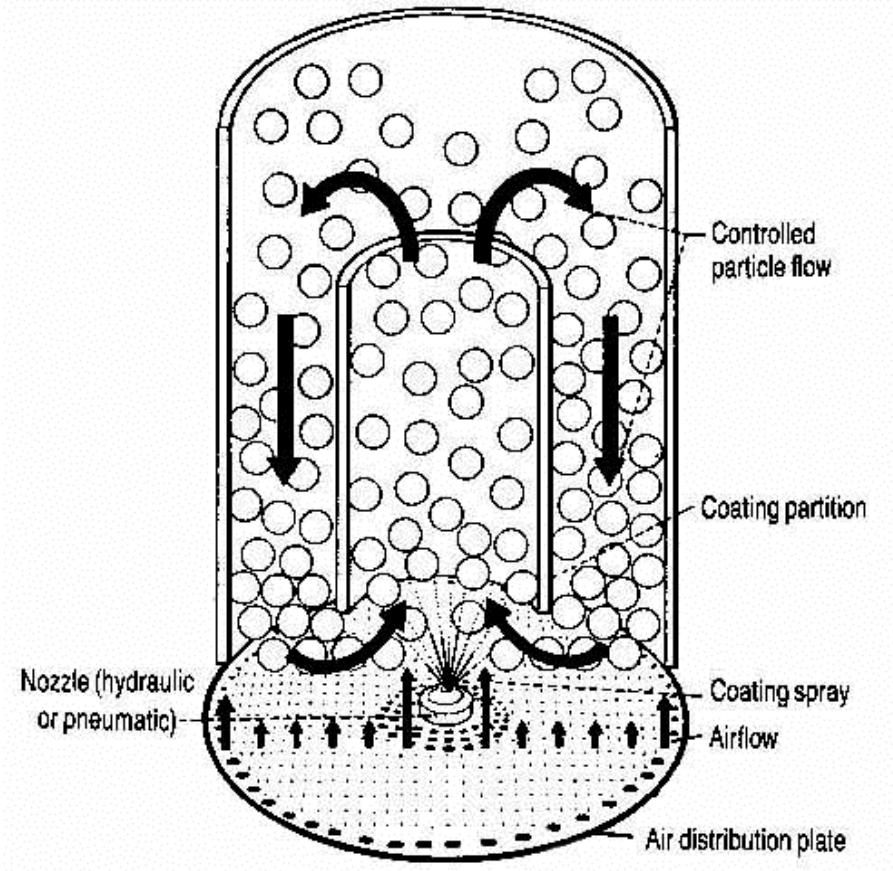


Figure 1.4: A bottom-spray fluidized-bed coating processing with a Wurster inserted column [Jones, 1985]

Film-coating Parameters

Drug release from polymeric film coated dosage forms is strongly influenced by variables influencing the coalescence of the polymer particles and hence the film formation process [Harris and Ghebre-Sellassie, 1997]. Process variables such as coating temperature [Yang and Ghebre-Sellassie, 1990], curing conditions after the coating process [Goodhart et al., 1984; Ghebre-Sellassie et al., 1988], type and level of plasticizer [Wheatley and Steuernagel, 1997], plasticization time [Lippold et al., 1989], type of additives or fillers, nature of the substrate [Porter, 1989], pH, and effect of surfactant levels [Bodmeier and Paeratakul, 1991a], must be optimized in order to obtain stable and reproducible drug release profiles throughout the product's shelf life.

Cellulose ethers are a major group of polymers used in the film coating process. Among cellulose ethers (i.e. cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate phthalate, and ethyl cellulose) that have been extensively used in a variety of film coating applications, ethylcellulose is the most widely used [Salib et al., 1976; Porter, 1989; Wheatley and Steuernagel, 1997]. In this study, role of cellulose ethers and processing parameters in an aqueous film coating technology were investigated.

Ethylcellulose (EC)

Ethylcellulose (EC) is a nonionic cellulose ether derived from the polymeric backbone of cellulose. The molecule has a structure of repeating anhydroglucose units with three reactive hydroxyl sites. EC is insoluble in water,

but miscible with various water-soluble materials. Therefore, it has been extensively used in combination with other water-soluble polymers, especially HPMC or polyethylene glycols (PEG), in order to provide more hydrophilic nature to the EC film and promote drug diffusion through the pores or channels. Glass transition temperature (T_g) of pure EC ranging from 128 to135˚C was reported in the literature [Entwistle and Rowe, 1979; Porter, 1989; Lippold et al., 1990]. EC provides additional gloss and shine to the tablet surface, as well as optimizes film toughness to minimize surface imperfections caused by handling. EC is preferred for modified release coatings because it is odorless, tasteless, and has a high degree of stability under normal storage conditions, including light and heat. The USP specifies an ethoxy content between 44.0-51.0 %w/w. The water dispersible form of EC provides significant advantages and makes processing of water insoluble polymers from an aqueous-based system possible. The high solid content and the low viscosity of the aqueous polymeric dispersions make their use much easier in their applications. In addition, the high surface area of the particles significantly reduces the drying time during coating by evaporation of water inducing the contact and readily coalescence of the particles' boundaries [Kumar and Banker, 1993; Porter, 1989].

Some commercially available products include:

- Powder (Aqualon®, Aqualon Division, Hercules Inc.)

It is available in a wide range of viscosity and substitution types for a wide range of applications.

- Aqueous dispersion (Aquacoat® ECD (30 %w/w solid content), FMC Corporation; Surelease®, Colorcon, Inc.)

In this research study, Aquacoat® ECD will be used for controlled release coating. Aquacoat® ECD dispersion contains 29-32 %w/w of ethylcellulose (polymer, N type, 10 cPs), 1.7-3.3 %w/w of cetyl alcohol (stabilizer), and 0.9-1.7 %w/w of sodium lauryl sulfate (stabilizer/emulsifier). Since the T_g of the EC is about 135˚C, then a plasticizer is required to assure that the complete coalescence of the latex particles will occur under the suitable conditions [Porter, 1989]. Aquacoat® ECD formulation is shown below [FMC Corporation, 1996].

R_x	Suspension (g)	%
Aquacoat® ECD	425.0	80.6
DBS	31.6	19.4
Water	88.0	-
Total	544.6	100.0

The performance of EC coatings obtained from aqueous dispersions may vary due to the differences in molecular weight of EC used, manufacturing method, type of additives, and method to incorporate plasticizers [Porter, 1989].

Drug Type

The nature of the drug used as a substrate for film coating was reported as having an impact on the final product performance. Solubility of drug as well as effect of pH on drug solubility can affect the release of the drug from the film coated dosage forms. At the same coating level, water-soluble drugs tend to be released from the EC coated beads (non-pareils) at a faster rate than water

insoluble drugs. Additionally, the high molecular weight of the drug may make it more difficult to diffuse through the membrane [Porter, 1989].

Several techniques have been developed for beads manufacturing. These include extrusion/spheronization(marumerization), loading drug onto sugar beads (nonpareil or Nu-pareil®) from a solution or suspension using fluid bed or pan coating systems, and loading drug by powder layering using a pan or a rotogranulator. Among these techniques, extrusion/spheronization, which the wet mass of materials is extruded using a suitable extruder and followed by rounding on a rapidly rotating, roughed plate of the spheronizer, is the most extensively used for a wide range of drug loading from 0-75%. This technique may be the only practical way of achieving pellets with a very high drug loading [Gamlen, 1985; Ku, 1993]. Beads prepared by this method offer several advantages of a low surface-to-volume ratio, ease of flow, uniform packing, and suitability of shape for film coating process [Chien, 1985; Rowe, 1985]. Most previous studies in aqueous polymeric coating were conducted using core beads prepared by loading the drug onto sugar beads (nonpareil) from a solution or suspension. The active drug was distributed only on the surface of the cores. In this research study, the extrusion/spheronization technique, which offers more advantages than other techniques, is used to prepare core beads. The active drug prepared by this technique is distributed throughout the matrix beads.

In this coating study, chlorpheniramine maleate (CPM) and theophylline anhydrous were chosen as the model water-soluble drug and slightly water-soluble drug, respectively. The structure of each drug substance is shown in

Figure 1.5. Both drugs have been extensively used in several research studies and they are well characterized in the literatures. Therefore, in the present study, preformulation studies on physicochemical properties of both drugs will not be investigated.

Chlorpheniramine maleate (CPM) is a short-acting antihistamine with weak sedative properties and a high therapeutic index commonly used in the treatment of allergies. The mechanism of action is competitively blocking H_1-receptor sites, thereby preventing the histamine from causing increased capillary permeability and the formation of tissue edema [Pearlman, 1979]. The onset of action is 15-30 minutes, effects are maximal within 1-2 hours, and the duration of action is 4-6 hours [Douglas, 1980]. Drug is slowly absorbed and its absorption is sensitive to local gastrointestinal conditions, such as water volume, presence of food, the effect of multiple dosing, and the formulation employed. The volume of distribution is between 2.5-5.9 L/kg after IV dosing, and 7.00-7.65 L/kg after oral dosing. Serum half-life of drug is about 20 hours in normal adults [Rumore, 1984].

CPM occurs as an odorless, colorless to white, and crystalline solid [Budavari et al., 1996; Eckhart and McCorkle, 1978]. The maleate salt of chlorpheniramine is very soluble in mg/ml level at 25°C in water (25%), ethanol, chloroform, and methanol, but it is slightly soluble in benzene, and ether. Melting point is in the range of 130-135 ˚C [Budavari et al., 1996; MDL Information Systems, 1987].

CPM is stable at normal temperatures and pressure. However, contacting with heat, flames, sparks, other sources of ignition, and with incompatible materials (i.e. oxidizing materials) should be avoided [MDL Information Systems, 1987]. Stability of CPM has been studied using accelerated heat and light conditions on solutions of various pH values. Percent recovery of CPM was in the range of 95-100% in various pH samples stored at 95°C for 1 week, and in samples exposed to light for 3 months [Eckhart and McCorkle, 1978]. In another stability study, CPM tablets were stored in a counting machine, which its intended use was to save time in an outpatient dispensing operation in a hospital, at ambient condition (i.e. 23±1 ˚C, 50±10% relative humidity) for 8-12 weeks. No difference in the chemical stability assay results, physical appearance, disintegration times, or dissolution characteristics of the controls and the samples was reported [Das Gupta and Gupta, 1979].

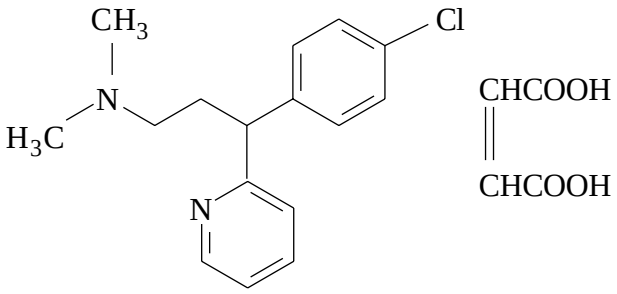
Theophylline is a xanthine derivative with a variety of therapeutic activities including diuretic, cardiac stimulant and smooth muscle relaxant. It is commonly used as a bronchodilator in the treatment of asthma, emphysema, bronchitis and other lung disorders [Edelson et al., 1998; Budavari et al., 1996]. During asthma attack, theophylline helps relax the smooth muscles in the bronchial passages of the lungs, widening the constricted airways and restoring normal breathing [Edelson et al., 1998]. Drug is generally well absorbed after oral administration, however, the variation does occur depending upon dosage form, formulation, and salt form being administered. Peak plasma levels of theophylline tablets are varied from 2-4 hours, whereas peak plasma levels of

sustained release tablets are at 6 hours with a duration of action of 10-12 hours, dependent on the formulation. Drug is widely and rapidly distributed into all tissues with high rates of blood flow and has a volume distribution of 0.3 L/kg. Serum half-life of drug is varied from patient-to-patient ranging from 2.5-9.5 hours [Cohen, 1975].

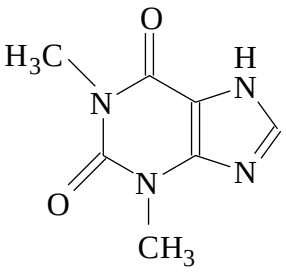
Theophylline occurs as a white, odorless, crystalline powder with a bitter taste [Budavari et al., 1996; MDL Information Systems, 1998; Cohen, 1975]. It exists in both anhydrous and monohydrate forms. The monohydrate salt of theophylline is slightly soluble in water (8.3 mg/ml or 1 g in 120 ml water) and chloroform (11.6 mg/ml or 1 g in 110 ml chloroform), sparingly soluble in ethanol (12.5 mg/ml or 1 g in 80 ml ethanol) and ether, and soluble in hot water, alkali hydroxides, ammonia, dilute hydrochloric acid or nitric acid. Theophylline is a weak acidic compound with the proton on the nitrogen in position 7 being dissociable and high pKa of 8.6 in an aqueous solution. Additionally, theophylline is a very weak basic with pKb of 11.5-13.5. Several basic salts, such as sodium and potassium salts, have been prepared to enhance the water solubility of theophylline [Cohen, 1975]. Melting point is in the range of 270-274˚C [Budavari et al., 1996; MDL Information Systems, 1998].

Theophylline is stable at normal temperatures and pressure. However, contacting with heat, flames, sparks, other sources of ignition, and with incompatible materials (i.e. oxidizing materials) should be avoided [MDL Information Systems, 1998]. Theophylline solutions are quite stable over the entire pH range. However, instability of theophylline in strongly alkaline

solutions (pH > 12) has been reported. The decomposition and apparent ring opening were found after storage for several weeks. Theophylline solutions are susceptible to oxidation at position 8. Due to its low solubility and relative high pKa, it tends to precipitate from aqueous solutions if the pH drops below 9 unless present in concentrations less than the water solubility. Additionally, all acidic salts are potentially incompatible with theophylline in solution. Theophylline has shown to form stable complexes with saccharin, phenobarbital, papaverine, caffeine, sulfosalicylic acid, benzyl alcohol, and α-, and β-napthalene acetate [Cohen, 1975].



Chlorpheniramine Maleate ($C_{16}H_{19}ClN_2 \bullet C_4H_4O_4$, MW 390.86)



Theophylline ($C_7H_8N_4O_2$, MW 180.17)

Figure 1.5: Structure of model drug substance used for film coating study

Subcoating or Seal Coat

The purpose of applying the seal coat to the substrate prior to application of controlled release coating is to retard the release of the drug, especially with highly water soluble drugs, and the rate-controlling membrane is derived from an aqueous latex coating system. Seal coats can be used to reduce the brittleness of the drug layer and thus reducing abrasion in early stages of coating application, seal off surface irregularities of substrate, prevent the prematrure dissolution of drug by water in the coating dispersion, and reduce porosity of the substrate that may affect film formation process [Porter, 1989]. To eliminate the drug migration into the polymer film during curing or storage, an intermediate seal coat may be used to separate the drug core from the polymer coating. A thin layer of HPMC, of which drug is not soluble, was applied to ibruprofen core beads prior to Aquacoat® application to eliminate the diffusion of the drug to the bead surface through the EC coating [Bodmeier and Paeratakul, 1994].

Plasticization

For aqueous EC coating, added plasticizers are necessary to reduce the glass transition temperature of EC polymer, improve the mechanical properties and enable the formation of tough, flexible films without cracks. Generally, aqueous EC dispersion requires the addition of 20-30 %w/w plasticizer based on EC polymer weight. The type and amount of plasticizer used during film coating to increase the flexibility of the coatings and facilitate coalescence of the coatings produced from aqueous latex systems is very critical. The appropriate plasticizer and amount used can help improve the barrier properties to drug release of the EC

film, resulting in a reduction in drug release rate [Porter, 1989; Saettone et al., 1995]. When increasing the amount of plasticizer in the coating, the drug release rate tended to be decreased due to the plasticizer, which altered the water permeability of the coating. This evidence was observed in the case of theophylline beads coated with EC dispersion plasticized with AMG (Myvacet®9-40) or DEP or DBS [Saettone et al, 1995]. However, this trend was not always true in some other studies [Chang et al., 1989; Ho and Suryakusuma, 1988].

Goodhart showed that 24-40 %w/w (based on film former) of plasticizer, TEC or DBS, with at least 30 minutes plasticization time, was necessary to soften the latex particles, promote film coalescence, and finally, retard the release of phenylpropanolamine HCl from the EC-Eudragit E-30D (6:4 ratio) coated beads [Goodhart et al., 1984].

Generally, when a high amount of plasticizer (higher than 30 %w/w) is used in any aqueous coating formulations, especially acrylic polymers, tackiness or sticking of films is likely to occur and antitacking agents, such as talc or glycerl monostearate (GMS), are recommended. Tackiness increases with increasing plasticizer concentration, especially at the higher curing temperatures, due to the softening of the polymer. In the case of Aquacoat®, films are easy to separate from each other and it has the lowest tackiness [Wesseling et al., 1999a]. Therefore, antitacking agents may not be necessary for an Aquacoat® coating system.

From an evaluation of the physical properties of a plasticized film cast from ethanol solution, at least 20 %w/w DBS and 20 %w/w AMG were found to

be the most efficient plasticizers for EC in terms of mechanical property (i.e. low elastic modulus, high elasticity) and thermal property (i.e. low T_g values) [Hyppola et al., 1996].

Plasticization time is the time elapsed between the addition of plasticizer to the latex and coating process. This is due to the distribution of plasticizers between aqueous and polymer phases, which is time dependent. Plasticization time was found to have an influence on the properties of polymer films [Lippold et al., 1989; Bodmeier et al., 1997]. The water insoluble plasticizers (i.e. DBS and DBP) required a longer time to reach the maximum concentration in the EC dispersion than the water-soluble plasticizers (i.e. DEP, TEC). The distribution between polymer and aqueous phases readily occurred when the more water-soluble plasticizers are mixed with the aqueous dispersion. Aqueous solubilities at 20˚C of 10% DBS and 10% TEC are 0.01% and 6.90%, respectively. Additionally, aqueous solubility of the plasticizers also affects the concentration gradient between aqueous and polymer phases [Frohoff-Hulsmann et al., 1999a].

Curing Condition

During coating of solid dosage forms with an aqueous dispersion, especially Aquacoat® dispersion, coalescence of the colloidal polymer particles into a homogeneous film is often incomplete. This is due to the bed temperature used (about 40˚C or 10-20˚C above MFT), which is not sufficient enough to complete film coalescence. Therefore, it is recommended to cure the coated products after the coating process in order to overcome this problem. Curing or further gradual coalescence is a thermal treatment or expose the coated products

to elevated temperatures above the glass transition temperature of the polymeric material to accelerate the film formation process and to avoid aging problems of the coated products [Ghebre-Sellassie et al., 1988; Lippold et al., 1989; Gilligan and Li Wan Po, 1991; Bodmeier and Paeratakul, 1991a; Wesseling and Bodmeier, 1999b]. However, the curing step was shown to have no influence on the drug release from beads coated with another EC dispersion, Surelease®, or an organic EC solution. This may be due to the differences in coating composition and preparation between Aquacoat® ECD and Surelease® and the differences in film formation mechanism [Shah et al., 1994; Wesseling and Bodmeier, 1999b].

Typically, the curing step results in a reduction of drug release when compared to drug release from uncured dosage forms [Lippold et al., 1989; Gilligan and Li Wan Po, 1991; Bodmeier and Paeratakul, 1991a; Schmidt and Niemann, 1993; Hutchings et al., 1994a; Bodmeier and Paeratakul, 1994; Guma et al., 1997; Amighi and Moes, 1997; Sakr et al., 1998; Frohoff-Hulsmann et al., 1999a]. Goodhart et al. observed a faster drug release rate from coated pellets cured at 45˚C for 48 hours, whereas a slower drug release was observed from pellets cured for an additional 96 hours at 65˚C. Explanation of this effect was that when the drying temperature was decreased, the hardness of the polymer particles was increased resulting in resistance to deformation of the film and incomplete film formation. At a higher temperature of 65˚C, a more homogeneous film with lower diffusivity was produced. Also, additional drying at a higher temperature promoted further gradual coalescence and further decreased in the drug release rate [Goodhart et al., 1984]. Gilligan and Li Wan Po

showed that the curing at 60˚C for at least 1 hour after coating was necessary to ensure that the EC-TEC coated Nu-pareil® beads of dextrometrophan hydrobromide containing HPMC produced consistency of release rates with no aging effects. It was necessary to coat the pellets at a temperature sufficient to promote further gradual coalescence and to include a post spray drying period into the coating procedure [Gilligan and Li Wan Po, 1991]. Bodmeier and Paeratakul observed that a limiting drug release pattern was approached from CPM-loaded nonpareil beads coated with EC pseudolatexes after curing the beads for 1 hour at 60˚C [Bodmeier and Paeratakul, 1991a].

In contrast, some studies found that some curing conditions may result in an increase of drug release when compared to drug release from uncured dosage forms. Sakr et al. reported that the release of theophylline from the granules coated with EC dispersion (Aquacoat®) plasticized with 30% DBS was influenced by oven-curing temperatures and times and the length of storage. The immediate drug release profile was obtained from the coated granules without exposure to any curing conditions after coating. At 70˚C curing temperature, the curing times of 70 and 260 minutes had no significant effects in drug release pattern. No significant differences in amount of drug release from coated granules cured at room temperature for 1 year and from coated granules cured at 45˚C for 5 minute were found. However, the theophylline release was slightly increased when the granules were cured at 45˚C for longer times of 10, 35, and 70 minutes or cured at a higher temperature of 70˚C for 10 minute [Sakr et al., 1998]. In another case of ibruprofen, a drug with a high affinity with the EC coating, an increase in drug

release was observed after the curing step due to diffusion of the drug into the coating. Therefore, an intermediate seal coat, HPMC, was used to reduce the diffusion of the drug into the EC coating [Bodmeier and Paeratakul, 1994]. Hutchings et al. found that when 30% DBS was employed as a plasticizer in the coating, propranolol hydrochloride release was faster when coated beads were exposed to higher curing time and temperatures. This result may be due to the migration of the DBS to the surface of the barrier coating or the higher solubility of drug DBS at the rigorous conditions, or the sticking and picking of the coating layer from adjacent beads at a high temperature. Whereas when 25% TBC was employed as a plasticizer in the coating, propranolol hydrochloride release was slower when coated beads were exposed to higher curing time and temperatures. This may be correlated with findings for the free films of Aquacoat® prepared with TBC, which showed greater elongation after exposure to higher curing temperatures [Hutchings, 1994a; Hutchings, 1994b].

Frohoff-Hulsmann et al. showed that when the amount of plasticizer increased from 9% to 20%, the curing temperature, which was necessary to reach a constant and low release rate, decreased. The temperatures used to cure the coated beads for 1 hour in the study were 70, 80, 90, and 100˚C. The amount and type of plasticizer used in the formulation can influence the film formation, and adequate curing time and temperature. The content of HPMC as a pore former in the coating had no effects on the optimum curing conditions [Frohoff-Hulsmann et al., 1999a]. Curing time required to obtain complete coalescence was less pronounced when plasticizer level in the film was increased. This was due to the

fact that the high amount of plasticizer drastically reduced the thermal properties of the polymer, such as the T_g and the MFT, and permitted the complete coalescence of latex particles during coating process [Bodmeier and Paeratakul, 1994; Amighi and Moes, 1996]. For instance, no curing step was necessary to obtain good film formation for CPM, a drug with low affinity for EC coating, coated beads when more than 25% TEC was added to EC dispersions. However, a curing step was required to stabilize the film when intermediate plasticizer levels between 15-25% were used [Bodmeier and Paeratakul, 1994].

The curing rates of coated beads are higher with higher storage temperature. Also, curing temperature has a more dramatic effect than curing time. This is due to the enhancement of the polymer chain mobility and the free volume values at high temperatures, which accelerate the coalescence of the latex particles [Wicks, 1986; Bodmeier and Paeratakul, 1991a; Hutchings et al., 1994a; Amighi and Moes, 1996]. However, attention must be paid to undesirable alterations of film and/or core properties, which are likely to occur when extreme storage conditions are adopted [Amighi and Moes, 1997]. Porter suggested that curing might not always be necessary since curing conditions (from 1-144 hours at 60˚C) had no significant influence on chlorpheniramine maleate release from beads coated with 10% of EC aqueous dispersion (Surelease®) [Porter, 1989]. In order to avoid unpredictable release profiles, it was not recommended to store the coated products at a temperature higher than 40˚C since it may cause a softening, hardening or leaking of the plasticizer of the coatings, or a stability problem of the active drug [Ghebre-Sellassie et al., 1987].

The conflicting information suggests that a further investigation of the influence of curing conditions on drug release is needed to obtain a better understanding. Additionally, optimum curing conditions for EC film have not been well characterized in the literature.

Water Soluble Additives

In some coated dosage forms including tablets and pellets, the release rate of the active drug from the dosage form is considered to be extremely slow. This incident was also seen for the release rate of pellets coated with Aquacoat® ECD containing only a plasticizer [Lippold et al., 1989; Gunder et al., 1995; Harris and Ghebre-Sellassie, 1997]. Therefore, it is very important to increase the release rate of the drug substances in order to ensure that they are sufficiently fast absorbed during passage through the gastrointestinal tract. The most effective method of enhancing the release rate of the active drug is to incorporate some pore forming agents in the release-controlling membranes [Kallstrand and Ekman, 1983; Ghebre-Sellassie et al., 1987; Bodmeier and Paeratakul, 1990; Bodmeier and Paeratakul, 1991b; Gunder et al., 1995]. Pore forming agents are water-soluble additives that are incorporated into a sustained release coating formulation to increase the release rate of the drug. Water-soluble cellulose ethers, such as MC and HPMC, have been widely used as pore forming agents. The use of MC as an additive in combination with EC for preparation of rapidly disintegrating tablets of the organic film coated aspirin crystals was reported in the literature. The release rate of aspirin crystals was dependent on the ratio of both cellulose ethers. Specifically, the release rate was increased when the amount of MC was

increased in the ratio due to higher solubility rate of MC [Coletta and Rubin, 1964]. The combination of HPMC and EC was also used as a model for the study of time-release cast films in an organic solvent system. A variety of release patterns was obtained by changing the proportions of EC and HPMC in the cast film. Solute, yellow dye, transport occurred through channels formed by the dispersed HPMC within the film. The formation of two types of channels or pores to permit transport of solute was governed by two factors. First factor was the hydration and dissolution of the HPMC, resulting in leaving pores in the film. The second factor was the hydrated HPMC, which retained in the film as a barrier, required the diffusion of the solute through the gel layer, resulting in reduction of the transport rate. However, the observed transport rate of solute was a function of the balance of the film thickness and HPMC concentration [Shah and Sheth, 1972]. Similarly, release rates of different drug types were enhanced by the addition of a hydrophilic polymer (HPC (75-100 cPs) or PEG 4000) to the EC casted film in the organic system. Enhancement coefficients of each system (i.e. EC-PEG or EC-HPC) were different due to the different mechanisms of hydrophilic polymer action [Donbrow and Samuelov, 1980]. In another EC-PEG organic coating system, the release of the active terbutaline sulfate increased as the amount of HPC in the coating solution increased. It was suggested that the formation of pores were increased in the coating layer as the amount of HPC increased [Umprayn et al., 1999]. Lindstedt et al. showed that the permeability of EC film was increased by incorporating HPMC (0-24%) in the film composition. Drug, potassium chloride (KCl), release from tablets coated with mixtures of EC

and up to 24% HPMC was controlled by osmotic pumping and drug diffusion mechanisms. At low HPMC content, a minor amount of HPMC was leached and no pores were formed. In contrast, at high HPMC content (24%), the formation of pores was caused by the leaching of the water-soluble HPMC [Lindstedt et al., 1989; Lindstedt et al., 1991]. However, another study reported that HPMC may have a limited degree of miscibility with EC; it may be incompatible at some level [Sakellariou et al., 1987]. Porter reported the effect of incorporation of the water-soluble MC polymer (15 cPs) into EC dispersion (Surelease®) on release of chlorpheniramine maleate from EC coated beads at 10% coating level. The amount of MC investigated was from 0-10 %w/w in dry film. For the control (no MC was added), extent of CPM released was longer than 12 hours. When more than 6 %w/w of MC was incorporated, CPM was released at a faster rate and shorter extent of less than 6 hours [Porter, 1989]. The effect of an addition of 0-12 %w/w HPMC on the release of dextromethorphan hydrobromide from aqueous EC coated non-pareil pellets was investigated. Numerous pores were present in the polymer film coating after dissolution. Post-coating condition was shown to be an important factor to ensure consistency of release rates from pellets containing 0-12 %w/w of HPMC [Gilligan and Li Wan Po, 1991]. Gunder et al. showed the effect of levels of the low-viscosity HPMC (Pharmacoat® 603, viscosity 3 cPs at 20˚C) incorporated into aqueous EC dispersion (Aquacoat® ECD) on the release of different drug type from coated pellets. During the first 2 hours of the release process, diffusion pellets contained water-filled pores in the release-controlling membrane after extraction of the HPMC. At the high levels of

HPMC (25-40%) used in the formulations, these pores closed irreversibly due to pore fusion if the release in an acidic medium occurred above the MFT. As a result, the release rate of drug was as slow as if it was from the control formulation (without HPMC). In contrast, in alkaline medium, the pore fusion did not occur due to ionized carboxylic groups of EC in alkaline environment [Gunder et al., 1995]. Recently, the release mechanisms of theophylline pellets coated with an aqueous EC dispersion (Aquacoat® ECD) containing different plasticizers and a pore former, HPMC (Pharmacoat® 603, viscosity 3 cPs at 20˚C), have been described. Release mechanism of theophylline from coated pellets was dependent on the aqueous solubility of the plasticizers as well as the ionic strength of the release medium. Additionally, the release mechanisms depended on the glass transition temperature of the EC and on the migration of the plasticizers and the pore former [Frohoff-Hulsmann et al., 1999a]. The properties of sprayed films prepared from the same combination of the coating were also investigated in order to obtain a better understanding of the drug release mechanisms of the coated pellets [Frohoff-Hulsmann et al., 1999b]. In addition to water-soluble polymers, some low molecular weight additives such as sucrose and surfactants (i.e. polysorbate 20) were also incorporated into EC organic-solvent based solutions. The macroporous membrane was created and release rate of drugs were increased [Lindholm et al., 1982; Lindholm, 1986a; Lindholm et al., 1986b]. In a slab model system, prepared by spraying an ethanolic solution of EC and acetaminophen on to flat tablet surfaces in a spray box, the addition of xylitol (25-75% by weight of EC), as a pore former, enhanced the release rate of

acetaminophen [van Bommel et al., 1989]. For the aqueous coating system, microporous osmotic pumps have been utilized in tablet coating applications. Bodmeier and Paeratakul showed that theophylline or KCl release from tablets coated with an aqueous acrylic latex (poly(ethylacrylate methylmethancrylate)) containing a dispersed pore former (60-80 %w/w) with pH-dependent solubility characteristics, dibasic calcium phosphate, was a function of pore former level and the membrane thickness, but was independent of the pH of the dissolution medium and the degree of agitation. Drug release increased with increasing the pore former level and drug was released via diffusion through pores created after dissolution of the calcium salt [Bodmeier and Paeratakul, 1990; Bodmeier and Paeratakul, 1991b]. Additionally, urea was also used as a pore former in different studies because of its small, readily water soluble, and uncharged molecule. The addition of urea (30-85 %w/w of Aquacoat ECD solids) to plasticized EC latex (Aquacoat ECD) resulted in the formation of the microporous latex coatings, when urea was eluted from the EC coatings. Therefore, the release of KCl or diltiazem HCl from coated osmotic tablets was enhanced. However, plasticizer type and level, and coating thickness also had some impacts on the release pattern of drugs from osmotic devices [Appel and Zentner, 1991].

In another matrix system, d-mannitol or bovine serum albumin (BSA) was also used as a pore former in biomaterials, polyurethane matrices (BioSpan®), containing hirudin. When the weight fraction of mannitol increased from 20-40%, the release rate and the total amount of hirudin released from the matrix were enhanced. More hirudin was released when d-mannitol was used as a pore

former than BSA. Moreover, large particle size of both pore formers enhanced the release rate and the total amount of hirudin release [Kim et al., 1998].

As can be seen from the above literature review, the use of a variety of hydrophilic additives to modify the release of a slightly water-soluble drug from matrix beads coated with aqueous cellulose dispersion has not been investigated in depth.

1.3 RESEARCH OBJECTIVES

In general, the overall objectives of this research were to investigate the use of cellulose ether polymers to formulate different pharmaceutical oral dosage forms, and to control the release of active ingredient from the specific oral delivery system over an extended period of time. Specifically, this research included the use of cellulose ethers to control the release of active drug from the following systems: 1). Single matrix tablet and 2). Multiparticulate dosage form. Formulations and processing parameters were optimized in order to achieve the desirable amount of drug release from each delivery system investigated. The study was divided into two major sections; the detailed research objectives of each system were as follows:

1.3.1 Single Unit System (Matrix Tablets)

Primary objectives

The primary objectives of this research system were to evaluate the different processing parameters and develop two stable, oral controlled release formulations of matrix tablets containing different molecular weight types (nominal viscosities) of HPMC, but both formulations had the same *in vitro* drug release. These two formulations, which were equivalent *in vitro*, were tested for bioequivalence during *in vivo* clinical study.

This research study was divided into four major parts to support the primary goal of this research.

1.3.1.1 Preformulation Studies for Alprazolam

Supporting objectives:

- To investigate the physiochemical properties of alprazolam, which is intended to be used as a model drug substance in the matrix tablet formulations. These properties included drug solubility, thermal property, particle size and particle size distribution, surface morphology, and crystallinity,
- To develop analytical methods, including ultraviolet spectroscopy and chromatographic analysis, for alprazolam quantitation.

1.3.1.2 Drug Recovery from Hydrophilic Matrix Tablets

Supporting objectives:

- To develop an analytical method for the recovery of the lipophilic drug from controlled release matrix tablets containing HPMC.
- To investigate the influence of formulation composition, such as HPMC molecular weight type and excipient type, on drug recovery.

1.3.1.3 Investigation of Formulation Parameters on Drug Release

a). Screening Study and Formulation Development

Supporting objectives:

- To perform a screening study to determine optimum parameters, such as tablet size, amount of drug loading, polymer levels, in order to obtain sustained release profiles.
- To develop a blending method for tablet manufacturing in order to obtain uniform distribution of low dose drug within a single dosage unit.

- To investigate the influence of excipient type and level on the release of the alprazolam formulated in controlled release tablets containing HPMC.
- To determine the influence of excipient type on the release mechanism of alprazolam from matrix tablets.
- To investigate formulations containing varying molecular weight types (nominal viscosity types) of HPMC polymer (i.e. HPMC K4MP and HPMC K100LVP), based on screening study.
- To investigate the influence of dissolution media on alprazolam release from matrix tablets.

b). Formulation and Characterization

Supporting objectives:

- To determine if oral controlled release tablet formulations containing varying molecular weight types (nominal viscosity) of HPMC polymer have an equivalent in vitro performance, when formulated with a lipophilic drug (alprazolam).
- To obtain a better understanding of the importance of influence of molecular weight type (nominal viscosity) of HPMC on in vitro product performance.
- To physically characterize the tablet formulations developed in terms of weight and hardness distributions, content uniformity and in vitro drug release.
- To statistically compare the dissolution profiles of the formulations developed using the similarity factor (f_2 factor).

- To investigate the stability of alprazolam in the tablet formulations developed, based on the dissolution profiles and similarity factor.

1.3.1.4 *In Vivo* Clinical Study

Supporting objectives:

- To investigate if two similar controlled release formulations of a lipophilic drug (alprazolam) having the same *in vitro* drug release, but containing different molecular weight types (nominal viscosities), are bioequivalent.
- To compare the pharmacokinetics and pharmacodynamics of alprazolam from two oral controlled release tablet formulations containing different molecular weight types (nominal viscosities) of HPMC polymer.
- To examine the effect of food on *in vivo* drug release from these HPMC matrix tablets.

1.3.2 Multiparticulate System (Film-Coated Beads)

Influence of processing parameters on drug release from cellulose ether coated matrix bead formulations.

Primary objective

The primary objective of this research was to investigate the influence of processing parameters including drug type, plasticization time and level, the incorporation of a water-soluble additive, and curing conditions on drug release from ethylcellulose coated matrix bead formulations.

This research study was divided into three major parts to support the primary goal of this research.

1.3.2.1 Curing Conditions

Supporting objectives:

- To optimize the curing conditions of ethylcellulose coated beads in order to obtain sustained release profiles for a water-soluble model drug and a slightly water-soluble model drug.
- To determine the influence of curing time and temperature for ethylcellulose films on drug release from matrix bead formulations.
- To determine the optimum curing conditions needed for completing film coalescence of matrix beads without disrupting film integrity.
- To investigate the influence of drug type, coating level, and subcoating application on the curing conditions of the ethylcellulose coated matrix beads.

1.3.2.2 Plasticization

Supporting objectives:

- To investigate the influence of plasticizer type (i.e. water miscible and water insoluble) and mixing time (plasticization time) on drug release from the ethylcellulose coated matrix beads containing either a water-soluble model drug or a slightly water-soluble model drug.
- To investigate the influence of drug type and coating level on the plasticization of the ethylcellulose coated matrix beads.

1.3.2.3 Water Soluble Additives

Supporting objectives:

- To investigate the influence of hydrophilic water-soluble additives on the release of a slightly water-insoluble drug from ethylcellulose coated beads.
- To obtain a better understanding of using water-soluble additives and their function in sustained release formulations.

CHAPTER 2

EXPERIMENTAL

2.1 MATERIALS

2.1.1 Single Unit System (Matrix Tablets)

The following materials were used during preformulation studies of alprazolam: Alprazolam USP (ALP; Controlled substance DEA Schedule IV; Spectrum Quality Products, Gardena, CA, USA); potassium chloride (KCl, EM Science, Gibbstown, NJ, USA); 1 N hydrochloric acid solution (Spectrum Quality Products, Gardena, CA, USA); tribasic sodium phosphate ($Na_3PO_4.12H_2O$, EM Science, Gibbstown, NJ, USA); Sulfuric Acid (H_2SO_4, EM Science, Gibbstown, NJ, USA); potassium phosphate monobasic (KH_2PO_4, EM Science, Gibbstown, NJ, USA); sodium hydroxide (NaOH, EM Science, Gibbstown, NJ, USA); phosphoric acid (H_3PO_4, EM Science, Gibbstown, NJ, USA); Polyoxyethylene sorbitan monooleate (Tween 80, Crillet® 4 NF; Croda Inc., Parsippany, NJ, USA) was used to disperse the drug particle during particle size study.

The following materials were used for the preparation of powder blends and matrix tablets in drug recovery and formulation studies: Alprazolam USP (ALP; Controlled substance DEA Schedule IV; Spectrum Quality Products, Gardena, CA, USA); hydroxypropyl methylcellulose USP (HPMC substitution type 2208, Methocel K100 Premium LVCR EP (K100LVP, 22.8% methoxyl content, 8.7% hydroxypropyl content, and 107 cPs apparent viscosity as a 2%

aqueous solution) or Methocel K4M Premium CR (K4MP, 22.6% methoxyl content, 9.6% hydroxypropyl content, and 4126 cPs apparent viscosity as a 2% aqueous solution), The Dow Chemical Company, Midland, MI, USA); microcrystalline cellulose N.F. (MCC; Avicel PH 200, FMC Corporation, Philadelphia, PA, USA); lactose monohydrate N.F. (LAC; Modified Spray-dried, Foremost Farms USA, Baraboo, WI, USA); dicalcium phosphate dihydrate (DCP; Di-Tab, Rhodia North America, Chicago Heights, IL, USA); dicalcium phosphate anhydrous (DCA; A-Tab, Rhodia North America, Chicago Heights, IL, USA); sucrose (SUC; DiPac, Domino Sugar, Baltimore, MD, USA); dextrose (DEX; Emdex, Penwest Pharmaceuticals Company, Patterson, NY, USA); calcium sulfate dihydrate (CSD; Compactrol, Penwest Pharmaceuticals Company, Patterson, NY, USA); silicon dioxide (Cab-O-Sil M5P, Cabot Corporation, Tuscola, IL, USA); and magnesium stearate USP/N.F. (Spectrum Quality Products, Gardena, CA, USA).

The following packaging components were used for the stability study of the tablet formulations, 1-gram Silica Gel Pak (Desiccare, Inc., Richland, MS, USA); 60 cc and 250 cc high density polyethylene (HDPE) wide-mouth white bottles and polypropylene (PP) cap (Foamed polyethylene (PE) and pressure sensitive liner (Berlin Packaging, Arlington Hgts, IL, USA).

For HPLC analysis, the chemicals used were analytical reagent grade. HPLC grade acetonitrile, tetrahydrofuran (distilled; THF), monobasic potassium phosphate, and sodium hydroxide were purchased from EM Science (Gibbstown, NJ, USA). Alprazolam USP reference standard was purchased from U.S.

Pharmacopoeia (Rockville, MD, USA). Whatman 0.45 µm (47 mm diameter) nylon membrane filters (Whatman International Ltd., Maidstone, England) and GHP 0.45 µm (GHP Acrodisc 13 mm, Pall Gelman Laboratory, Ann Arbor, MI, USA) syringe filters were used to filter mobile phase and samples, respectively. Water was purified with a Milli-Q UV Plus system (Millipore, Molsheim, France).

For the dissolution study of the matrix tablets, 1 N hydrochloric acid (HCl) solution (J. T. Baker, Phillipsburg, NJ, USA) and purified water were used for preparation of 0.1 N HCl solution. For USP buffer pH 6.0 preparation, potassium phosphate monobasic (KH_2PO_4, EM Science, Gibbstown, NJ, USA), sodium hydroxide (NaOH, EM Science, Gibbstown, NJ, USA), and purified water were used. The 10 µm filters (Vankel Technologies Group, Cary, NC, USA) were used to filter all samples collected during dissolution tests.

2.1.2 Multiparticulate System (Film-Coated Beads)

The following materials were used for the preparation of uncoated matrix beads: Chlorpheniramine maleate (CPM, Spectrum Quality Products, Gardena, CA, USA), Theophylline anhydrous USP (Spectrum Quality Products, Gardena, CA, USA), microcrystalline cellulose N.F. (MCC; Avicel PH 101, FMC Corporation, Philadelphia, PA, USA), and purified water. A 30 %w/w aqueous dispersion of ethylcellulose (Aquacoat® ECD, FMC Corporation, Philadelphia, PA, USA) and hydroxypropyl methylcellulose USP (HPMC substitution type 2910, Methocel E5P, The Dow Chemical Company, Midland, MI, USA) were

used as coating materials. Different types of water miscible and water insoluble plasticizers including polyethylene glycol 400 (PEG 400, Carbowax®, Fisher Scientific, Fair Lawn, NJ, USA), triethyl citrate PG/NF (TEC, Citroflex 2, Morflex Inc., Greensboro, NC, USA); dibutyl sebacate NF (DBS, Morflex Inc., Greensboro, NC, USA); acetylated monoglycerides (AMG, Myvacet 9-45, Eastman Chemical Co., Kingsport, TN, USA) were used during the coating process. In some formulations, the pore forming agents included hydroxypropyl methylcellulose (HPMC substitution type 2910, Methocel E5P, The Dow Chemical Company, Midland, MI, USA); polyethylene glycol 8000 (PEG 8000), sucrose, or mannitol (Spectrum Quality Products, Gardena, CA, USA) was added to the coating dispersion.

For dissolution studies of the film-coated beads, monobasic potassium phosphate, sodium hydroxide (EM Science, Gibbstown, NJ, USA), phosphoric acid (EM Science, Gibbstown, NJ, USA), and purified water were used to prepare dissolution media. The 10 µm filters (Vankel Technologies Group, Cary, NC, USA) were used to filter all samples collected during the dissolution tests.

2.2 METHODS

2.2.1 Single Unit System (Matrix Tablets)

2.2.1.1 Preformulation Studies for ALP

Determination of ALP Solubility

Solubility study of the active drug, ALP, was investigated in different media as follows:

1). Purified water

2). 0.05 M Sulfuric Acid (H_2SO_4)

3). 0.1 N hydrochloric Acid (HCl), pH 1.1 (dissolution medium for ALP tablets)

4). Buffer pH 1.2 (Simulated Gastric Fluid, SGF)

5). USP buffer pH 2.0

6). Buffer pH 5.0

7). Buffer pH 6.8 (Simulated Intestinal Fluid, SIF)

8). USP buffer pH 8.0

An excess amount of ALP powder was added to each scintillation glass vial containing 10 ml of each medium. Each vial was mechanically stirred, sonicated, and then continuously shaken at 37±0.5˚C using a laboratory shaker (Lab-Line® Orbit Environ-shaker, Lab-line Instruments, Inc., Melrose Park, IL) to facilitate saturated drug dissolution. The amount of ALP in the solution after equilibrating for 1 day and 2 days was determined by ultraviolet spectroscopy described in a later section. The samples were prepared for UV analysis by

filtering them through a 0.45 mm GHP syringe filter (GHP Acrodisc 13 mm). Appropriate dilutions were made with each medium prior to analysis.

Finally, solubility results in each medium after 1 and 2 days equilibration were compared to ensure the equilibrium saturated solubility of ALP at 37±0.5˚C.

Thermal Analysis

Thermal properties of ALP powder were evaluated by Differential Scanning Calorimetry (DSC) using a Modulated Differential Scanning Calorimeter (Model DSC 2920; TA Instruments, New Castle, DE, USA). The standard DSC (heat flow as a function of temperature) was chosen. The scan rate was 10˚C/minute in a dynamic nitrogen environment between 50˚C and 300˚C. The sample weighed about 2-4 mg and was contained in closed aluminum pans. Duplicate determinations were carried out for each sample.

To investigate if ALP had undergone the recrystallization process, repeated heating and cooling processes were used. The sample was heated from 50˚C to 300˚C at the scan rate of 10˚C/minute, cooling from 300˚C down to 50˚C at the scan rate of 5˚C/minute, heating from 50˚C to 300˚C at the scan rate of 10˚C/minute, cooling from 300˚C down to 50˚C at the scan rate of 20˚C/minute, and then heating from 50˚C to 300˚C at the scan rate of 10˚C/minute.

Particle Size and Particle Size Distribution Study (Laser Light Scattering)

Particle size distribution of ALP was determined using a Shimadzu SALD1100 laser diffraction type particle size analyzer (Shimadzu Scientific Instrument Inc., Columbia, MD, USA). The laser operates at a wavelength of 780

nm with an output of 3 mW. Particle size distribution data consists of volume percent distribution, light energy distribution, cumulative volume distribution, and differential distribution. Particle size distribution curves were plotted between percent cumulative undersized and particle size of ALP. Two replicate samples were dispersed in 0.02% Tween 80 immediately prior to analysis, agitated to ensure a uniform dispersion by using a mechanical stirrer and ultrasonic wave bath, and were read in duplicate.

Scanning Electron Microscopy (SEM)

Scanning electron microscopy was used to examine the particle size, surface morphology and crystal shape of ALP powder. Drug powder was mounted on brass SEM stages using 3M double sided tape and was then coated with gold-palladium for 60 seconds under an argon atmosphere using a Pelco® Model 3 Sputter Coater (TED Pella, Inc., Tusin, CA, USA) in a high vacuum evaporator equipped with an omni-rotary stage. Samples were examined with a Jeol scanning electron microscope (Model JSM-35C, Jeol USA, Inc., Peabody, MA, USA) or Hitachi S-4500 field emission scanning electron microscope (Hitachi Instruments Inc., Irvine, CA, USA) at 4.0 kV. The scanning electron micrographs were taken by a Polaroid® 545 Land Camera with 4" x 5" exposure film.

Powder X-ray Diffractometry

The ALP powder samples were packed in the X-ray holder from the top prior to analysis. X-ray diffraction patterns were obtained with a Philips vertical

scanning diffractometer (Phillips Vertical Scanning Diffractometer, Type PW1729; Philips Electronic Instruments, Mount Vernon, NY, USA) and Philips data acquisition software (Type APD3520) over a 2-theta range of 5˚ to 50˚ (where theta is the scattering angle) with a step size of 0.05˚ 2-theta. The analysis was carried out at room temperature under ambient conditions. Duplicate determinations were made for each of the samples.

Analytical Methods

Ultraviolet Spectroscopy

The UV spectroscopic method for ALP quantitation used in this study was modified from an assay method of ALP in 0.05 M sulfuric acid (H_2SO_4) solution developed by Acikkol et al [Acikkol et al., 1991]. This method was modified to determine the amount of ALP in each medium used during the solubility study and the amount of drug release from a matrix tablet into a dissolution medium during the dissolution study. The amount of drug was quantified by ultraviolet spectroscopy (Hewlett Packard Diode Array Spectrophotometer, Model 8452A, with 1-cm quartz cell) at the maximum wavelength of ALP.

For standard curve preparation, a 0.05 M H_2SO_4 solution was used as a diluent for determination of ALP in each medium during the solubility study; whereas a 0.1 N hydrochloric acid (HCl) solution was used as a diluent for determination of drug release in a dissolution medium during the dissolution study. For standard curve preparation, about 0.01 g of ALP powder was weighed into a 100 ml-volumetric flask. About 80 ml of an appropriate diluent was added to dissolve the drug. The stock solution was sonicated for 15 minutes to ensure complete dissolution of all drug particles before adjusting to a final volume with an appropriate diluent. Final concentration of stock solution was about 0.1 mg/ml. The stock solution was then diluted with a diluent to concentrations in the range of 0.001–0.020 mg/ml. A calibration curve was prepared by plotting the absorbance values of each standard against the concentration of each standard.

Finally, the quantity of ALP was calculated from the regression equation of the calibration curve. Linear correlation over the concentration range of 0.001–0.020 mg/ml for ALP should be close to 1 ($r^2 = 1$).

For sample preparation, an appropriate dilution of each sample was made with an appropriate diluent such that the final concentration was within the linear portion of the standard curve for ALP prior to analysis.

Chromatographic Analysis

The reverse-phase HPLC method used to determine the amount of ALP in the powder blends and pulverized matrix tablets was a modification from the assay method of ALP Tablets listed in USP 24/NF 19 monograph [United States Pharmacopeial Convention, 1999]. The chromatographic system (Shimadzu, Columbia, MD, USA) consisted of a system controller (Model SCL-10A-VP), a PDA detector (Model SPD-M10A VP, deuterium lamp), a chromatographic data control and acquisition system (Class-VP software version 4.2), pumps (Model LC-10AT VP), and an autoinjector (SIL-10A). A Luna 5µ C8(2) (5 µm, 100 x 4.6 mm, Phenomenex, Torrance, CA, USA), USP packing type L7, column and a security guard cartridge C8 (4 x 3.0 mm, Phenomenex, Torrance, CA, USA) were used.

The mobile phase was composed of a mixture of 35.34 mM phosphate buffer (pH 6.0±0.1), acetonitrile and tetrahydrofuran in a ratio of 68:28:4 (v/v/v). The 35.34 mM phosphate buffer solution was prepared by dissolving monobasic potassium phosphate in purified water, and then adjusting the pH to 6.0±0.1 with 5.3 M sodium hydroxide solution. Prior to use, the mobile phase was filtered

through a 0.45 µm nylon membrane filter (Whatman, 47 mm diameter), and degassed with vacuum and sonication for 10 minutes. The flow rate of the mobile phase was 2 ml/min (isocratic) and the injection volume was 20 µl. The absorbance was monitored at 222 nm. The run time was 10 min. A calibration curve was prepared by dissolving ALP USP reference standard with the diluent (purified water-acetonitrile, 50:50, v/v), and the stock solution was diluted to concentrations in the range of 0.005 to 0.06 mg/ml. Replicate standards were injected to ensure repeatability prior to sample analysis. Integration of chromatographic peaks was performed using the default values of 3500 and 0.75 for peak threshold and peak width, respectively. Peaks were integrated using a tangential skim or valley-to-valley method. System suitability criteria were established: the correlation coefficient (r^2) of the calibration curve, not less than 0.998; relative standard deviation (RSD) of five replicate injections, ≤ 2.0%; number of theoretical plates, > 500 plates/column; and the peak asymmetry, ≤ 1.5 [United States Pharmacopeial Convention, 1999]. A check standard of known concentration was inserted between every five samples. All samples were filtered through 0.45 µm GHP syringe filters (GHP Acrodisc 13 mm) into HPLC vials.

2.2.1.2 Drug Recovery from Hydrophilic Matrix Tablets

Sample Preparation Methods

Each sample contained placebo powder and a known amount of ALP. A mixture of HPMC polymer (either Methocel K4MP or K100LVP), microcrystalline cellulose, other excipient(s), silicon dioxide, and magnesium

stearate was prepared by geometric dilution in a V-blender. Either ALP powder or an aliquot of stock solution containing a known amount of ALP was added to an aliquot of the placebo powder blend. Two sample preparation methods (I and II) were investigated to determine ALP recovery. Each sample listed in Table 2.1 was prepared in replicates of three using sample preparation method indicated below.

Sample Preparation Method I

Acetonitrile (ACN) alone was used as the extraction solvent. After final volume adjustment, each sample was filtered through a 0.45 µm GHP syringe filter (GHP Acrodisc 13 mm) into a glass vial. Finally, the drug content was determined by HPLC. The samples investigated (A to J) using method I and orders of addition are described in Table 2.1. The quantitative composition of each placebo powder (A to J) is listed in Table 2.2.

Sample Preparation Method II

The composition of placebo powder blend used for sample K preparation and analyzed using method II is described in Table 2.2. A physical blend of placebo powder blend and ALP powder were blended and transferred to a 1-L volumetric flask. To the physical blend, 170 ml of hot water (~ 90˚C) was added with stirring to disperse the physical blend before addition of 330 ml of cold water (~ 5˚C). The slurry was stirred in an ice bath at 2˚C for 3 hours to dissolve the HPMC gel. Then, about 450 ml of ACN was added and stirring was continued for 4 hours at 25˚C. The sample was adjusted to final volume and then 50 %v/v

ACN mixture was obtained. Finally, the mixture was filtered through a 0.45 µm GHP syringe filter (GHP Acrodisc 13 mm) into a glass vial for HPLC analysis.

Table 2.1 Sample Preparation Method I Used for Determination of ALP Content

Sample	Form of ALP added	Solvent (Temperature)	Sample Preparation Procedure
A	**stock solution in ACN**	**100 % ACN (22˚C)**	**Placebo powder blend[1], add ACN, add ALP Stock Solution, mix and adjust to volume.**
B	**powder**	**100 % ACN (22˚C)**	**Placebo powder blend[1], add ACN, sonicate for 30 min., add ALP Powder, sonicate for 30 min., mix and adjust to volume.**
C	**powder**	**100 % ACN (22˚C)**	**ALP Powder, add ACN, sonicate for 30 min., add Placebo powder blend[1], mix and adjust to volume.**
D	**powder**	**100 % ACN (22˚C)**	**Placebo powder blend[1], add ALP Powder, add ACN, sonicate for 30 min., mix and adjust to volume.**
E	**powder**	**100 % cold ACN (5˚C)**	**Placebo powder blend[1], add ALP Powder, add cold ACN, sonicate for 30 min., stir at 25˚C for 12 hrs, mix and adjust to volume.**
F	**powder**	**100 % cold ACN (5˚C)**	**ALP Powder, add cold ACN, sonicate for 30 min, add Placebo powder blend[1], stir at 25˚C for 12 hrs, mix and adjust to volume.**
G	**powder**	**100 % cold ACN (5˚C)**	**Placebo powder blend[1], add cold ACN, sonicate for 30 min., add ALP Powder, sonicate for 30 min., stir at 25˚C for 12 hrs, mix and adjust to volume.**
H	**powder**	**100 % cold ACN (-10˚C)**	**Placebo powder blend[1], add ALP Powder, add cold ACN, sonicate for 30 min., stir at 25˚C for 12 hrs, mix and adjust to volume.**
I	**stock solution in ACN**	**100 % cold ACN (-10˚C)**	**Placebo powder blend[1], add ALP Stock Solution, add ACN (-10˚C), sonicate for 30 min., stir overnight at 25˚C, mix and adjust to volume.**
J	**powder**	**100 % cold ACN (-20˚C)**	**Placebo powder blend[1], add ALP Powder, add ACN (-20˚C), stir at -17˚C for 2 hrs, mix and adjust to volume.**

[1] Placebo powder contained 23 %w/w of HPMC-K4MP, 20 %w/w of microcrystalline cellulose, 56 %w/w of dicalcium phosphate dihydrate, 0.5 %w/w of silicon dioxide, and 0.5 %w/w of magnesium stearate.

Table 2.2 Placebo Powder Composition for Sample Preparation

Placebo powder for sample	HPMC Type (level)	Excipient Type (level)	Other Excipients in Tablet Formulation
A to K	K4MP (23 %w/w)	dicalcium phosphate dihydrate (56 %w/w)	microcrystalline cellulose (20 %w/w), silicon dioxide (0.5 %w/w), magnesium stearate (0.5 %w/w)
L	K100LVP (40 %w/w)	dicalcium phosphate dihydrate (39 %w/w)	microcrystalline cellulose (20 %w/w), silicon dioxide (0.5 %w/w), magnesium stearate (0.5 %w/w)
M	K4MP (40 %w/w)	sucrose (39 %w/w)	microcrystalline cellulose (20 %w/w), silicon dioxide (0.5 %w/w), magnesium stearate (0.5 %w/w)
N	K4MP (40 %w/w)	dextrose (39 %w/w)	microcrystalline cellulose (20 %w/w), silicon dioxide (0.5 %w/w), magnesium stearate (0.5 %w/w)
O	K4MP (40 %w/w)	dicalcium phosphate anhydrous (39 %w/w)	microcrystalline cellulose (20 %w/w), silicon dioxide (0.5 %w/w), magnesium stearate (0.5 %w/w)
P	K4MP (40 %w/w)	calcium sulfate dihydrate (39 %w/w)	microcrystalline cellulose (20 %w/w), silicon dioxide (0.5 %w/w), magnesium stearate (0.5 %w/w)

Influence of molecular weight type (nominal viscosity) of HPMC on ALP recovery

The two different molecular weight types of HPMC polymer (Methocel K100 having an apparent viscosity of 107 cPs and Methocel K4MP having an apparent viscosity of 4126 cPs) were incorporated into the placebo powder blends (Table 2.2 - samples K and L). Sample K contained the high molecular weight polymer (23 %w/w of HPMC K4MP), whereas sample L contained the low molecular weight polymer (40 %w/w of HPMC K100LVP). Both samples K and L were prepared by using sample preparation method II as described in the previous section.

Influence of excipient type on ALP recovery

The water-soluble excipients investigated include sucrose and dextrose. The water insoluble excipients investigated include anhydrous dicalcium phosphate and calcium sulfate dihydrate. The composition of the placebo powder blends used to prepare samples M-P are shown in Table 2.2. All samples were prepared by using sample preparation method II as described in the previous section.

Determination of drug content in a matrix tablet

Matrix tablet preparation:

Two hydrophilic matrix tablet formulations containing either HPMC K4MP or K100LVP polymer were prepared for a 300-gram batch size. Batch

composition in percent weight by weight is shown in Table 2.3. All ingredients were blended using a geometric dilution technique in a V-blender. Matrix tablet preparation will be described in detail in the following section. Tablets weighing 400 mg were prepared by direct compression using standard tablet tooling (concave, 11 mm diameter) and tablet press (Stokes Dual Pressure Press Model B2, Serial No. B59671, F.J. Stokes Machine Company, Philadelphia, PA, USA). Tablet size, shape and hardness were identical for both formulations.

Content uniformity assay of matrix tablets

A content uniformity assay of ground individual tablets and a composite assay of 10 ground tablets from each formulation were determined using sample preparation method II. ALP content in the matrix tablet(s) was quantified by HPLC.

Table 2.3 ALP Matrix Tablet Formulations (10 mg ALP/400 mg tablet)

Formulation	HPMC Type (level)	Excipient Type (level)	Other Excipients in Tablet Formulation
Q	K4MP (37 %w/w)	lactose (42 %w/w)	microcrystalline cellulose (20 %w/w), silicon dioxide (0.5 %w/w), magnesium stearate (0.5 %w/w)
R	K100LVP (45 %w/w)	lactose (34 %w/w)	microcrystalline cellulose (20 %w/w), silicon dioxide (0.5 %w/w), magnesium stearate (0.5 %w/w)

2.2.1.3 Investigation of Formulation Parameters on Drug Release

In order to develop a 14- to 16-hour sustained release matrix tablet formulation, the influence on ALP release of the parameters including tablet size, drug loading, polymer level, polymer molecular weight type, excipient type and level, and dissolution medium, were investigated. A screening formulation study was carried out in order to select the optimum tablet size, drug loading, and polymer level. Influence of excipient, polymer molecular weight type, and dissolution medium on drug release was investigated during formulation development.

Screening Study

Each tablet formulation was prepared in a 300-gram batch size. General formulation compositions and levels are shown in Table 2.4. Powder blend was prepared by geometric dilution in a V-blender. A blending method was developed to obtain uniformity of the dosage form, especially for low dosing level. The blending procedure is described in detail in the next section.

Tablet Size

Hydrophilic matrix tablet formulations contained ALP as a model drug, a hydrophilic polymer (HPMC K4MP), an excipient (microcrystalline cellulose (Avicel PH 200) or lactose monohydrate), and a lubricant (magnesium stearate).

Three different sizes of tooling (8, 9, and 11 mm diameter, concave tooling) were then used to prepare the matrix tablets. Tablet weight was 120, 240, and 400 mg for 8, 9, and 11 mm diameter tooling, respectively. Tablets were

compressed to the hardness range between 10-14 kg for 8 and 9 mm diameter tooling, and to the hardness range between 6.5-9.5 kg for 11 mm diameter tooling. A dissolution study of each tablet size from the formulations developed was performed at least in triplicate for screening purpose in order to obtain a product with 14- to 16-hour sustained release period.

Drug Loading

Hydrophilic matrix tablet formulations contained ALP, HPMC K4MP or HPMC K100LVP, microcrystalline cellulose (Avicel PH 200), magnesium stearate, and the tablet weight was adjusted with dicalcium phosphate.

Two levels of drug ALP were used to prepare 11-mm diameter tablets with hardness range between 6.5-9.5 kg. Either 5-mg dose (1.25 %w/w) or 10-mg dose (2.50 %w/w) of ALP was contained in a 400-mg tablet.

Polymer Level

Hydrophilic matrix tablet formulations contained 2.5 %w/w ALP, HPMC K4MP, microcrystalline cellulose (Avicel PH 200), silicon dioxide, magnesium stearate, and the tablet weight was adjusted to 400 mg with lactose.

Different levels of HPMC polymer (30-65 %w/w) were used to prepare 11-mm diameter tablets with hardness range between 6.5-9.5 kg.

Table 2.4 General Formulation of ALP Matrix Tablets for Screening Study

Rx	**%w/w**
Ingredient	
Alprazolam	1.25 - 2.50
HPMC K100LVP or K4MP	30.00 - 65.00
Microcrystalline cellulose (PH200)	0.00 - 20.00
Silicon dioxide	0.00 - 0.50
Mg stearate	0.50
Excipient	qs
Total	100.00

Formulation Development

Excipient Type

A hydrophilic matrix tablet formulation was developed to contain ALP, HPMC K4MP polymer, a swelling excipient (microcrystalline cellulose, Avicel PH 200), a glidant (silicon dioxide), a lubricant (magnesium stearate), and other excipients. Each formulation was prepared for a 300-gram batch size. The composition of each tablet formulation is shown in Table 2.5. The excipient type was varied and included water soluble excipients (LAC, SUC, DEX) and/or water insoluble excipients (DCP, DCA, CSD). Method of preparation is described in detail in the next section.

Table 2.5 Quantitative Composition of ALP Matrix Tablet Formulations for Excipient Type Study

Ingredient	**Formulation (% w/w)**								
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
Alprazolam USP (10 mg/400 mg tablet)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
HPMC K4MP	40.0	40.0	40.0	40.0	40.0	40.0	40.0	40.0	40.0
Microcrystalline cellulose (MCC)	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
Silicon dioxide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Lactose monohydrate (LAC)	**36.5**	**27.4**	**18.3**	**9.1**	-	-	-	-	-
Dicalcium phosphate dihydrate (DCP)	-	**9.1**	**18.3**	**27.4**	**36.5**	-	-	-	-
Sucrose (SUC)	-	-	-	-	-	**36.5**	-	-	-
Dextrose (DEX)	-	-	-	-	-	-	**36.5**	-	-
Dicalcium phosphate anhydrous (DCA)	-	-	-	-	-	-	-	**36.5**	-
Calcium sulfate dihydrate (CSD)	-	-	-	-	-	-	-	-	**36.5**
Total	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

HPMC Molecular Weight Type (Nominal Viscosity)

As can be seen in Table 2.6, a hydrophilic matrix tablet formulation was developed to contain ALP as a model drug, an insoluble swelling excipient (microcrystalline cellulose, Avicel PH 200), a soluble excipient (lactose monohydrate), a hydrophilic polymer (HPMC), a glidant (silicon dioxide), and a lubricant (magnesium stearate). The two different molecular weight types of HPMC polymer (Methocel K4MP or Methocel K100LVP) were substituted into the matrix tablet formulation to make the two formulations to be tested for equivalence *in vitro*. The level of HPMC polymer in each formulation was varied from 30-45 %w/w in order to accommodate the similar dissolution profiles. Method of preparation is described in detail in the next section.

Table 2.6 Typical Formulation of ALP Matrix Tablets for Molecular Weight Type Study

Rx	**%w/w**
Ingredient	
Alprazolam	2.50
(10 mg/400 mg tablet)	
HPMC K100LVP or K4MP	30.00-45.00
Microcrystalline cellulose (PH200)	20.00
Silicon dioxide	0.50
Mg stearate	0.50
Lactose, Fast-Flo	qs
Total	100.00

Controlled Release Tablet Preparation

The components were combined geometrically and mixed using a rotating V-blender. The blending method for a low level of drug loading (2.5 mg/120 mg tablet or 5 mg/240 mg tablet, 2.08 %w/w; 10 mg/400 mg tablet, 2.5 %w/w) was developed. The following section describes the blending method in detail for preparation of the tablets for the HPMC molecular weight type study. A similar preparation method was also applied to other formulations investigated. However, a different hardness range was varied for each size of tooling used. Either 8 or 9 mm diameter tooling was used to prepare tablets with hardness range between 10-14 kg, whereas 11 mm diameter tooling was used to prepare tablets with hardness range between 6.5-9.5 kg. Figure 2.1 shows the schematic of matrix tablet preparations.

Preparation of Active direct compression blend

1). Sieve all ingredients through No.40 mesh screen to deaggregate the particles.

2). Weigh out each ingredient according to batch charge for 300-g batch size (750 tablets).

3). Add ALP USP and Silicon Dioxide into a V-blender (1.2 L. volume) and mix for 10 minutes.

4). Add about 1/3 the amount of Microcrystalline Cellulose N.F. into the V-blender from step 3) and mix for 10 minutes.

5). Add another 1/3 the amount of Microcrystalline Cellulose N.F. into the V-blender from step 4) and mix for 10 minutes.

6). Add the last portion (1/3) of Microcrystalline Cellulose N.F. into the V-blender from step 5) and mix for another 10 minutes.

7). Add about 1/2 the amount of Lactose Monohydrate N.F. into the V-blender from step 6) and mix for 10 minutes.

8). Add the last portion (1/2) of Lactose Monohydrate N.F. into the V-blender from step 7) and mix for another 10 minutes.

9). Add HPMC K100LVP or K4MP into the V-blender from step 8), mix for 10 minutes, carefully remove the powder blend from the V-blender, pass through a No.40 mesh screen, and transfer back into the V-blender.

10). Mix for 10 minutes, remove the powder blend from the V-blender, pass through a No.40 mesh screen, and transfer back into the V-blender.

11). Add 1.5 g of Magnesium Stearate USP/N.F. into the V-blender, and mix for 5 minutes.

12). Label contents “Active Direct Compression Blend-Formulation __”.

Compression

13). Transfer the active direct compression blend from step 12) to the hopper of the tablet machine.

14). Compress the active direct compression blend using concave, 11 mm diameter tablet tooling into a tablet weighing 400 mg±5% (380–420 mg weight variation) with a target hardness of 8 kg (acceptable range 6.5–9.5 kg).

Tablet press: Stokes Dual Pressure Press Model B2 (F.J. Stokes Machine Company, Philadelphia, PA)

Hardness Tester: Heberlein Type WTP-3 (Fab. Nr. 1082, Heberlein & Co AG).

15). Sample 3 tablets approximately every 50 tablets, confirm weight and hardness to meet the specification in step 14). Adjustment of the tablet press is allowed during compression process in order to obtain tablets with above specifications. Approximately, a tablet yield of 200-300 tablets is needed. After process is complete, tablets, active direct compression blend and waste are collected in separate container.

16). Randomly confirm weight of 20 tablets and hardness of 10 tablets from the entire batch.

17). Package tablets into HDPE bottles with PP caps and desiccant to protect from light and moisture. Label “Formulation ____” on the bottle.

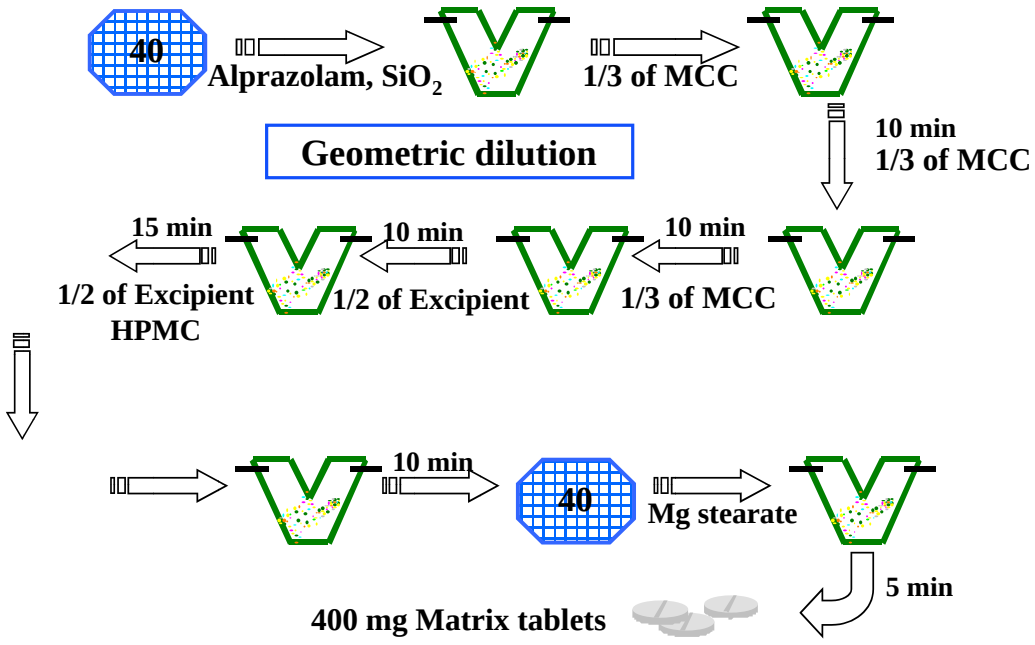


Figure 2.1 Schematic of matrix tablet preparation

Characterization of Matrix Tablets

Each tablet formulation was characterized as follows:

Weight and hardness variations

The weight of 20 tablets and the hardness of 10 tablets (Heberlein Hardness Tester Type WTP-3, Fab. Nr. 1082, Heberlein & Co AG) were determined on tablets sampled randomly across the lot.

The acceptable average tablet weight was 380-420 mg (400 mg target) for the tablet weight and the average tablet hardness was 6.5-9.5 kg (8 kg target).

Content Uniformity Assay

A content uniformity assay of 10 tablets from each formulation was performed using an extraction method developed in the previous section. The extraction method comprised using hot water to swell the HPMC polymer, followed by the addition of cold water to completely dissolve HPMC, and then adding acetonitrile to dissolve the ALP. The content uniformity assay procedure is described in detail as follows:

1). Individually weigh each of the 10 tablets and record actual weight.
2). Grind each tablet in a glass mortar and pestle.
3). Transfer tablet powder blend onto a weighing paper.
4). Transfer powder from a paper into a 250-ml volumetric flask.
5). Carefully rinse all powder with 42 ml of hot water (~90˚C). Put the magnetic stir bar into the flask, and stir to wet and swell the polymer.
6). Rinse with another 83 ml of cold water (~5˚C). Stir to dissolve the polymer in an ice bath for about 3 hours.

7). Add acetonitrile (ACN) up to the neck of the flask. Keep stirring for another 4 hours or until the solution temperature reaches room temperature.

8). Remove the stir bar and adjust volume to the mark with acetonitrile. Mix well.

Caution: When ACN is added, sample needs to be shaken or stirred for 1–2 minutes because of volume contraction between ACN and water.

9). Filter sample through 0.45 um GHP syringe filter into a glass vial for HPLC assay. ALP was quantified using a validated HPLC method as previously described.

The acceptance criteria was 90–110% of label claim and %RSD < 6%.

Composite Assay

A composite assay of 10 tablets from each formulation was performed using an extraction method developed in the previous section. The content uniformity assay procedure is described in details as follows:

1). Weigh 10 tablets together and record actual weight.

2). Grind tablets in a glass mortar and pestle.

3). Transfer tablet powder blend onto a weighing paper.

4). Transfer powder from paper into a 2-L volumetric flask.

5). Carefully rinse all powder with 336 ml of hot water (~90˚C). Put the magnetic stir bar into the flask, and stir to wet and swell the polymer.

6). Rinse with another 664 ml of cold water (~5˚C). Stir to dissolve the polymer in an ice bath for about 3 hours.

7). Add acetonitrile up to the neck of the flask. Keep stirring for another 4 hours or until the solution temperature reaches room temperature.

8). Remove the stir bar and adjust volume to the mark with acetonitrile. Mix well.

Caution: When ACN is added, sample needs to be shaken or stirred for 1–2 minutes because of volume contraction between ACN and water.

9). Filter sample through 0.45 um GHP syringe filter into a glass vial for HPLC assay. ALP was quantified using a validated HPLC method as previously described.

The acceptance criteria was 90–110% of label claim.

In Vitro Dissolution study and Dissolution Profiles Comparison

The dissolution test of ALP controlled release tablets was modified from Test 4, Official monograph of Procainamide hydrochloride extended release tablets [United States Pharmacopeial Convention, 1999]. For each tablet formulation, a dissolution test of six tablet samples were conducted at 37˚C using USP Apparatus 2 (paddle) and a rotation speed of 50 RPM. The dissolution medium consisted of 900 ml of 0.1 N HCl solution (pH = 1.1). The 0.1 N HCl solution was prepared from the dilution of 1 N HCl solution with purified water. The final pH of the solution was between 1.05-1.15. A 4-ml sample was taken from the medium at 1, 2, 4, 6, 8, 10, 12, 14, and 16 hours. At the end of dissolution study, the actual drug content in each vessel was confirmed by breaking the rest of gel matrix into small parts and then stirring at a rotating speed of 120 rpm for about an hour. Each sample was filtered through a 10 μm filter

prior to analysis. The amount of drug release was determined by UV spectroscopy as previously described in the preformulation section 2.2.1.1.

For HPMC MW type study, specification of ALP release from final tablet formulations should be:

Time (hr)	% ALP Released
2	Less than 45%
4	45 – 65%
8	75 – 90%
12	Greater than 90%

To compare the influence of dissolution media on the ALP release from the matrix tablets, USP buffer pH 6.0 or purified water was used as a dissolution medium instead of 0.1 N HCl solution (pH 1.1). Drug release from same tablet formulation was compared in each medium.

- Statistical Comparison of Dissolution Profiles

Dissolution profiles were constructed and the similarity factor (f_2 factor) was used to compare the dissolution profile of each formulation. This model is most suitable for dissolution profile comparison when three to four or more dissolution time points are available. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the two curves. The following equation defines a similarity factor (f_2):

$$f_2 = 50 \bullet \log\left\{\left[1 + (1/P)\sum_{i=1}^{P}(\mu_{ti} - \mu_{ri})^2\right]^{-1/2} \bullet 100\right\}$$

where f_2 is the similarity factor, log is logarithm to base 10, P is number of sampling time points, $\sum$ is the summation of over all time points, μ_{ti} is the dissolution measurement (in mean percent labeled amount) at time point t of the first batch (test batch) profile, μ_{ri} is the dissolution measurement (in mean percent labeled amount) at time point t of the second batch (reference batch) profile. Two dissolution profiles should be conducted under exactly the same conditions and the sampling time points are identical. The f_2 values are sensitive to the number of dissolution time points. Therefore, only one point past the plateau of the dissolution profiles or only the time point after 85% dissolution of both batches was recommended for use to calculate the similarity factor. This was due to the inclusion of 'P' for the late time points of the profiles into the formula, which can insure a high f_2 value and leads to bias in the similarity assessment [FDA, 1997a; FDA, 1995b; Shah et al., 1998; Shah et al., 1999].

The following criteria of f_2 limit were used to define different average distances between two dissolution profiles at multiple time points by appropriate substitution in f_2 equation above [Shah et al., 1998].

% Average Difference	f_2 Limit
2	83
5	65
10	50
15	41
20	35

If f_2 value calculated from the equation is 45, this indicated that two dissolution profiles are about 15% average difference at all key time points. If the f_2 value is close to 100, the two profiles are nearly identical. In general, the FDA standard of an f_2 between 50-100 (≤ 10% average difference) indicates similarity or equivalence between two dissolution profiles [FDA, 1995a; FDA, 1997a; Shah et al., 1998; Shah et al., 1999; Moore and Flanner, 1996].

Stability Study of Matrix Tablets

Final tablet formulations for in vivo clinical study were placed on stability using the recommended ICH guidelines. The tablets were packaged in HDPE bottles with PP cap (foamed PE and pressure sensitive liner), and stored at 25±2°C, 60±5% relative humidity for 3, 6, and 12 months and at 40±2°C, 75±5% relative humidity for 1, 2, 3, and 6 months). The results from dissolution testing were statistically evaluated for differences using similarity factor as described in the previous section.

2.2.1.4 In Vivo Clinical Study

The *in vivo* clinical study in human subjects was performed in collaboration with Robert L. Talbert, Pharm.D., Division Head and SmithKline Professor, Department of Clinical Pharmacy, University of Texas Health Science Center at San Antonio.

The principal determinations for bioequivalence for the probe drugs used in testing various polymers were area-under-the-curve (AUC), maximal concentration (Cmax), and time of maximal concentration (Tmax). The current FDA guidelines for bioequivalence are that two formulations whose rate and extent of absorption differ by -20% to +25% or less are generally considered bioequivalent. This is based on the concept that a difference of -20% to +25% would not lead to change in therapy for a patient. To verify that the -20%/+25% rule for bioequivalence was satisfied, the student paired t-test was used to compare the log transformed data of the AUC, Cmax, and Tmax obtained from the bioequivalence study. It was estimated that 10 subjects must be randomized to detect a +/- 20% difference in AUC with 95% confidence. FDA guideline recommended that 12 persons be tested in crossover design for evaluation of inter-subject bioequivalence. Given that our estimates were based on a small population and the recommendation from the FDA, 15 subjects were screened with the goal of obtaining 10-12 completers. The testing protocol was approved by the Institutional Review Board (IRB) of the University of Texas Health Science Center.

Protocol Design

The clinical bioequivalence testing was conducted as a randomized, open-label, four-way crossover design. The study site was the General Clinical Research Center (GCRC) at the South Texas Veterans Health Care System in San Antonio, TX (VA medical center). Two developed ALP tablet formulations containing different molecular weight types of HPMC polymer (i.e. HPMC-K4MP (polymer A) and HPMC-K100LVP (polymer B)) were used during the study. Each formulation (K4M-42 or K100LV-27 formulations) was tested in the fed and fasted state. The randomization scheme was shown in Table 2.7.

Randomization was controlled through a computerized randomization procedure. After obtaining written informed consent, 15 normal volunteers were screened using medical and medication history, physical examination and routine clinical laboratory tests including Chem-20 including hepatic enzymes, ß-HCG in females, and CBC with platelet count. The entire sampling period was 72 hours since the median half-life ($t_{1/2}$) of ALP is about 12 hours and to ensure adequate characterization of the AUC, sampling needs to cover approximately 5 half-lives. ALP 10 mg matrix tablets were given in the fasted state after the initial baseline blood sample of 10 ml (time=0 hr.) for determination of plasma ALP concentration was taken. The sampling schedule for subsequent blood samples was 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours. Samples obtained at 48 and 72 hours were done in an outpatient setting. The total number of samples to be obtained was 14 (140 ml of blood). The pharmacodynamic effects of

controlled release ALP was monitored using subject rated sedation on visual analogue scale (VAS) for wakefulness, observer rated sedation, and symbol digit matching test (SDMT, see Appendix A). Clinical evaluation using these scales was performed at each schedule blood draw. For subjects randomized to receive ALP tablet with food, a standardized meal was served from the GCRC kitchen and all subjects received the meal at the same time and each meal had the same content of calories and fat. Subjects randomized to receive ALP tablet in the fasted state were required to have not eaten for eight hours prior to administration and for two hours after administration of the study medication.

Samples were obtained through a saline-lock intravenous catheter (SL-IV). Other procedures, which were not done in the course of normal medical care for a healthy patient, include the baseline physical exam, initial laboratory screening (Chem-20, LFT, ß-HCG in females, and CBC as stated above), ALP administration, overnight admission to GCRC, returning to the GCRC for 48 and 72 hour sampling and administration of previously mentioned sedation and SDMT rating scales.

Table 2.7 Randomization Scheme for Bioequivalence Study

Day/Randomization	**Day 1**	**Day 2**	**Day 3**	**Day 4**
Polymer A-Fasted	**X**			
Polymer B-Fasted		**X**		
Polymer A-Fed			**X**	
Polymer B-Fed				**X**

Note: Polymer A = HPMC-K4MP; Polymer B = HPMC-K100LVP

Since ALP is a legend (prescription) drug product and it causes drowsiness and sleep, the volunteers must be studied in a controlled environment and observed until the drug effects have subsided. A physician was available on call for the first 1-3 hours after dosing to insure that any adverse effects of ALP were managed appropriately. The most common and expected side effect was drowsiness. Other side effects, which may occur in about 1 in 10 persons, includes fatigue, dizziness, headache, nausea, vomiting, and memory loss. It is unlikely that any of these side effects will persist after 24 hours.

Subjects included English-speaking, healthy, non-pregnant, non-nursing persons aged 18-65 years of age. Patients with abnormal values on initial laboratory screening or positive pregnancy test were excluded. Patients with know hypersensitivity to ALP or any benzodiazepine were excluded. All female subjects of childbearing potential were instructed to use birth control while taking part in the study and to inform the investigators if at anytime they thought they were pregnant. Subjects were recruited through flyers posted on the grounds of the University of Texas Health Science Center at San Antonio campus (See Appendix B for example of patient recruitment flyers). Consent was obtained after subject candidates contacted the primary investigator and were deemed eligible for enrollment (See Appendix C for example of consent forms). All copies of informed consent were kept in the Clinical Pharmacy office in McDermontt Room 3.414.

This study had no therapeutic intent. There were no known or expected benefits or risks that occurred in non-English-speaking subjects. The study was

not powered to detect any potential unknown differences and no evaluation of therapeutic endpoints was planned. It was unlikely that the dissolution profiles of the two ALP tablets tested were affected by any ethnic influences in and all English-speaking population.

All study subject's medical information was kept confidential. If the results of the study are published in a scientific journal or book, study subjects will not be identified in any way.

Sample Analysis

After each 10-ml blood sample collection, plasma was immediately separated and frozen until the assay.

ALP plasma concentrations were quantitated using a validated reverse phase HPLC method with UV detection, developed by Y. W. Francis Lam, Pharm.D., Associate Professor of Pharmacology and Medicine, University of Texas Health Science Center at San Antonio.

An Ultrasphere C18 column was used for analysis. Column temperature was maintained at 30˚C. The mobile phase was composed of a mixture of 50 mM phosphate buffer (pH 4.0) and acetonitrile in a ratio of 70:30 (v/v). The flow rate of the mobile phase was 1 ml/min (isocratic) and the injection volume was 25 µl. The absorbance was monitored at 221 nm. Nitrazepam was used as an internal standard. The linearity was obtained with ALP concentration ranging from 5-250 ng/ml. The correlation coefficient (r^2) of the calibration curve should not be less than 0.994. The sensitivity of the assay method was 2 ng/ml.

2.2.2 Multiparticulate System (Film-Coated Beads)

Influence of processing parameters on drug release from cellulose ether coated matrix bead formulations.

2.2.2.1 Uncoated Matrix Bead Preparation

A 300-g matrix bead formulation of a highly water soluble drug, chlorpheniramine maleate (CPM), or a slightly water soluble drug, theophylline anhydrous, were prepared by mixing the active drug with microcrystalline cellulose in a V-blender for 20 minutes. Matrix bead formulations are shown in Table 2.8. The wet mass of the powder blend was prepared in a Kitchen Aid Mixer (Model KSM90, Kitchen Aid, Inc, St. Joseph, MI), operated at a low speed, by slow addition of purified water (binder), and then the blend was passed through the extruder (Benchtop Granulator, Model no. 5666, LCI Corporation, Charlotte, NC, USA), operated at a constant extruding speed of 50 rpm and fitted with a 1.2-mm screen. The extrudate was immediately spheronized (Spheronizer, Caleva, Model 120, GEI Processing, Towaco, NJ, USA) at a rotational speed of 1000 rpm for the optimum residence time needed to produce uniform spherical particles. The beads were rotated in the spheronizer for 5 to 8 minutes. Wet beads sized between 14 and 18 mesh were collected, dried for at least 18 hours in the oven at 40˚C and then beads sized between 16 and 20 mesh were collected for the coating experiments. The wet beads that were out of the specified particle size range were recycled into the extruder and spheronizer in order to obtain a high yield of uncoated beads.

Table 2.8 Uncoated Matrix Bead Formulation

Composition	CPM Beads		Theophylline Beads	
	%w/w	Batch Composition (g)	%w/w	Batch Composition (g)
Chlorpheniramine maleate (CPM)	15	45	-	-
Theophylline anhydrous	-	-	40	120
Microcrystalline cellulose (Avicel PH101)	85	255	60	180
Purified Water* (ml)	85	255	82	246
Total Batch Size	100	300	100	300

Note: * Purified water is removed after drying the core beads in the oven.

2.2.2.2 Coated Matrix Bead Preparation

The 30 %w/w ethylcellulose dispersion (Aquacoat®ECD, FMC Corporation, Newark, DE) was moderately mixed prior to addition of the water-miscible plasticizer (triethyl citrate (TEC)) or the water-insoluble plasticizer (dibutyl sebacate (DBS), or distilled acetylated monoglycerides (AMG, Myvacet 9-45)) at a level of 24-30 %w/w based on dry polymer weight. The plasticizer was incorporated into the EC dispersion for either a 2- or 24-hour plasticization time using a mechanical stirrer.

In some coating formulations for CPM beads, a subcoating solution was applied prior to the application of the EC dispersion. The subcoating solution consisted of 7.5 %w/w HPMC E5 plasticized with 2 %w/w (based on polymer weight) of PEG 400 for 2 hours. Then, it was applied to the uncoated matrix beads at a 2% coating level.

In some coating formulations for theophylline beads, after plasticization, a solution of water-soluble additive (HPMC E5, PEG 8000, sucrose, or mannitol) was added to the coating dispersion upon mixing at 5-20% w/w (based on dry polymer weight) level and mixed for another 15 minutes. Then, purified water was added and continuously mixed for another 10 minutes at a moderate mixing speed to obtain a final dispersion of 15-20% total solids.

A 250-300 g batch of 16–20 mesh drug-loaded matrix beads were then coated with the mixed dispersion in a fluid bed coater with a Wurster insert (Strea-1, Aeromatic AG, Aeromatic Inc., Towaco, NJ, USA) at the optimum

spraying time and rate in order to obtain 5-21% theoretical coating levels for Theophylline beads and 15-36% theoretical coating levels for CPM beads. The following parameters were used:

Inlet air temperature: 45-50˚C

Outlet air temperature: 38-42˚C

Nozzle size: 1.2 mm

Atomization pressure: 1.3 bar

Spray rate: 2.4 g/min

Preheating time: 15 min

Postdrying time: 15 min at 60˚C

Spray time: 2–4 hours

The inlet air temperature was adjusted to maintain the outlet air temperature of 38-42˚C, which was about 10˚C above the minimum film forming temperature of the EC-plasticizer dispersion.

After spraying, beads were rotated in the coater column maintaining bed temperature (post column drying temperature) for an additional 15 minutes at 60˚C to avoid sticking problems. The film coated beads with different coating levels were oven-cured at 40˚C, 60˚C or 80˚C for up to 72 hours. The schematic of the film-coated beads preparation is summarized in Figure 2.2.

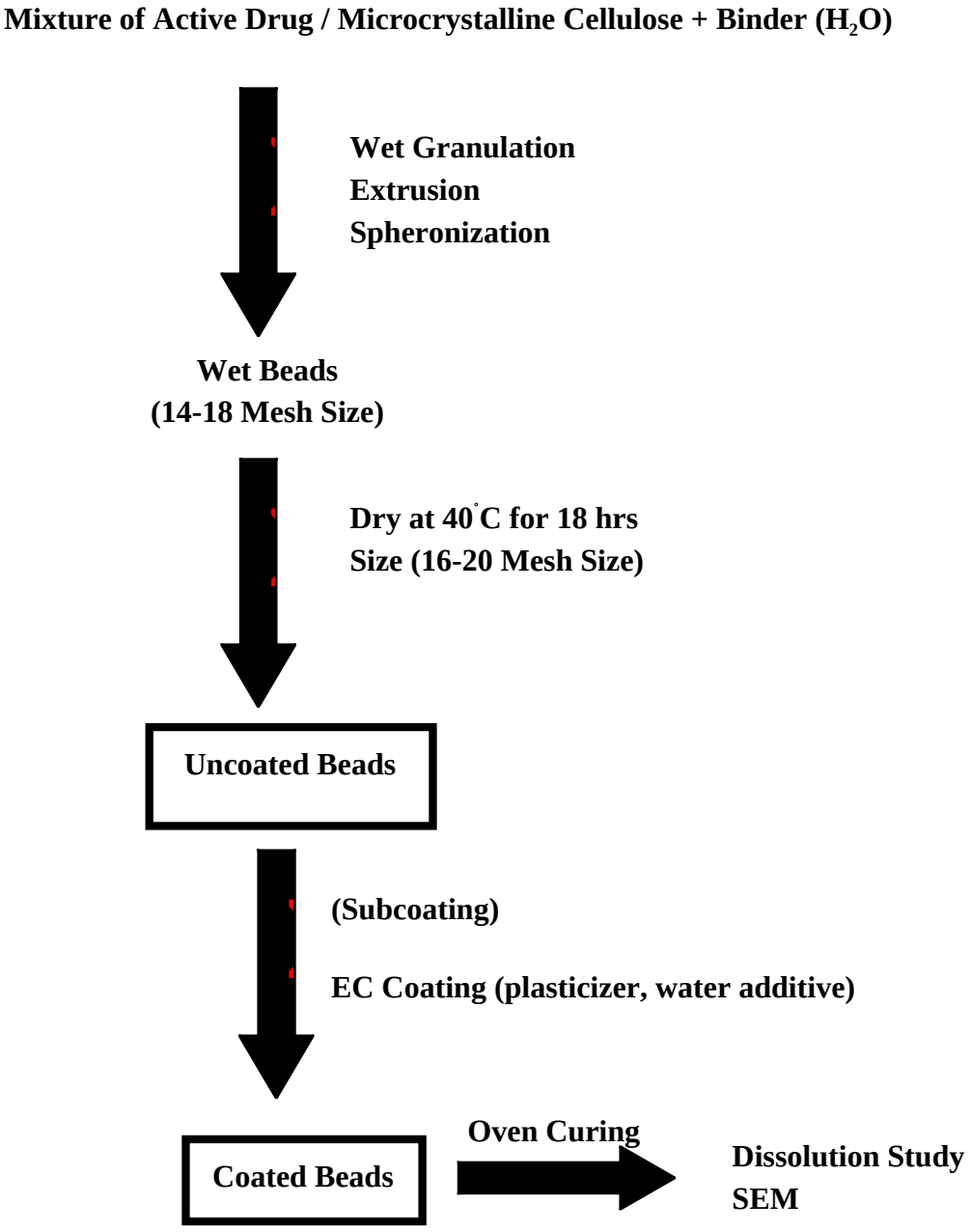


Figure 2.2 Film coated beads preparation

2.2.2.3 Characterization of Matrix Beads

In Vitro Release Studies

In vitro dissolution study was performed at least in triplicate. For CPM coated beads, the *in vitro* release studies were carried out according to Test 1 method for determination of drug release from Chlorpheniramine Maleate Extended-Release Capsules specified in USP 24/NF 19 [United States Pharmacopeial Convention, 1999]. The dissolution profiles of the uncoated and coated beads were determined using USP Apparatus 1 (basket) (Vankel VK 6010 and Vanderkamp VK 650 A with an autosampling unit, Vankel VK 800) operated at 100 rpm in 500 ml purified water at 37±0.5˚C. Dissolution samples of 4 ml were collected at 1.5, 3, 6, 8, and 10 hours. For actual drug content in each vessel, the last dissolution sample was collected after vigorously stir with a medium shear mixer (Polytron Silverson type mixer; Brinkmann Instruments, Wettburg, NY, USA) at a mid-range speed for 30 seconds. Each sample was filtered through a 10 µm filter prior to analysis.

For theophylline coated beads, the *in vitro* release studies were carried out according to Test 5 method for determination of drug release from Theophylline Extended-Release Capsules specified in USP 24/NF 19 [United States Pharmacopeial Convention, 1999]. The dissolution profiles of the uncoated and coated beads were determined using USP Apparatus 2 (paddle) (Vankel VK 6010 and Vanderkamp VK 650 A with an autosampling unit, Vankel VK 800) operated at 50 rpm in 900 ml pH 3.0±0.05 phosphate buffer for the first 3.5 hours, followed

by the addition of 5.3 M sodium hydroxide to adjust to a pH of 7.4±0.05 at 37±0.5˚C for the remaining 6.5 hours. Dissolution samples of 4 ml were collected at 1, 3.5, 5, 7, and 10 hours. For actual drug content in each vessel, the last dissolution sample was collected after vigorously stir with a medium shear mixer (Polytron Silverson type mixer) at a middle speed for 30 seconds. Each sample was filtered through a 10 µm filter prior to analysis.

Ultraviolet Spectroscopy

Drug assay was conducted using an ultraviolet spectrophotometer at a wavelength of 262 nm for CPM quantitation and at a wavelength of 272-274 nm for theophylline quantitation (Hewlett Packard Diode Array Spectrophotometer, Model 8452A, with 1-cm quartz cell).

For standard curve preparation of CPM, about 0.1 g of CPM powder was weighed into a 100 ml-volumetric flask. About 80 ml of purified water was added to dissolve the drug. The stock solution was sonicated for 5 minutes to ensure complete dissolution of all drug particles before adjusting to a final volume with purified water. Final concentration of stock solution was about 1 mg/ml. The stock solution was then diluted with purified water to concentrations in the range of 0.02–0.09 mg/ml.

For standard curve preparation of theophylline, about 0.05 g of theophylline powder was weighed into two 100 ml-volumetric flasks. Two standard curves of theophylline were prepared for quantitaion of drug in acidic medium (buffer pH 3.0±0.05) and in basic medium (buffer pH 7.4±0.05). About 80 ml of an appropriate diluent (dissolution medium) was added to dissolve the

drug. Each stock solution was sonicated for 15 minutes to ensure complete dissolution of all drug particles before adjusting to a final volume with an appropriate diluent. Final concentration of each stock solution was about 0.5 mg/ml. Each stock solution was then diluted with its diluent to concentrations in the range of 0.005–0.02 mg/ml.

For both drug substances, each calibration curve was prepared by plotting the absorbance values of each standard against the concentration of each standard. Finally, the quantity of drug was calculated from the regression equation of the calibration curve. Linear correlation over the concentration range prepared should be close to 1 ($r^2 = 1$).

For sample preparation, an appropriate dilution of each sample was made with a diluent (dissolution medium) such that the final concentration was within the linear portion of the standard curve for the drug prior to analysis.

Scanning Electron Microscopy (SEM)

Scanning electron microscopy was used to examine the surface morphology of the beads. Beads were mounted on brass SEM stages using 3M double sided tape and were then coated with gold-palladium for 60 seconds under an argon atmosphere using a Pelco® Model 3 Sputter Coater (TED Pella, Inc., Tusin, CA, USA) in a high vacuum evaporator equipped with an omni-rotary stage. Samples were examined with a Jeol scanning electron microscope (Model JSM-35C, Jeol USA, Inc., Peabody, MA, USA) or Hitachi S-4500 field emission scanning electron microscope (Hitachi Instruments Inc., Irvine, CA, USA) at 4.0 kV. The scanning electron micrographs were taken by a Polaroid® 545 Land Camera with 4" x 5" exposure film.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 SINGLE UNIT SYSTEM (MATRIX TABLETS)

3.1.1 Preformulation Studies for ALP

Determination of ALP Solubility

Drug solubility, especially for poorly water soluble or insoluble drugs, such as ALP, is an important factor during formulation studies. Solubility studies of ALP in different media were performed by shaking the vials containing an excess amount of ALP in different media at 37±0.5˚C. The amount of ALP in each medium after equilibrating for 1 or 2 days was determined by UV spectrophotometry. As shown in Table 3.1 for the comparison of solubility results from day 1 and day 2, the solubility values of ALP from both days in each medium are not significantly different, indicating equilibrium saturated solubility condition. An approximate aqueous solubility of ALP at 37±0.5˚C was 44 µg/ml (1 part of ALP per 22727 parts of water), indicating water-insoluble drug [United States Pharmacopeial Convention, 1999]. ALP is more soluble in acidic media with an apparent pKa value close to 3.50 [Laihanen et al., 1996a]. The solubility of ALP is also pH dependent. As can be seen from Table 3.1, ALP has a higher solubility in an acidic pH solution (i.e. about 14 mg/ml in 0.1 N HCl solution, about 21 mg/ml in 0.05 M H_2SO_4) than in a basic pH solution or alkaline media

(i.e. about 40 µg/ml in buffer pH 5.0, 6.8, and 8.0 (SIF)). Similarly, solubility results determined at 25±1˚C of different crystal modifications at pH 1.6 and pH 5.0 were 8-10 mg/ml and 0.1 mg/ml, respectively [Laihanen et al., 1996a].

During dissolution studies conducted on the dosage forms, sink conditions are an important experimental parameter that must be controlled. Sink conditions are approximated when the saturation volume is five to ten times higher than the test volume. Therefore, the saturated drug solubility (C_{sat}) is much higher than drug concentration in the medium at any given time (C_{sol}), $C_{sat} >> C_{sol}$. For low solubility drugs, a specified dosage level may be close to the saturation point in the dissolution medium such that the sink conditions cannot be attained. Therefore, accurate dissolution profiles are difficult to obtain [Hanson, 1990]. In this research study, dissolution studies of ALP tablets were carried out in 0.1 N HCl solution (pH 1.1), where ALP has a higher solubility and the sink conditions for ALP release occur. In contrast, dissolution of ALP in purified water or alkaline media did not occur under sink conditions due to its low solubility.

Table 3.1 ALP Solubility at 37±0.5˚C

Medium	Solubility of ALP (mg/ml)	
	Day 1	Day 2
Purified water	0.044	0.045
0.05 M H_2SO_4	20.641	21.547
0.1 N HCl Solution (pH 1.1)	14.544	14.038
Buffer pH 1.2 (SGF)	12.227	11.141
USP buffer pH 2.0	1.968	2.191
Buffer pH 5.0	0.042	0.038
Buffer pH 6.8 (SIF)	0.045	0.041
USP buffer pH 8.0	0.038	0.045

Thermal Analysis

The DSC results presented in Figure 3.1 demonstrated a sharp endothermic peak for ALP at 232-233˚C, which corresponded to its melting point. The melting point reported for ALP is 228-229˚C [Budavari et al., 1996]. This also indicated the crystalline nature of the drug. In addition, no peaks were found during repeated heating and cooling processes (except the peak during the first heating cycle, which corresponded to the melting point) indicating an irreversible melting process and that the drug has not undergone a recrystallization process (Figure 3.2).

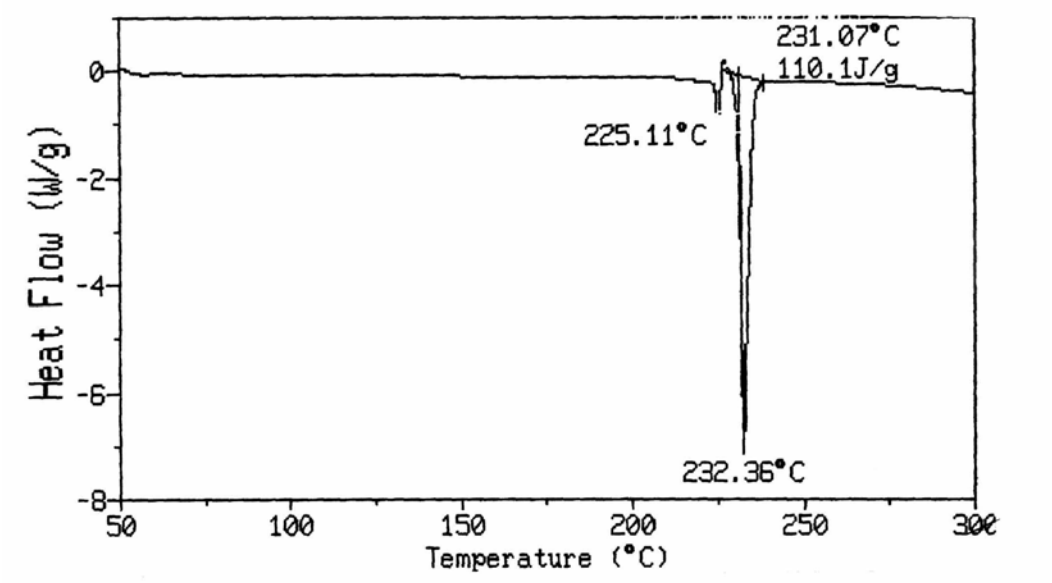


Figure 3.1 Endothermic peak of ALP during the melting process

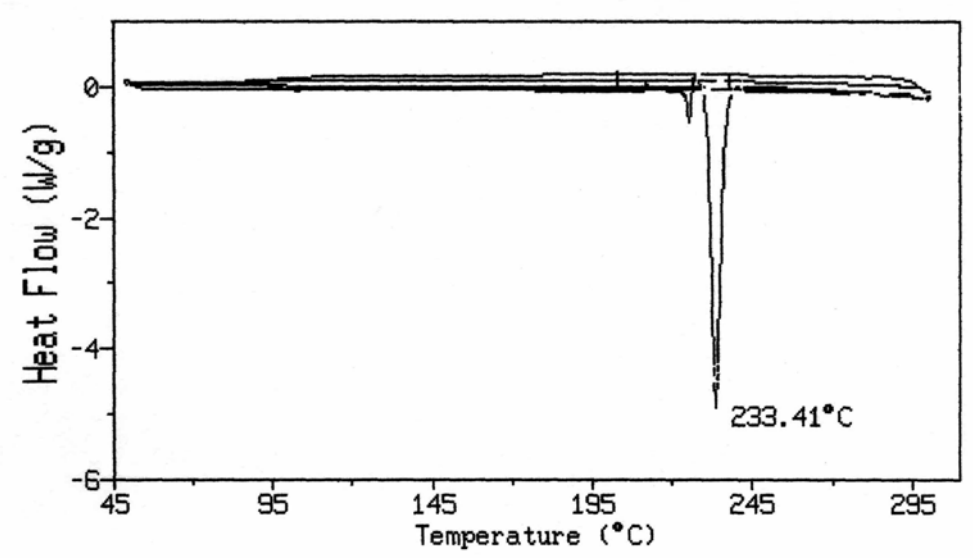


Figure 3.2 Thermographic pattern of ALP during the heating and cooling processes

Particle Size and Particle Size Distribution Study (Laser Light Scattering)

Figure 3.3 shows particle size distribution curves plotted between percent cumulative undersized and the particle size of ALP in microns (μm). Average particle size (cumulative 50 percent undersized) of ALP is in the range of 8-9 μm.

Scanning Electron Microscopy (SEM)

A SEM technique was used to examine qualitatively the particle size as well as the surface morphology and crystal shape of the drug particles. SEM micrographs of ALP powder in Figure 3.4 shows an irregular crystalline structure. The average particle size was in the range of 2-5 μm, which is slightly smaller than the average particle size determined by the laser light scattering technique. Additionally, ALP particles tended to be agglomerated.

Powder X-ray Diffractometry

Figure 3.5 shows the plot of number of counts plotted on the y-axis versus the 2-theta range of 5° to 50° plotted on the x-axis. X-ray powder diffraction patterns of both ALP samples displayed multiple peaks. This indicated the crystalline characteristics of the drug, similar to the previous results obtained from DSC and SEM.

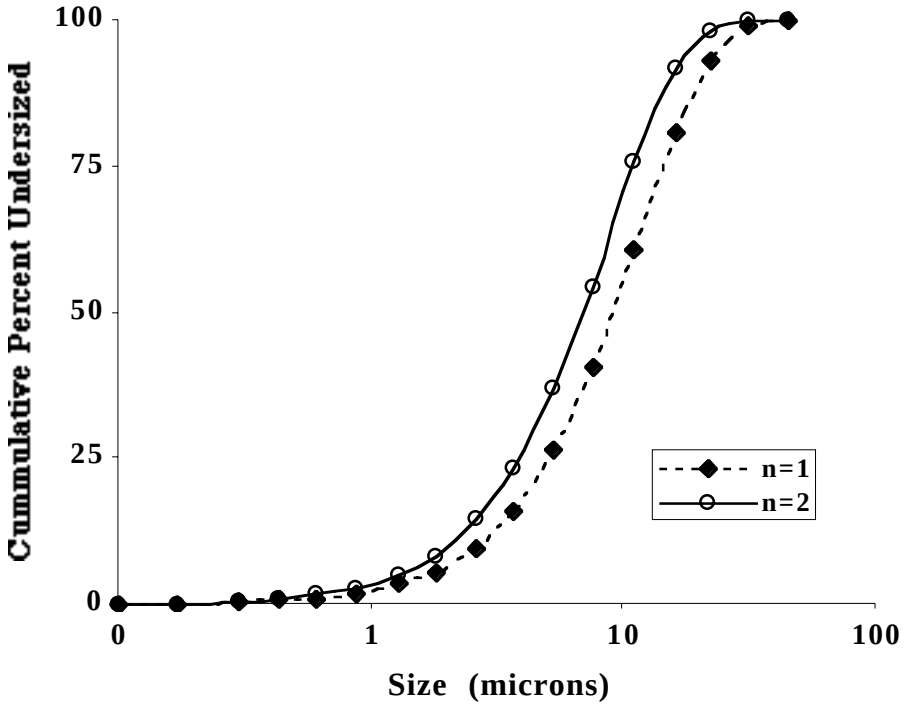


Figure 3.3 Particle size analysis of ALP powder

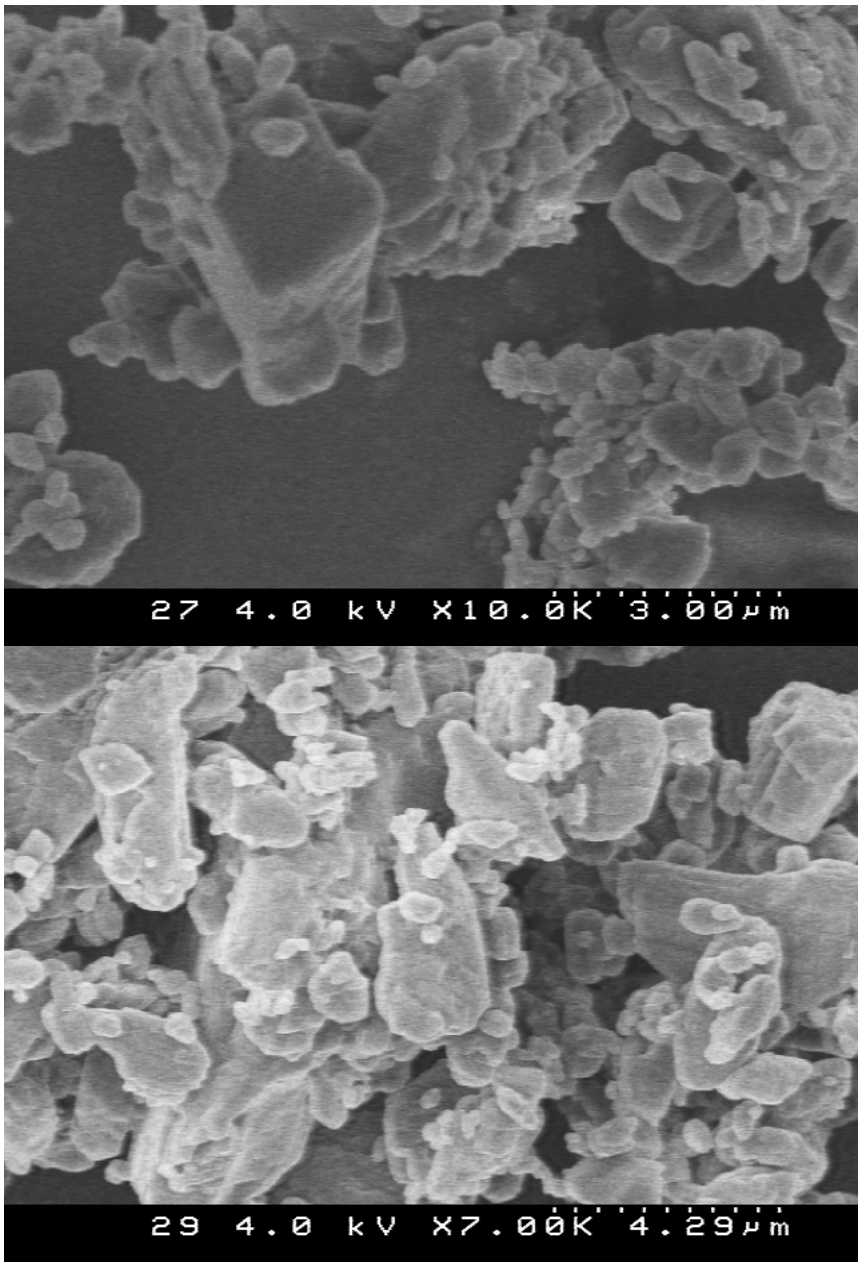


Figure 3.4 Scanning electron micrographs of ALP powder

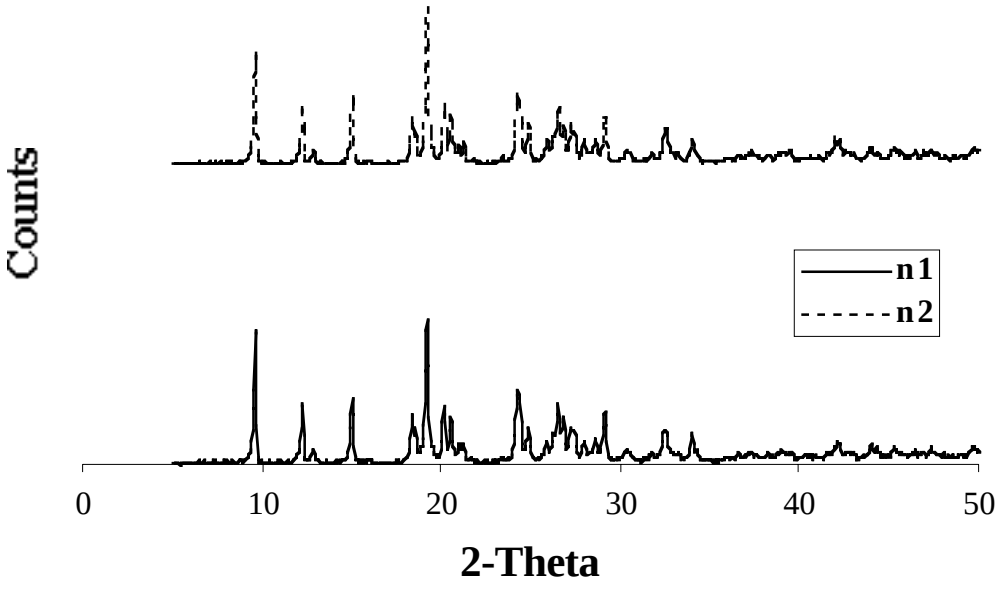


Figure 3.5 X-ray diffractometry pattern of ALP powder

Analytical Methods

Ultraviolet Spectroscopy

The UV spectroscopic method for the quantitation of ALP in each solvent used during the solubility study and the amount of drug released from a matrix tablet into a dissolution medium during the dissolution study was modified from the method described in the literature [Acikkol et al., 1991]. For the determination of ALP dissolved in each medium during the solubility study, 0.05 M H_2SO_4 was used as a diluent for standard curve preparation. For the determination of ALP in each dissolution sample, 0.1 N HCl solution was used as a diluent for standard curve preparation. The maximum wavelength of ALP in each diluent was determined to be 264 nm, where ALP had maximum absorbance. Typical UV standard curves in the range of 0.001-0.020 mg/ml of ALP are shown in Figure 3.6. The linearity of the standard curve was excellent with a correlation coefficient (r^2) of 0.999. The precision of the UV method was determined by measuring the absorbance of the same working standard in replicates of five, which had an RSD of less than 1%.

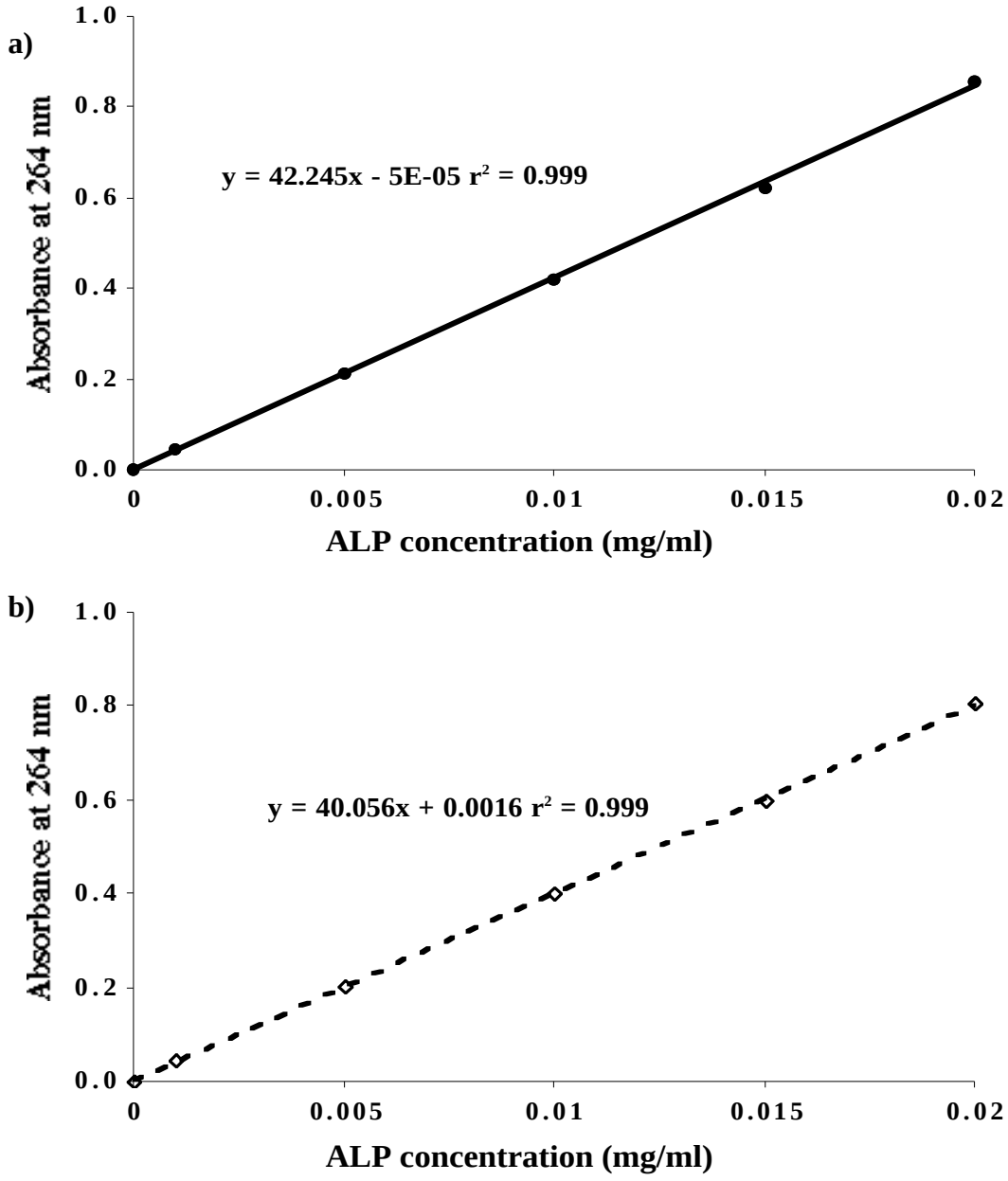


Figure 3.6 Typical UV standard curves of ALP in each diluent: a) 0.05 M H_2SO_4 solution; b) 0.1 N HCl solution.

Chromatographic Analysis

A reverse-phase HPLC method was developed for quantification of the highly lipophilic model drug substance, ALP, contained in matrix tablet formulations. System suitability was performed according to generally accepted laboratory practices to ensure that the HPLC system and recovery procedure were capable of providing accurate and precise data [Synder et al., 1997]. The wavelength of 222 nm was selected because ALP had a maximum absorbance at this level. No interference between any of the components of the powder blend and ALP were found at this wavelength. A typical HPLC chromatogram is shown in Figure 3.7. The number of theoretical plates (N) was about 3,000 plates/column and the peak asymmetry was approximately 1.1. The retention time of ALP was about 4.2 minutes. The sample diluent (50 %ACN in water) and sample placebo blend showed no interferences in the region of interest, and excellent method specificity was demonstrated. The linearity of the calibration curve in the range of 0.005-0.060 mg/ml was excellent with a correlation coefficient (r^2) of 0.999. The precision of the chromatographic method was determined by making five replicate injections of a working standard solution. The precision was excellent as indicated by the low magnitude of the RSD (0.9%). Therefore, the system suitability specifications were met.

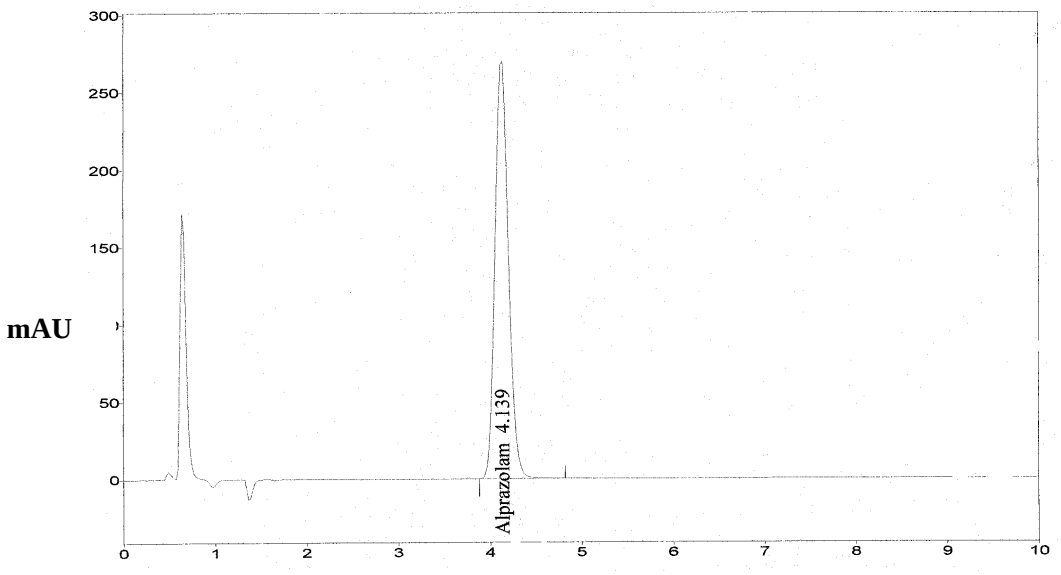


Figure 3.7 A typical HPLC chromatogram of ALP in a tablet or powder blend containing HPMC polymer.

3.1.2 Drug Recovery from Hydrophilic Matrix Tablets [Williams III et al., 2001]

Sample Preparation Methods

Different solvents and sample preparation methods were investigated in order to recover the lipophilic drug, ALP, from pulverized HPMC matrix tablets or matrix powder blends. Two studies were conducted in order to determine the percent drug recovery from the same powder blend formulation (Tables 2.1 and 2.2). The first study was focused on finding an extraction solvent, which would dissolve ALP and not dissolve the hydrophilic HPMC polymer. Acetonitrile was selected as an extraction solvent in sample preparation method I because it has a high solubilizing power for ALP, it is a component of the mobile phase, and it is a poor solvent for HPMC as determined in the study. Sample preparation method II was focused on finding a cosolvent system, which would dissolve both ALP and HPMC polymer. Acetonitrile was the solvent selected to dissolve ALP, whereas water was selected as the solvent to dissolve HPMC polymer.

Sample Preparation Method I

Using ACN alone as the extraction solvent, samples A and B were prepared using the same sample preparation method, but differing in the method of incorporating ALP. For sample A, ALP was dissolved in ACN and then added as a solution, whereas ALP powder was used in sample B. The percent recoveries of ALP from samples A and B were 100.54±1.83% and 86.81±2.45%, respectively (Table 3.2). Similar to sample B, drug recoveries from samples C

and D using ALP powder and different orders of addition were low, 95.11±1.80% and 91.59±2.38%, respectively (Table 3.2). This was because the gelation rate of the HPMC polymer was faster than the dissolution rate of ALP powder in the extraction solvent, ACN. HPMC was poorly soluble in ACN, but gelled upon exposure to ACN. Therefore, drug was entrapped within the swelling gel layers of HPMC polymer before it could be completely dissolved. Also, ACN, at temperatures of –20˚C to 5˚C, was used as the extraction solvent for samples E-J (Table 2.1). These methods were performed in order to minimize the solubility of HPMC in ACN at the low temperatures and increase drug recovery. Drug recoveries from samples prepared from ALP powder were significantly low ($p < 0.05$; except for sample I), and ranged from 90–96% (Table 3.2), regardless of the sample preparation method used and the order of addition of drug and placebo powder blend containing HPMC (samples E, F, G, H, and J, Table 2.1). However, sample I prepared from the ALP stock solution using cold ACN at -10˚C as a solvent was 99.10±1.53%, which was similar to the recovery found for sample A using ACN at 22˚C as a solvent (Tables 2.1 and 3.2). Therefore, the solvent temperature did not improve the recovery of ALP. Some drug particles were entrapped within the gel layers of HPMC before complete dissolution in the extraction solvent. The results indicated that it is necessary to dissolve HPMC prior to dissolving the drug substance in order to prevent entrapment of drug particles and incomplete dissolution as the HPMC swells and gels upon contact with ACN. Therefore, sample preparation method II was investigated to identify a cosolvent system capable of dissolving both drug and polymer.

Sample Preparation Method II

In sample preparation method II, ACN was used as the extraction solvent for ALP, and water was used as the solvent for HPMC. Water was a poor solvent for ALP because the aqueous equilibrium solubility at 37˚C was 44 µg/ml (1 part of ALP per 22727 parts of water) as determined in the preformulation section 3.1.1. Therefore, stronger solvents were still necessary to enhance the dissolution of ALP. Recovery of ALP from sample K that was prepared by swelling HPMC in hot water (~ 90˚C) and dissolving HPMC in cold water (~ 5˚C) prior to extraction of the drug in ACN at 22˚C was 100.52±2.41%, even though drug powder was used in the preparation (Table 3.2). Once the HPMC polymer was completely dissolved in the aqueous solution, its gelling and hydrating properties did not influence drug dissolution. This method was shown to achieve complete recovery of ALP from matrix placebo blends. This method was employed for investigating formulation compositions (samples K, L, M, N, O, and P) as discussed in the following section.

Table 3.2 Recovery of ALP from Powder Blends Using Different Sample Preparation Methods

Sample	Theoretical Amount of ALP (mg/ml)	Assay Amount of ALP (mg/ml)	% ALP Recovery
	Sample Preparation Method I: Acetonitrile Alone		
A (K4MP)	0.02000	0.02011	100.54 ± 1.83
B (K4MP)	0.04960	0.04306	86.81 ± 2.45
C (K4MP)	0.05040	0.04793	95.11 ± 1.80
D (K4MP)	0.04970	0.04552	91.59 ± 2.38
E (K4MP)	0.05200	0.04997	96.09 ± 1.49
F (K4MP)	0.05260	0.05036	95.74 ± 1.08
G (K4MP)	0.05040	0.04835	95.94 ± 1.55
H (K4MP)	0.05550	0.05272	94.99 ± 2.34
I (K4MP)	0.04000	0.03964	99.10 ± 1.53
J (K4MP)	0.05450	0.04939	90.62 ± 1.13
	Sample Preparation Method II: Acetonitrile/Water		
K (K4MP)	0.05030	0.05056	100.52 ± 2.41
L (K100LVP)	0.05010	0.05090	101.60 ± 1.59

Influence of molecular weight type (viscosity grade) of HPMC on ALP recovery

Table 3.2 shows the percent ALP recoveries from samples K and L prepared from placebo blends containing different grades of HPMC polymer (100.52±2.41% and 101.60±1.59%, respectively). Sample K contained high molecular weight (high nominal viscosity) type of HPMC (Methocel K4MP, 4126 cPs apparent viscosity as a 2% aqueous solution) and sample L contained low molecular weight (low nominal viscosity) type of HPMC (Methocel K100LVP, 107 cPs apparent viscosity as a 2% aqueous solution). Both HPMC types possess similar degree of methoxyl substitution (19-24% methoxyl), hydroxypropyl substitution (7-12% hydroxypropoxyl), and similar gelation rates. However, they are different in terms of degree of polymerization resulting in different molecular weight, which is reflected in the viscosity of an aqueous solution [The Dow Chemical Company, 2000]. Although sample K contained HPMC with a molecular weight or nominal viscosity about 40 times greater than sample L, the percent drug recoveries were similar at about 100% using sample preparation method II. This indicated that the molecular weight type or nominal viscosity of the polymer did not influence the dissolution of the lipophilic drug using sample preparation method II because HPMC was completely dissolved before ALP.

Influence of excipient type on ALP recovery

The results shown in Table 3.3 describe the influence of excipient type on the recovery of ALP from matrix powder blends using sample preparation method II. The percent recovery of ALP from samples containing water-soluble

excipients, sucrose and dextrose, was 100.26±1.92% and 97.60±0.79%, respectively. Similar results were obtained for samples containing water insoluble excipients, dicalcium phosphate anhydrous and calcium sulfate dihydrate (98.90±1.36% and 102.68±2.03%, respectively). The chromatogram shown in Figure 3.7 is characteristic of the chromatogram obtained for each of the investigated excipients. The results indicated that the excipients comprising the matrix tablet formulations did not influence the recovery of ALP.

Sample preparation method II allowed for complete recovery of ALP from matrix powder blends containing HPMC and different types of tableting excipients.

Table 3.3 ALP Recovery from Powder Blends Containing Different Types of Excipients Using Sample Preparation Method II

Sample	Excipient Type	Theoretical Amount of ALP (mg/ml)	Assay Amount of ALP (mg/ml)	%ALP Recovery
M	Sucrose	0.05070	0.05083	100.26 ± 1.92
N	Dextrose	0.05010	0.04890	97.60 ± 0.79
O	Dicalcium phosphate anhydrous	0.05040	0.04985	98.90 ± 1.36
P	Calcium sulfate dihydrate	0.05020	0.05155	102.68 ± 2.03

Determination of drug content in a matrix tablet

Sample preparation method II was used to determine the content uniformity and composite assay of two lots of tablets. Two tablet formulations containing different grades of HPMC (K4MP or K100LVP) and lactose monohydrate as the excipient (Table 2.3) were tested. For content uniformity results of each tablet formulation, the mean ALP level of 10 tablets for formulation Q (K4MP) and formulation R (K100LVP) was 101.90±3.41% (3.35 %RSD) and 98.80±2.16% (2.18 %RSD) of label claim. For both formulations, the ALP content in each tablet was uniform as indicated by the low magnitude of the RSD. The results obtained for the composite assay of 10 tablets from formulations Q and R were 99.35±2.06% and 97.98±1.92%, respectively. Therefore, the results from the drug content uniformity indicated that sample preparation method II achieved complete recovery of ALP from the tablets.

3.1.3 Investigation of Formulation Parameters on Drug Release

The main goal for this formulation study was to develop two oral controlled release formulations of matrix tablets, which were equivalent in their *in vitro* dissolution profiles. These formulations were intended for *in vivo* clinical studies.

Screening Study

A screening study was carried out in order to optimize the basic formulation parameters and obtain matrix tablets that could sustain the release of ALP between 14 and 16 hours. The basic formulation parameters including tablet size, drug loading, and polymer level were optimized. General formulation compositions and levels are shown in Table 2.4. *In vitro* dissolution studies and similarity factor assessments were used as tools during formulation development.

Tablet Size

Two different tooling diameters with the same concave shape were used to prepare matrix tablets using the same blend formulation. Tablets with 8-mm diameter had a smaller surface area when compared to tablets with 9-mm diameter. As can be seen from Figure 3.8, the larger diameter tablet (larger surface area) had a lower degree of drug release at each time-point. This is due to the hydrated gel layer of the larger diameter tablet, which has a larger surface area to sustain the release of the drug. In addition, drug release from the larger tablet is extended beyond 8 hours and prolonged to more than 12 hours, whereas the

drug release from the smaller diameter tablet approaches 100% at 7 hours. The dissolution profiles shown in Figure 3.8 display an average difference greater than 20% (f_2 = 31). Similar results are shown in Figure 3.9 for another formulation containing MCC. The dissolution profiles in Figure 3.9 also display an average difference greater than 20% (f_2 = 27). Different excipients in each formulation (MCC or LAC) did not have an impact on the drug release. However, both formulations required a large amount of the very fine powder of HPMC K4MP (65 %w/w) in order to achieve sustained release. This high amount of HPMC K4MP has limited flow properties during the direct compression process for tablet manufacturing. Therefore, tablet size or tooling diameter was increased to 11 mm and the HPMC level was reduced in the following studies in order to optimize between the flowability of the formulation and the sustained release profiles. Figure 3.10 shows the sustained release profile obtained from 11-mm diameter tablets. Even though the amount of HPMC K4MP in the formulation was only 37 %w/w, drug release was delayed up to 12 hours. Therefore, tablet size can influence both amount and extent of drug release from a matrix tablet as well as the amount of HPMC necessary in the formulation to maintain a sustained release profile. Generally, a high level of HPMC is necessary for smaller tablets to obtain a desirable sustained release profile. When tablet size is increased, resulting in an increased surface area for drug release, the amount of drug release is slower due to the change in the surface area and the amount of initial gel formation. Additionally, when the tablet size was increased, the amount of HPMC necessary for sustaining the drug release could be significantly reduced. Flowability of the

blend can also be improved by decreased amounts of fine particle HPMC and increased amounts of flowable excipients to replace a portion of HPMC, such as spray-dried lactose or other directly compressible fillers [Alderman, 1984].

However, opposite results were reported for promethazine HCl matrix tablets containing 25 mg of drug, 120 mg of HPMC K15M and 0.75% of magnesium stearate. Tablets were compressed to the same weight, same formulation and same flat-faced shape, but differed in tablet size or diameter. When tablet diameter was increased from 0.25 to 0.375 or 0.5 inches, resulting in an increased tablet surface area, the square root of time release rate was increased from 4.13 to 4.61 or 5.99% $min^{-1/2}$, respectively [Ford et al., 1987]. These different results may be due to differences between the active drugs used in the hydrophilic matrix systems such as their aqueous solubility and release mechanism.

From results previously described, an 11-mm concave tooling was selected for use throughout the formulation development. The target tablet weight was 400 mg.

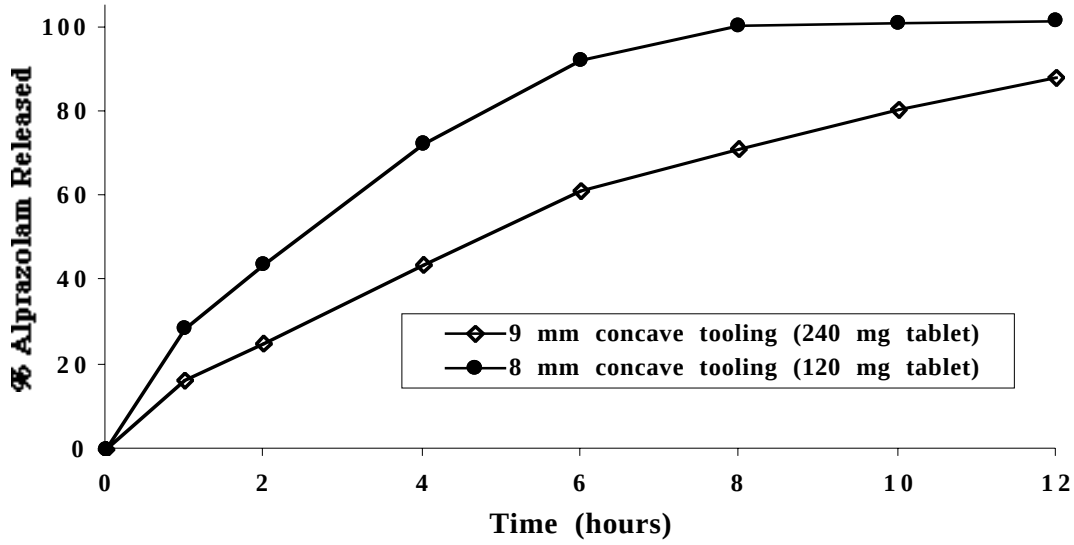


Figure 3.8 Effect of tablet size on ALP release from a matrix tablet (2.08 %w/w ALP, 65 %w/w, HPMC K4MP, 0.5 %w/w Mg stearate, lactose qs.)

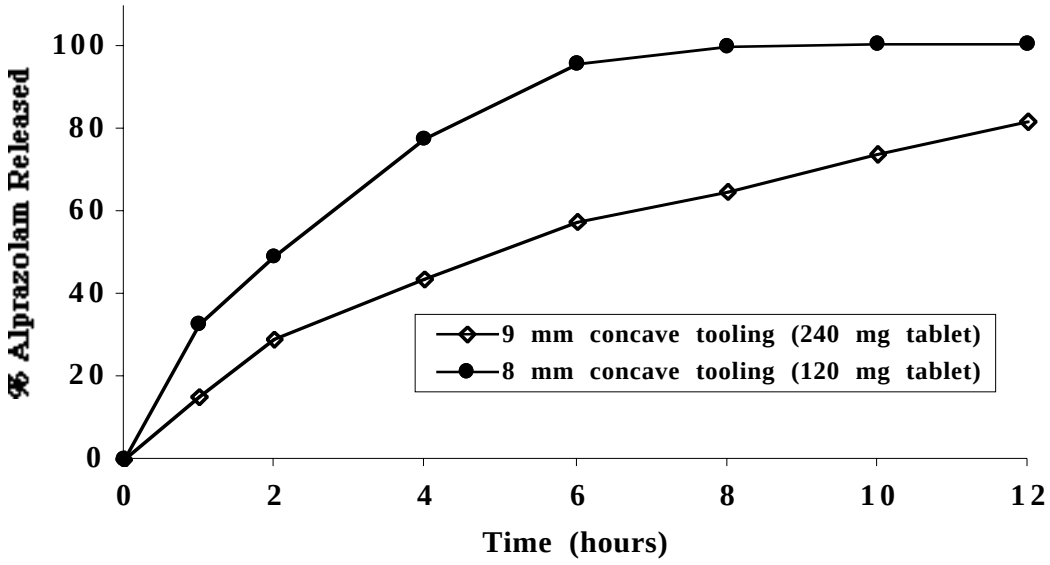


Figure 3.9 Effect of tablet size on ALP release from a matrix tablet (2.08 %w/w ALP, 65 %w/w HPMC K4MP, 0.5 %w/w Mg stearate, MCC qs.)

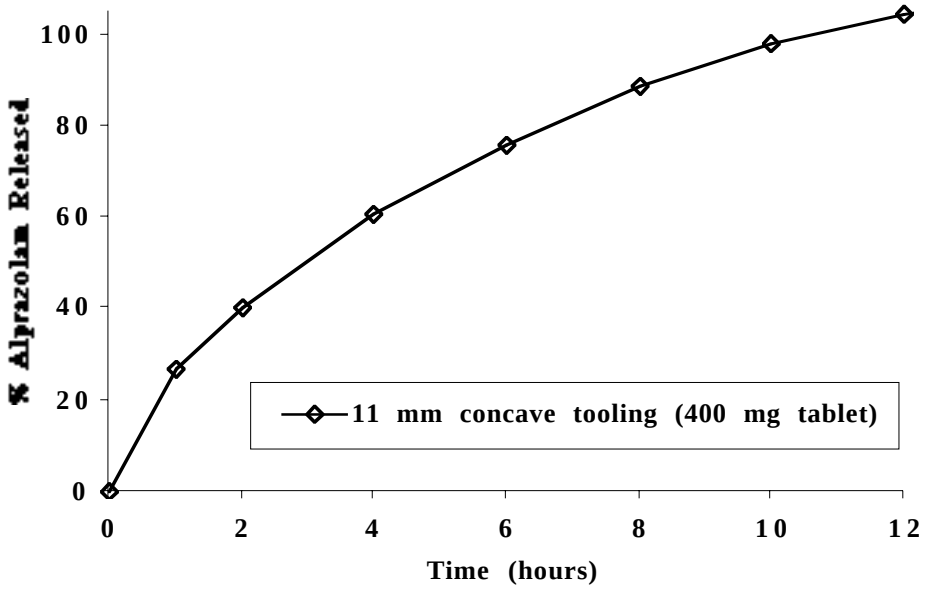


Figure 3.10 Drug release profile of ALP matrix tablet (2.5 %w/w ALP, 37 %w/w HPMC K4MP, 20 %w/w MCC, 0.5 %w/w Mg stearate, 0.5 %w/w silicon dioxide, lactose qs.)

Drug Loading

For multiple dosing of ALP tablets, the commercial product, Xanax® (Pharmacia & Upjohn Company, Kalamazoo, MI), is available in 0.25, 0.5, 1, 2, and 4 mg strengths. In order to prepare a sustained release product with a 14 to 16 hour release period, a higher dose of ALP was loaded into a single matrix tablet. The maximum recommended daily human dose of ALP is 10 mg [Pharmacia & Upjohn Company, 2000]. Therefore, two levels of ALP (i.e. 5 or 10 mg) were loaded into each tablet intended for a single daily dose. However, either 5 or 10 mg ALP was only 1.25 or 2.50 %w/w, respectively, when compared to a total tablet weight of 400 mg. Content uniformity of each tablet prepared by direct compression was such a challenge. If the active drug, ALP, was not distributed evenly between tablets, it may potentially cause adverse reactions or overdose symptoms in patients. In this study, the blending method to achieve good content uniformity was also developed and described in a following section.

In this section, the effect of different drug loadings on the amount of drug release was evaluated. As can be seen from Figures 3.11 and 3.12, the amount of drug loading has no effect on the release of ALP from a matrix tablet. Specifically, dissolution profiles obtained from tablets containing HPMC K4MP and either 5 or 10 mg drug loading were similar with a similarity factor of 90 (only 2% average difference, Figure 3.11). This may due to both levels of drug loading were extremely low (1.25 or 2.50 %w/w), when compared to a total tablet weight of 400 mg. Similarly, dissolution profiles obtained from tablets containing

HPMC K100LVP and either 5 or 10 mg drug loading were similar with a similarity factor of 71 (5% average difference, Figure 3.12). Dose dumping was not observed from tablets containing either 5 or 10 mg ALP. Therefore, a higher drug loading of 10 mg was used during formulation development because uniformity of the dosage form would be more feasible.

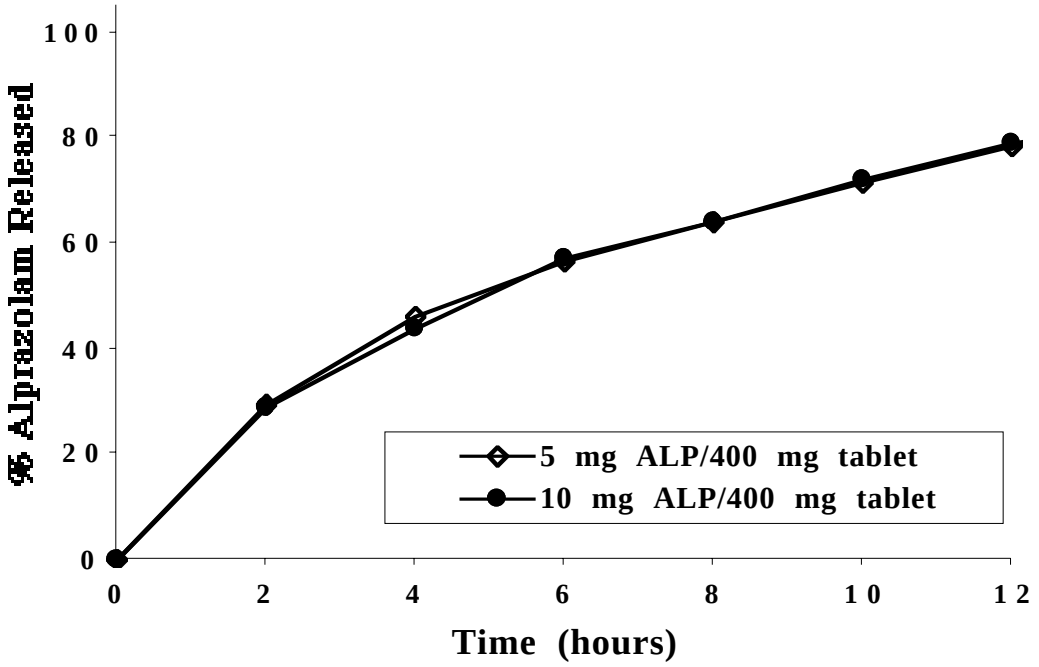


Figure 3.11 Influence of drug loading on drug release from matrix tablets (23%w/w HPMC K4MP, 20 %w/w MCC, 0.5 %w/w Mg stearate, dicalcium phosphate qs.)

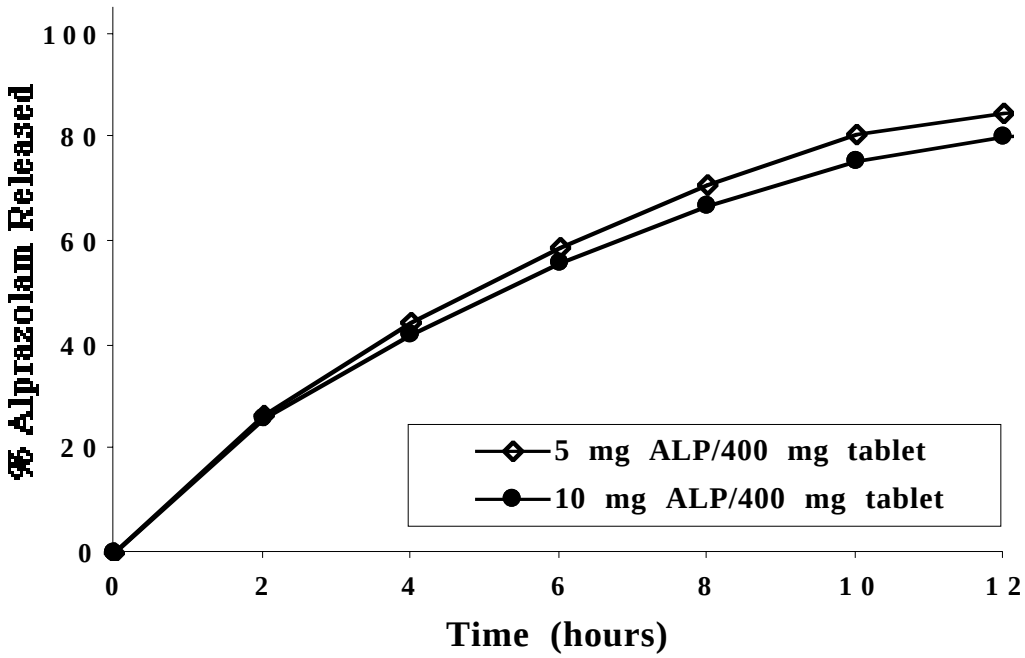


Figure 3.12 Influence of drug loading on drug release from matrix tablets (40 %w/w HPMC K100LVP, 20 %w/w MCC, 0.5 %w/w Mg stearate, dicalcium phosphate qs.)

Polymer Level

Figure 3.13 shows the influence of HPMC polymer level on the ALP release from matrix tablets. As described in several studies, polymer concentration is the most important factor to control drug release from a matrix tablet. When the polymer level in the formulation increases, the amount and extent of drug release will be decreased [Ford, 1985a; Ford, 1985b; Shah et al., 1993; Xu and Sunada, 1995; Velasco et al., 1999; Helena Amaral et al., 2001]. This is due to an increase in polymer concentration resulting in an increased viscosity of the gel as well as the formation of a gel layer with a longer diffusional path. As a result, a decrease in the effective diffusion coefficient of the drug and a reduction in the drug release rate were obtained [Velasco et al., 1999].

When comparing dissolution profiles in Figure 3.13, the formulation containing 33 %w/w of polymer was 5% and 15% average difference from the formulations containing 35 %w/w (f_2 = 67) and 40 %w/w (f_2 = 41) of polymer, respectively. About 10% average difference (f_2 = 48) was found when comparing formulations containing 35 and 40 %w/w of polymer. Additionally, at least 30 %w/w of HPMC K4MP is necessary within the tablet formulation in order to prepare product with at least 12-hour release. However, excipients used in the formulation, the HPMC molecular weight type, and other factors may have some influence on the amount of drug release as described in the following sections.

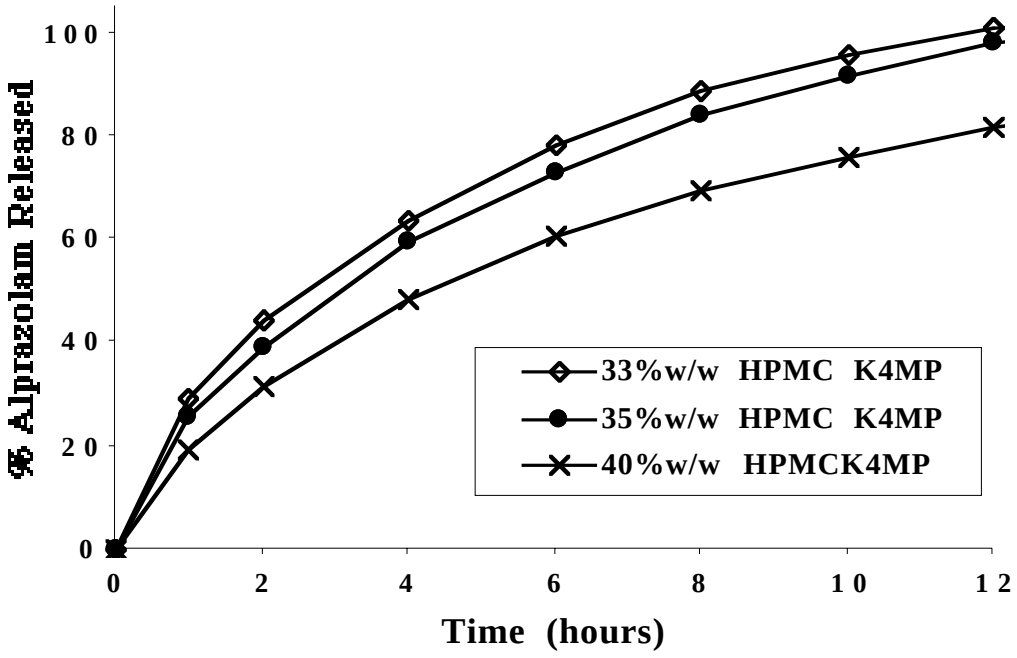


Figure 3.13 Influence of HPMC K4MP level on drug release from matrix tablet (2.5 %w/w ALP, 20 %w/w MCC, 0.5 %w/w Mg stearate, 0.5 %w/w silicon dioxide, lactose qs.)

Formulation Development

The following study was carried out in order to investigate the influence of excipient, polymer molecular weight type, and dissolution media on drug release. These parameters were optimized in order to obtain matrix tablets that could sustain the release of ALP between 14 and 16 hours. *In vitro* dissolution studies and similarity factor assessments were used as tools during formulation development.

Excipient Type [Williams III et al., 2001]

Physical Characterization of ALP Matrix Tablets

As seen in Table 2.5, each tablet formulation contained equivalent amounts of ALP (10 mg/400 mg tablet), HPMC K4MP hydrophilic polymer (160 mg/tablet), MCC, silicon dioxide and magnesium stearate, and other excipient(s) investigated (146 mg/tab). The type of excipient (formulations A, E, F, G, H, I) was varied from formulation-to-formulation. Formulations A to E were prepared using different levels of LAC and DCP. Table 3.4 shows the physical characterization of tablets from each formulation. The percent weight variation of tablets randomly sampled from each formulation was less than 2%, and tablet hardness was in a narrow range of 6.80-8.10 kg. Tablet potency determined from a composite assay of 10 tablets ranged between 90-100% of label claim.

Table 3.4 Results of Physical Characterization of ALP Controlled Release Tablets.

Formulation	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
Excipient type	LAC:DCP (100:0)	LAC:DCP (75:25)	LAC:DCP (50:50)	LAC:DCP (25:75)	LAC:DCP (0:100)	SUC	DEX	DCA	CSD
Hardness (kg)	6.80	7.49	7.33	7.12	7.35	7.56	7.51	8.10	7.93
Average Weight (mg)	401.90	402.25	400.05	400.15	397.10	395.65	403.20	402.40	393.30
% Wt Variation	0.47	0.56	0.01	0.04	0.72	1.09	0.80	0.60	1.68
Tablet Potency (% Label)	93.20	98.98	94.75	95.76	93.19	96.43	95.91	93.94	95.06

Note: LAC = Lactose Monohydrate; DCP = Dicalcium Phosphate Dihydrate; SUC = Sucrose; DEX = Dextrose; DCA = Dicalcium Phosphate Anhydrous; CSD = Calcium Sulfate Dihydrate

Drug Release Profiles

Figure 3.14 shows the dissolution profiles of tablet formulations A, F, and G containing the water-soluble excipients (36.5 %w/w), LAC, SUC and DEX, respectively. A comparison of the similarity factor and percent average difference, referring to the similarity between the formulations, is shown in Table 3.5. The similarity factor (f_2) is used to quantitate agreement between two dissolution profiles. If the f_2 value is close to 100, the two profiles are nearly identical. In general, the FDA standard of f_2 between 50-100 (≤ 10% average difference) indicates similarity between two dissolution profiles [Shah et al., 1998; Shah et al., 1999; Moore and Flanner, 1996]. Dissolution profiles of formulation A (LAC) and formulation F (SUC) showed only a 2% difference (f_2 = 88). Although the release of ALP from tablets containing DEX (formulation G) was slightly faster than that from tablets containing SUC (formulation F) or LAC (formulation A), the dissolution profile of tablets containing DEX (formulation G) was similar to those of LAC (formulation A) and SUC (formulation F), having a f_2 value of 62 and 58 (10% difference), respectively (Table 3.5). The amount of drug release from formulations containing these soluble excipients reached 90% within 12-14 hours. Similar results from the previous study were reported for the release of either slightly soluble theophylline (8.33 mg/ml in water) or soluble naproxen sodium (196.7 mg/ml in water) from tablets containing LAC, SUC, or DEX (50-65 %w/w). In addition, no significant difference in those release profiles was found for the tablets containing either HPMC K4M or HPMC E4M [The Dow Chemical Company, 2000]. Despite the differences in drug solubility

between ALP, theophylline and naproxen sodium, similar release profiles were reported. Similar release results obtained due to the relatively high amount of the soluble excipient in these tablet formulations (36.5-65 %w/w) that led to the formation of the hydrated gel layers with high drug permeability.

Drug release profiles of tablets containing the water insoluble excipient (36.5 %w/w), DCP (formulation E), DCA (formulation H), and CSD (formulation I) are shown in Figure 3.14. The f_2 values calculated for the formulations containing insoluble excipients (E vs. H, H vs. I, and E vs. I) also showed a 5-10% average difference (Table 3.5). The amount of drug release from those formulations was only 75-85% within 12-14 hours and the release extended beyond 16 hours.

Figure 3.14 also shows the release profiles from formulations containing the soluble excipients, LAC (formulation A), and DEX (formulation G), compared to those from formulations containing insoluble excipients, DCP (formulation E), DCA (formulation H), and CSD (formulation I). The percent average difference, based on f_2 values, between dissolution profiles of formulations containing a soluble excipient compared to formulations containing an insoluble excipient was in the range of 15-20%, indicating dissimilarities in the profiles (Table 3.5). The formulations containing insoluble excipients, especially the DCP formulation, released the active drug at a slower rate and to a lesser extent than those containing a soluble excipient. The hydrated gel layer was more permeable for drug release when a soluble excipient was contained in the

formulation [The Dow Chemical Company, 2000; Hirschorn and Kornblum, 1971].

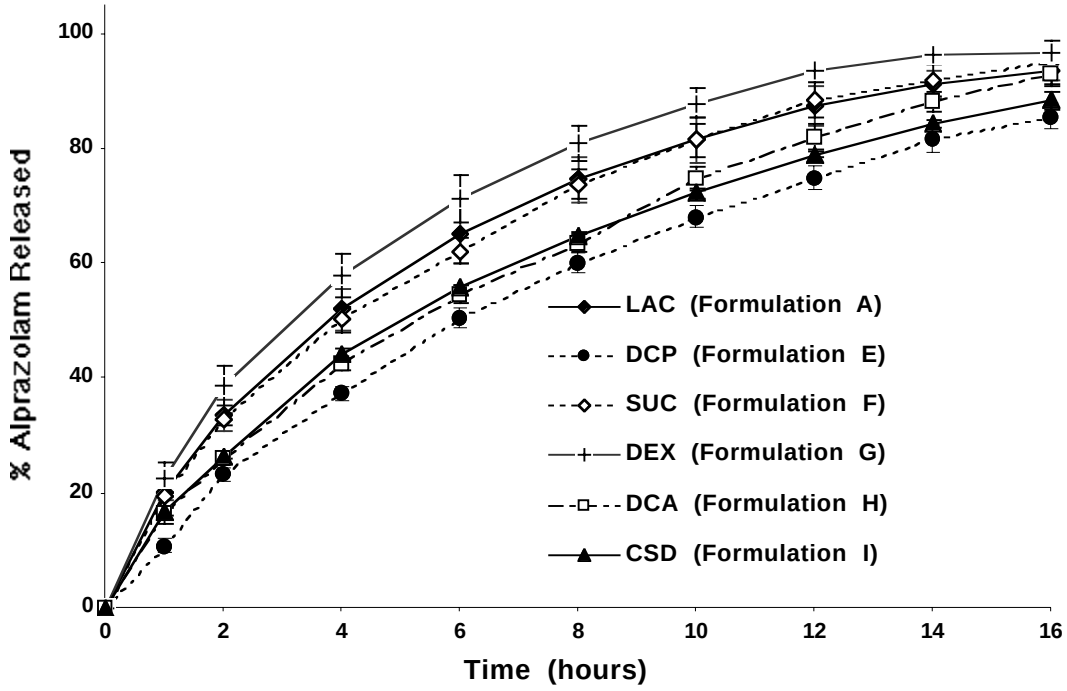


Figure 3.14 Comparison of dissolution profiles of ALP matrix tablet formulations containing water-soluble and water-insoluble excipients

Table 3.5 Summary of f_2 Similarity Factor Comparison of the Tablet Formulations Investigated

Number	Comparison		f_2	% Average difference[1]
	Reference formulation	Test formulation		
1	A (LAC:DCP, 100:0)	B (LAC:DCP, 75:25)	67	5
2	A (LAC:DCP, 100:0)	C (LAC:DCP, 50:50)	71	5
3	A (LAC:DCP, 100:0)	D (LAC:DCP, 25:75)	70	5
4	A (LAC:DCP, 100:0)	E (LAC:DCP, 0:100)	44	15
5	A (LAC:DCP, 100:0)	F (SUC)	88	2
6	A (LAC:DCP, 100:0)	G (DEX)	62	10
7	A (LAC:DCP, 100:0)	H (DCA)	54	10
8	A (LAC:DCP, 100:0)	I (CSD)	54	10
9	B (LAC:DCP, 75:25)	C (LAC:DCP, 50:50)	57	10
10	B (LAC:DCP, 75:25)	D (LAC:DCP, 25:75)	58	10
11	B (LAC:DCP, 75:25)	E (LAC:DCP, 0:100)	38	20
12	B (LAC:DCP, 75:25)	F (SUC)	63	10
13	B (LAC:DCP, 75:25)	G (DEX)	76	5
14	B (LAC:DCP, 75:25)	H (DCA)	45	15
15	B (LAC:DCP, 75:25)	I (CSD)	46	15
16	C (LAC:DCP, 50:50)	D (LAC:DCP, 25:75)	94	2
17	C (LAC:DCP, 50:50)	E (LAC:DCP, 0:100)	48	15
18	C (LAC:DCP, 50:50)	F (SUC)	79	5
19	C (LAC:DCP, 50:50)	G (DEX)	52	10
20	C (LAC:DCP, 50:50)	H (DCA)	61	10
21	C (LAC:DCP, 50:50)	I (CSD)	59	10
22	D (LAC:DCP, 25:75)	E (LAC:DCP, 0:100)	47	15
23	D (LAC:DCP, 25:75)	F (SUC)	78	5
24	D (LAC:DCP, 25:75)	G (DEX)	52	10
25	D (LAC:DCP, 25:75)	H (DCA)	60	10
26	D (LAC:DCP, 25:75)	I (CSD)	58	10
27	E (LAC:DCP, 0:100)	F (SUC)	46	15
28	E (LAC:DCP, 0:100)	G (DEX)	36	20
29	E (LAC:DCP, 0:100)	H (DCA)	63	10
30	E (LAC:DCP, 0:100)	I (CSD)	66	5
31	F (SUC)	G (DEX)	58	10
32	F (SUC)	H (DCA)	57	10
33	F (SUC)	I (CSD)	56	10
34	G (DEX)	H (DCA)	43	15
35	G (DEX)	I (CSD)	43	15
36	H (DCA)	I (CSD)	82	5

Note: [1] % Average difference refers to the similarity between the test formulation to the reference formulation with an average difference of specified percentage based on the criteria (the average differences of 2%, 5%, 10%, 15%, and 20% correspond to f_2 limit of 83, 65, 50, 41, 35, respectively).

The use of LAC and DCP in the tablet formulation produced drug release profiles of intermediate duration (Figure 3.15). There were slight differences in release profiles for formulations containing LAC at levels of 100%, 75%, 50%, and 25% of the excipient investigated (36.5 %w/w of the total formulation; formulations A, B, C, and D, respectively). In terms of f_2 value, formulations containing LAC at levels greater than 25% of 36.5 %w/w excipient (formulations A, B, C, and D) were similar (5% average difference between the two profiles comparison). The release profile from tablet formulations containing no LAC (formulation E) was different from those containing LAC (formulations A, B, C, and D), with an f_2 indicating a 15-20% average difference. As can been seen in Figure 3.15, the LAC level was less important compared to whether or not LAC was used in the formulation. Only when the DCP level was sufficiently high (36.5 %w/w) in the tablet formulations (formulation E) was the release rate and extent decreased. This was due to the incorporation of LAC, which increased the interspace volume and porosity of the matrix and resulted in faster diffusion of drug from the matrix, and an increased rate of erosion of the matrix tablet [The Dow Chemical Company, 2000; Tahara et al., 1995].

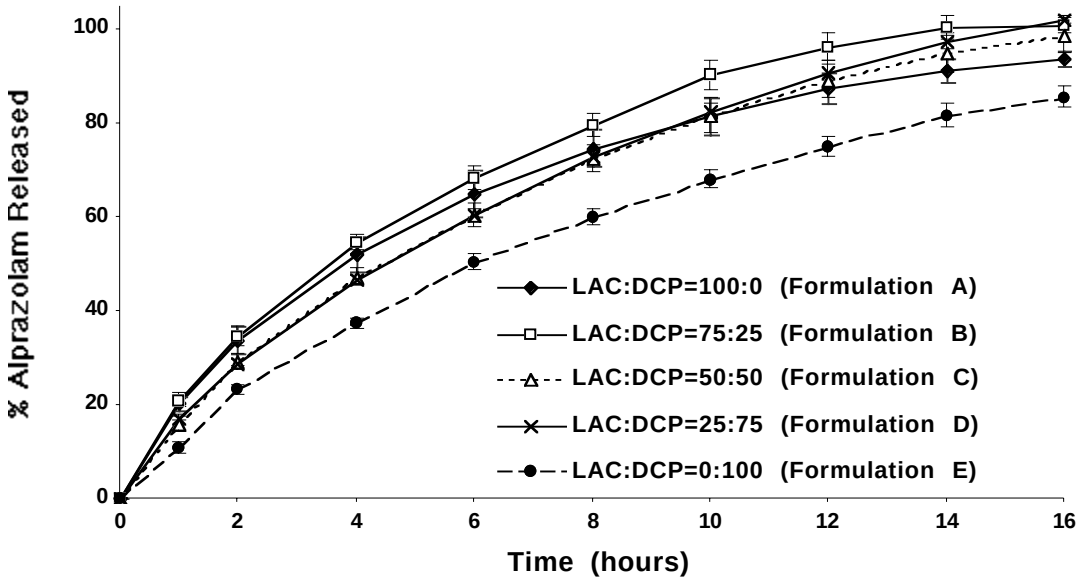


Figure 3.15 Dissolution profiles of ALP matrix tablet formulations containing binary mixtures of water-soluble lactose (LAC) and water-insoluble dicalcium phosphate dihydrate (DCP)

Mathematical Modeling of Drug Release Profiles

The most common approach to determine the drug release mechanism of matrix tablets is to fit the well-known equations of Hixson-Crowell [Hixson and Crowell, 1931] and Peppas [Peppas, 1985; Peppas and Ritger, 1987a; Peppas and Ritger, 1987b]. Different mathematical models of ALP release from a tablet are proposed in order to describe the release mechanism based on the release data obtained from the formulations investigated.

- Hixson-Crowell cube root kinetics equation

In the case of dissolution of a drug with poor aqueous solubility like ALP, dissolution occurs mainly after the erosion process resulting in release of drug particles from the matrix tablet, as represented by the Hixson-Crowell cube root kinetics equation [Tahara et al., 1995; Hixson and Crowell, 1931] illustrated in Equation 1,

$$\left(\frac{W_d}{W_i}\right)^{1/3} = 1 - k_1 t \qquad (1)$$

where W_d is dry weight of tablet at the designated time after immersion in the medium, W_i is the initial dry weight of tablet, t is time, and k_1 is the erosion rate constant for the tablet. From Equation 1, when drug dissolution from particles is considerably slower than tablet erosion, dissolution profiles of the drug (Q_d) is more accurately represented by Equation 2,

$$\left(1-\frac{Q_d}{A}\right)^{1/3} = 1 - k_2 t \qquad (2)$$

where Q_d is amount of drug dissolved at time t, A is the total amount of drug present in the matrix, t is time, and k_2 is the apparent rate constant for the drug dissolution. When Equation 2 was plotted for each formulation, as shown in Figure 3.16, a linear relationship was obtained from each formulation indicating that the dissolution of ALP occurred predominantly after release of the solid drug particles from the tablets, regardless of the excipient type used in the tablets. Table 3.6 shows the linear regression results of fitting the drug release data from each formulation to the Hixson-Crowell cube root kinetics equation (Equation 2). The linear regression coefficient (r^2) of all formulations investigated ranged from 0.994 to 0.999 and indicated best fit of the release data according to the Hixson-Crowell cube root kinetics equation (Equation 2). The apparent rate constant for ALP dissolution (k_2) ranged from 0.030 to 0.052 hr^{-1}. This indicated the difference in dissolution rate of ALP from tablets containing different types of excipient. The rate of ALP dissolution from tablets containing water-soluble excipient (LAC (formulation A-D), SUC (formulation F), DEX (formulation G); 0.038-0.052 hr^{-1}), was faster than the dissolution rate of ALP from tablets containing water-insoluble excipient (DCP (formulation E), DCA (formulation H), CSD (formulation I); 0.030-0.034 hr^{-1}). The hydrated gel layers were more permeable for ALP release when the tablets contained soluble excipients, resulting in faster rates of dissolution. Tahara et al. reported similar results for the

release of poorly water soluble drug, U-78875 (0.08 mg/ml in pH 6.8 medium), from a tablet containing a different substitution type of HPMC (HPMC 2910, 50 cPs) and lactose [Tahara et al., 1995]. This indicated that drug release mechanism depends primarily on drug solubility, regardless of the HPMC substitution type or excipient type used in the tablets. From the dissolution release rate constants (k_2) obtained from the slope of the plots in Table 3.6, tablets containing soluble excipients, such as LAC, SUC or DEX (formulations A, B, C, D, F, and G) had faster release rates when compared to the release rates of tablets containing insoluble excipients, such as DCP, DCA or CSD (formulations E, H, and I).

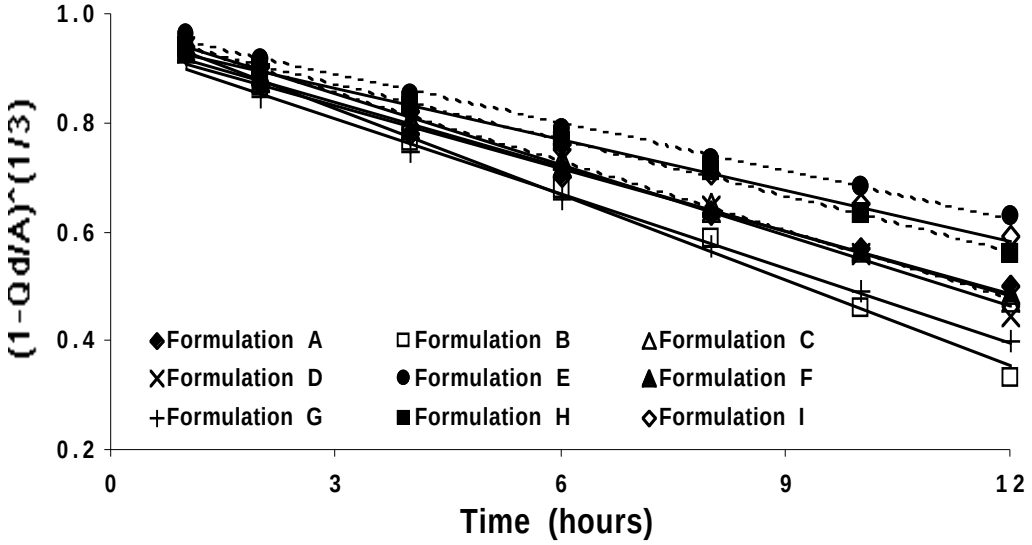


Figure 3.16 Plot of ALP released as a function of time according to Hixson-Crowell cube root kinetics equation (equation 2)

Table 3.6 Results of Linear Regression for ALP Release Fitted to Hixson-Crowell Cube Root Kinetics Equation (Equation 2)

Formulation	Slope, k_2 (hr^{-1})	r^2	y-intercept
A	**0.038**	**0.994**	**0.947**
B	**0.052**	**0.995**	**0.982**
C	**0.042**	**0.999**	**0.981**
D	**0.044**	**0.997**	**0.986**
E	**0.030**	**0.995**	**0.979**
F	**0.040**	**0.998**	**0.959**
G	**0.046**	**0.997**	**0.945**
H	**0.034**	**0.998**	**0.973**
I	**0.031**	**0.995**	**0.960**

Peppas' equation

Peppas' transport equation has been developed to allow for the influences of hydration and swelling on drug release. Based on Peppas'equation, Korsmeyer et al. derived a simple relationship, which may be used to describe drug release from polymeric systems in which release deviates from Fickian diffusion as expressed in Equation 3 [Peppas, 1985; Peppas and Ritger, 1987a; Peppas and Ritger, 1987b; Korsemeyer et al., 1983]. Equation 4 was used to investigate the ALP release kinetics from tablet formulations containing different types of excipients:

$$\frac{M_t}{M_\infty} = kt^n \qquad (3)$$

$$\log\left(\frac{M_t}{M_\infty}\right) = \log k + n \log t \qquad (4)$$

where M_t/ M_∞ is the fraction of drug release, t is the release time, k is a constant incorporating structural and geometric characteristics of the controlled release device, and n is the diffusional release exponent indicative of the mechanism of drug release for drug dissolution. To characterize the release mechanism, the dissolution data ($M_t/M_\infty < 0.6$, first 4-6 hours of release) were evaluated according to Equation 4 [Peppas, 1985; Peppas and Ritger, 1987a; Peppas and Ritger, 1987b; Korsemeyer et al., 1983]. Figure 3.17 shows a plot of the log fraction of drug dissolved as a function of time for each formulation. The linear regression results are given in Table 3.7. The linear regression coefficient (r^2) of all formulations investigated ranged from 0.986 to 0.999 and indicated best

fit of the release data according to Equation 4. According to Peppas and Korsmeyer [Peppas, 1985; Peppas and Ritger, 1987a; Peppas and Ritger, 1987b; Korsemeyer et al., 1983], the value of the diffusional exponent, n, determined from the slope of all formulations containing different types of excipients ranged from 0.67 to 0.85, indicating a non-Fickian (anomalous) release behavior of ALP from the matrix tablet controlled by a combination of diffusion and macromolecular chain relaxation mechanisms. The slight difference in the diffusional release exponent value (n) may be due to the different types of excipients used in the tablet formulations, however all n values indicated the same type of release mechanism of ALP from the matrix tablet. Skoug et al. reported that the release of ALP from sustained release tablets (no formulation compositions were described) demonstrated a significant increase in n from about 0.65 to 0.74 for tablets containing 0.5 mg and 3 mg of the active, respectively. The mechanism of release for both 0.5 and 3 mg tablets was classified as anomalous diffusion, similar to the results reported in this study [Skoug et al., 1993]. Therefore, neither the amount of drug loading, nor the formulation composition, had an influence on the ALP release mechanism for the formulations investigated. Additionally, similar release kinetics (n = 0.69) were obtained for the release of the practically water insoluble drug, atenolol, from a matrix tablet containing HPMC K100LV, HPMC K4M, lactose, povidone and magnesium stearate [Eyjolfsson, 1999]. Therefore, differences in molecular weight distribution of HPMC polymers, as well as excipient type and level used in the tablet formulations, have less impact on the drug release mechanism.

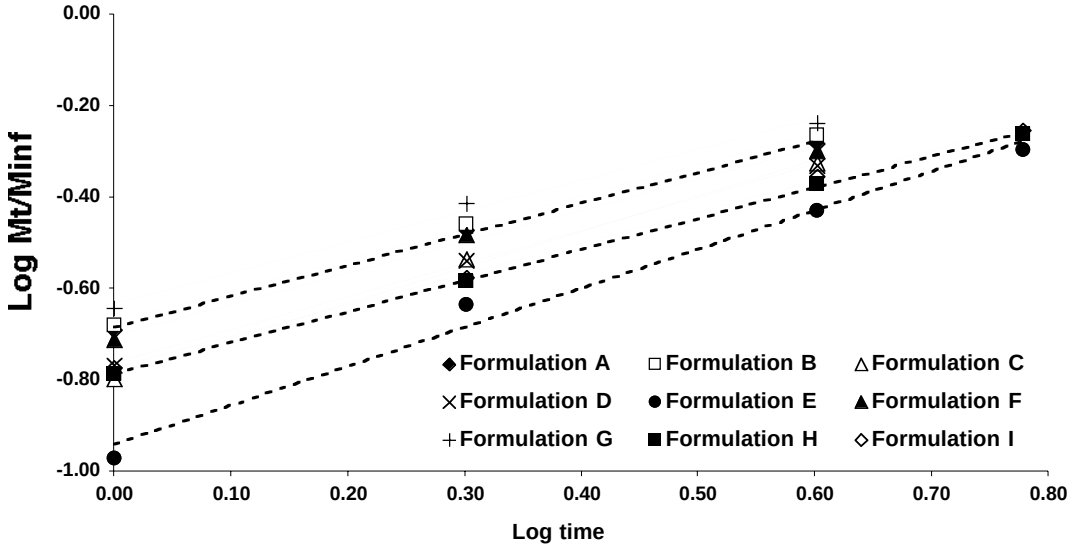


Figure 3.17 Plot of Fraction of ALP dissolved as a function of the logarithm of time according to Peppas' equation (equation 4)

Table 3.7 Results of Linear Regression for ALP Release Fitted to Peppas' Equation (Equation 4)

Formulation	Slope, n	r^2	k
A	0.677	0.998	0.206
B	0.691	0.999	0.211
C	0.784	0.996	0.163
D	0.723	0.999	0.172
E	0.852	0.986	0.113
F	0.688	0.996	0.197
G	0.675	0.994	0.232
H	0.680	0.999	0.164
I	0.678	0.999	0.168

HPMC Molecular Weight Type (Viscosity Grade)

During screening studies of ALP controlled release matrix tablets, the influence of molecular weight type (viscosity grade) of HPMC polymer on the amount of ALP release was investigated. As shown in Figure 3.18, the amount of ALP release from a tablet formulation containing a low molecular weight type HPMC, HPMC-K100LVP, was faster than the amount of ALP release from a similar tablet formulation containing a high molecular weight type HPMC, HPMC-K4MP. Additionally, the release of the drug from tablets containing HPMC-K4MP was extended beyond 10 hours; whereas the release of the drug from tablets containing HPMC-K100LVP approached 100% at 10 hours. Both release profiles are an approximate 15 %average difference with an f_2 factor of 41. Even though both HPMC types possess a similar degree of methoxyl substitution and hydroxypropyl substitution and similar gelation rates, they are different in terms of their degree of polymerization resulting in different molecular weights, which is reflected in the viscosity of an aqueous solution. Specifically, HPMC-K4MP has a molecular weight or nominal viscosity about 40 times greater than HPMC-K100LVP [The Dow Chemical Company, 2000].

Similar to ALP tablets investigated in this study, promethazine HCl tablets containing a low viscosity grade polymer, HPMC-K100, had a faster dissolution rate than tablets containing a higher viscosity grade polymers, such as HPMC-K4M, HPMC-K15M, HPMC-K100M, at a constant HPMC:drug ratio. However, the high viscosity grade polymers, HPMC-K4M, HPMC-K15M, and HPMC-

K100M, showed similar release rates despite the variation in their molecular size. This may due to a higher apparent diffusion coefficient of HPMC-K100 to the drug substance [Ford et al., 1985a; Ford et al., 1985b]. Even though both active drugs, ALP and promethazine HCl, are different in terms of their aqueous solubilities, the release patterns that resulted from different molecular weight types of HPMC used in the tablets are similar. Generally, tablets containing a low molecular weight type HPMC have a faster drug release rate and a shorter release period than tablets containing a high molecular weight type HPMC.

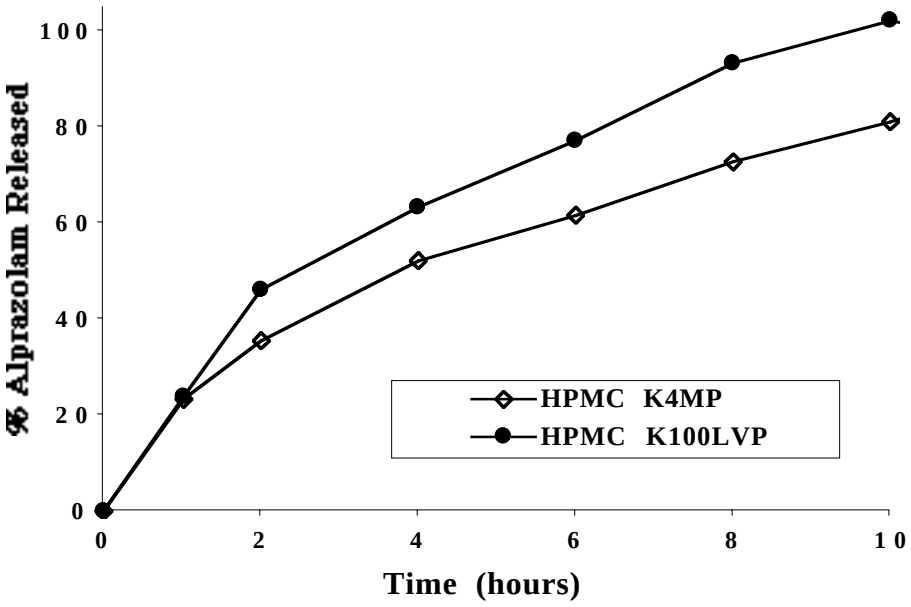


Figure 3.18 Influence of HPMC molecular weight type (viscosity grade) on drug release from matrix tablets (1.25 %w/w ALP, 40 %w/w HPMC, 20 %w/w MCC, 0.5 %w/w Mg stearate, 0.5 %w/w silicon dioxide, lactose qs.), (f_2 factor = 41, 15 %average difference)

From formulations previously shown in Table 2.6, the varying levels of HPMC K4MP or HPMC K100LVP ranged from 30-45 %w/w were used to develop and optimize the two controlled-release tablet formulations. They had similar *in vitro* dissolution profiles and were intended for an *in vivo* clinical study.

Finally, two tablet formulations containing different HPMC molecular weight types (i.e. formulations K100LV-27 and K4M-42) were developed. Tablet size, shape and hardness were identical for both formulations. The compositions of each tablet formulation in %w/w and in 300-gram batch sizes (750 tablets) are shown in Table 3.8. Manufacturing procedures were previously described in section 2.2.1.3 and Figure 2.1. Following the successful pilot scale production of a 300-gram batch size, the clinical batch using the same batch size for each tablet formulation (i.e. formulation K4M-42-lot M0009 and formulation K100LV-27-lot M0010) was prepared according to cGMP at the Veteran's Administration Cooperative Studies Program, Clinical Research Pharmacy Coordinating Center, Albuquerque, NM. Both clinical batches were tested for initial product release prior to conducting the *in vivo* clinical study.

As can be seen from Table 3.8, a higher amount of HPMC (45 %w/w) is necessary for tablets containing low molecular weight type or low viscosity grade, HPMC K100LVP, in order to obtain identical release profiles with tablets containing high molecular weight type or high viscosity grade HPMC, HPMC K4MP (37 %w/w). Tablet release profiles are shown within the tablet characterization section (Figure 3.19).

Table 3.8 Formulations of ALP Matrix Tablets for the Molecular Weight Type Study

HPMC-K100LVP Polymer

Rx	**K100LV-27**	
Ingredient	**%w/w**	**grams in 300 grams**
Alprazolam (10 mg/400 mg tablet), 99.7% potency	2.5075	7.5225
HPMC K100LVP	45.0000	135.0000
Microcrystalline cellulose (PH200)	20.0000	60.0000
Lactose, Fast-Flo	31.4925	94.4775
Silicon dioxide	0.5000	1.5000
Mg stearate	0.5000	1.5000
Total	100.0000	300.0000

HPMC-K4MP Polymer

Rx	**K4M-42**	
Ingredient	**%w/w**	**grams in 300 grams**
Alprazolam (10 mg/400 mg tablet), 99.7% potency	2.5075	7.5225
HPMC K4MP	37.0000	111.0000
Microcrystalline cellulose (PH200)	20.0000	60.0000
Lactose, Fast-Flo	39.4925	118.4775
Silicon dioxide	0.5000	1.5000
Mg stearate	0.5000	1.5000
Total	100.0000	300.0000

Characterization of Matrix Tablets

Tablets from the two clinical batches containing different molecular weight types of HPMC (formulations K100LV-27 and K4M-42) were characterized in terms of weight and hardness variations, content uniformity, batch composite, and *in vitro* dissolution.

Table 3.9 displays the physical characterization of tablets from each clinical batch. The percent weight variation of 20 tablets randomly sampled from each batch was less than 1%, which indicated flowable properties of the powder blend during the direct compression process. The average tablet hardness was 6.46 kg for the K4M-42 formulation (lot M0009) and 6.13 for the K100LV-27 formulation (lot M0010).

Table 3.10 summarizes the initial product release results of tablets from both tablet formulations prepared for the clinical study. Tablet potency of each formulation determined by the previously developed content uniformity assay of 10 tablets, was 101.67% (3.59 %RSD) and 94.82% (4.55 %RSD) of label claim for the K4M-42 (lot M0009) and K100LV-27 (lot M0010) formulations, respectively. Both formulations prepared using the previously developed blending method showed a uniformity of ALP content in each tablet as indicated by the low magnitude of the RSD.

The extent of drug release in 0.1 N HCl solution (pH 1.1) from each tablet formulation, at a specific time point, is shown in Table 3.10. The release profiles for both tablet formulations are shown in Figure 3.19. The f_2 factor calculation

for the dissolution profile comparison of formulations K4M-42 (lot M0009) and K100LV-27 (lot 0010) are shown in Table 3.11. A high f_2 factor of 91 (2 %average difference) was obtained, indicating that the two profiles were nearly identical. According to FDA guidelines for f_2 factor previously described in section 2.2.1.3, an f_2 factor between 50-100 (≤ 10% average difference) indicates similarity or equivalence between two dissolution profiles [FDA, 1995a; FDA, 1997a; Shah et al., 1998; Shah et al., 1999; Moore and Flanner, 1996]. Therefore, the two clinical batches containing different molecular weight types of HPMC polymer were *in vitro* equivalent.

After reviewing the initial release results of both clinical batches shown in Table 3.10, all results were within the release specifications listed in section 2.2.1.3.

Table 3.9 Summary of Tablet Weight and Hardness Variations of ALP Matrix Tablet Formulations Containing Different Molecular Weight Type HPMC

Formulation	**K4M-42 (M0009)**		**K100LV-27 (M0010)**	
Tablet No.	**Weight (mg) n=20**	**Hardness (kg) n=20**	**Weight (mg) n=20**	**Hardness (kg) n=20**
1	397	7.40	398	6.25
2	399	6.60	401	5.75
3	400	6.40	396	6.80
4	398	6.00	402	7.25
5	406	6.30	403	5.50
6	402	6.10	397	6.25
7	406	6.60	396	6.20
8	403	6.60	397	5.30
9	403	6.80	396	6.30
10	400	7.60	397	4.90
11	402	6.60	399	7.10
12	406	6.20	398	5.90
13	400	5.50	394	6.20
14	398	5.80	400	6.50
15	398	7.10	394	5.25
16	399	7.00	398	5.30
17	399	6.25	403	7.60
18	404	7.20	394	6.00
19	398	5.70	394	6.00
20	398	5.50	397	6.25
Average	**400.80**	**6.46**	**397.70**	**6.13**
SD	**2.98**	**0.61**	**2.89**	**0.70**
%RSD	**0.74**	**9.37**	**0.73**	**11.42**

Table 3.10 Summary of Initial Product Release Results for the Clinical Study of ALP Matrix Tablets Containing Different Molecular Weight Type HPMC

Formulation	**K4M-42**	**K100LV-27**
Clinical Lot No.	**M0009**	**M0010**
Manufacturing date	6/6/00	6/7/00
HPMC Type	K4MP	K100LVP
HPMC Level	37	45
Hardness (kg)	6.46	6.13
Avr. Tablet Weight (mg)	400.80	397.70
% Wt variation	0.20	0.58
Tablet potency (% Label)	101.67 (3.59 %RSD)	94.82 (4.55 %RSD)
Dissolution Time (hr)	**% Released (± SD) (Based on label claim)**	
0	0.00 ± 0.00	0.00 ± 0.00
1	24.81 ± 2.75	24.14 ± 2.11
2	38.22 ± 2.83	38.01 ± 3.64
4	58.03 ± 4.22	58.35 ± 5.94
6	72.47 ± 4.99	72.92 ± 4.09
8	82.93 ± 4.75	84.31 ± 3.40
10	91.42 ± 4.06	93.69 ± 3.60
12	97.06 ± 3.21	99.51 ± 2.74
14	102.06 ± 3.47	102.65 ± 1.54
16	102.78 ± 1.41	102.95 ± 2.05

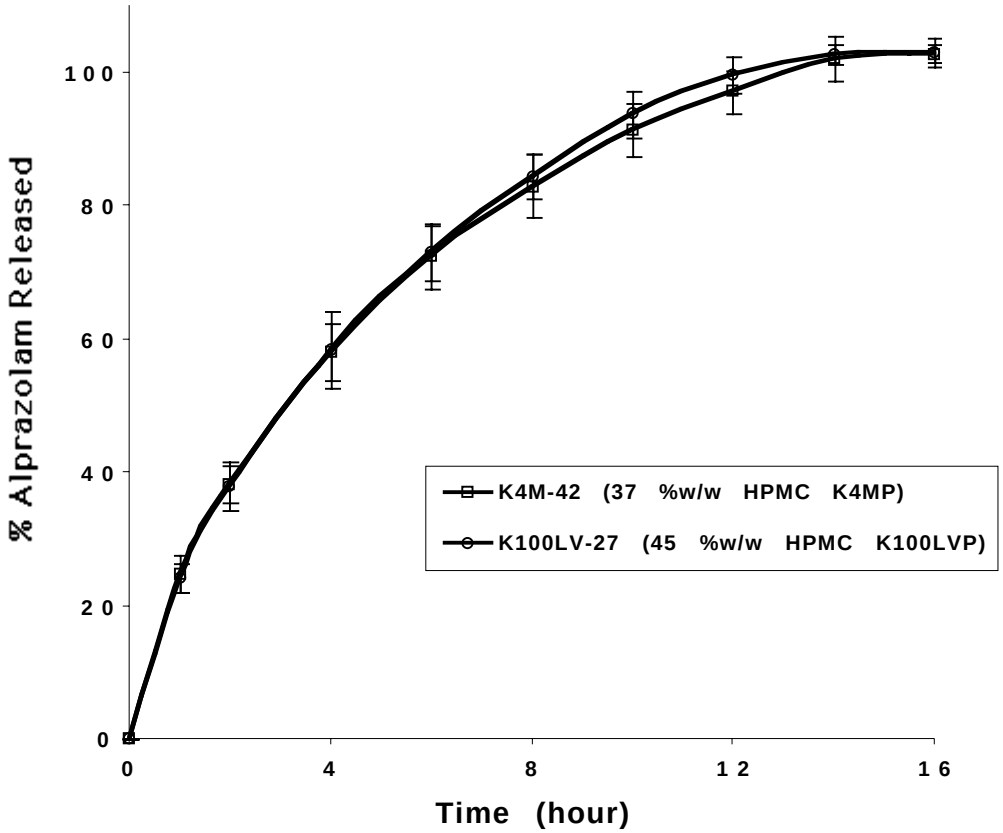


Figure 3.19 Similar release profiles (f_2 factor = 91, 2 %average difference) of ALP matrix tablets obtained from formulations containing different HPMC levels and different molecular weight types of HPMC (2.5 %w/w ALP, 20 %w/w MCC, 0.5 %w/w Mg stearate, 0.5 %w/w silicon dioxide, lactose qs.)

Table 3.11 Similarity Factor (f_2) for Dissolution Profile Comparison of Formulations K4M-42 and K100LV-27

Reference batch: K100LV-27 (45 %w/w HPMC K100LVP, lot M0010)
Test batch: K4M-42 (37 %w/w HPMC K4MP, lot M0009)

Formula	**Time (hr)**	**% Drug dissolved**		**f_2 $(\mu_{ti}-\mu_{ri})^2$**
		Reference	**Test batch**	**Test**
	1	24.14	24.81	0.4426
	2	38.01	38.22	0.0469
	4	58.35	58.03	0.0992
	6	72.92	72.47	0.2044
	8	84.31	82.93	1.8985
	10	93.69	91.42	5.1317
P (number of time points)	6			
$\Sigma (\mu_{ti}-\mu_{ri})^2$				7.8232
$[1+(1/P)x\Sigma (\mu_{ti}-\mu_{ri})^2]^{-1/2}$				0.6588
$f_2=50xlog\{[1+(1/P)x\Sigma (\mu_{ti}-\mu_{ri})^2]^{-1/2}\}x100\}$				**91***

Note: * The similarity between the test batch to the reference batch with an average difference of 2% based on the criteria [Shah et al., 1998].

Dissolution Medium

Drug release analysis of ALP matrix tablets was carried out in 0.1 HCl solution with an acidic pH of 1.1 at 37±0.5˚C such that sink conditions were met. Drug solubility in this medium, as obtained from preformulation studies in section 3.1.1 was approximately 14 mg/ml (C_{sat}). The maximum drug concentrations (C_{sol}) in 900 ml dissolution medium were 0.0056 mg/ml and 0.0111 mg/ml for tablets containing 5 and 10 mg active, respectively. In this case, C_{sat} was 1260 to 2500 times higher than C_{sol}. In contrast, dissolution of ALP tablets in alkaline medium was not under sink conditions, due to its inherently low saturated solubility of ALP. For example, drug solubility in simulated intestinal fluid (SIF) pH 6.8 obtained during preformulation studies in section 3.1.1 was approximately 0.04 mg/ml (C_{sat}). The maximum drug concentrations (C_{sol}) in 900 ml dissolution medium are were 0.0056 mg/ml and 0.0111 mg/ml for tablets containing 5 and 10 mg active, respectively. Because of this, C_{sat} was only 3 to 7 times higher than C_{sol}.

To investigate the influence of dissolution media on the release of ALP from the matrix tablets, USP buffer pH 6.0 or purified water was used as a dissolution medium rather than 0.1 N HCl solution (pH 1.1). Drug release profiles of the same tablet formulation in different media were compared. Figures 3.20 and 3.21 show the release profiles of K4M-42 and K100LV-27 formulations in acidic medium (0.1 N HCl solution) and basic medium (USP buffer pH 6.0). The extent of ALP release from both tablet formulations in USP buffer pH 6.0 is significantly lower than the extent of drug release from both formulations in 0.1 N

HCl solution. Additionally, the extent of drug release in buffer pH 6.0 is incomplete and less than 50% at 12 hours, which is due to the dissolution of ALP from the tablets in buffer pH 6.0 did not occur under sink conditions. This also indicates that no dose dumping of ALP occurred at both acidic and basic pH conditions, which may confirm the safety for oral administration of ALP tablets during the *in vivo* clinical study. Similarly, dissolution profiles of another ALP tablet formulation developed during the screening study, which were conducted in both 0.1 N HCl and purified water, are shown in Figure 3.22. The rate and extent of ALP release from the matrix tablets in purified water was significantly lower and incomplete, which was due to a decrease in drug solubility and loss of sink conditions.

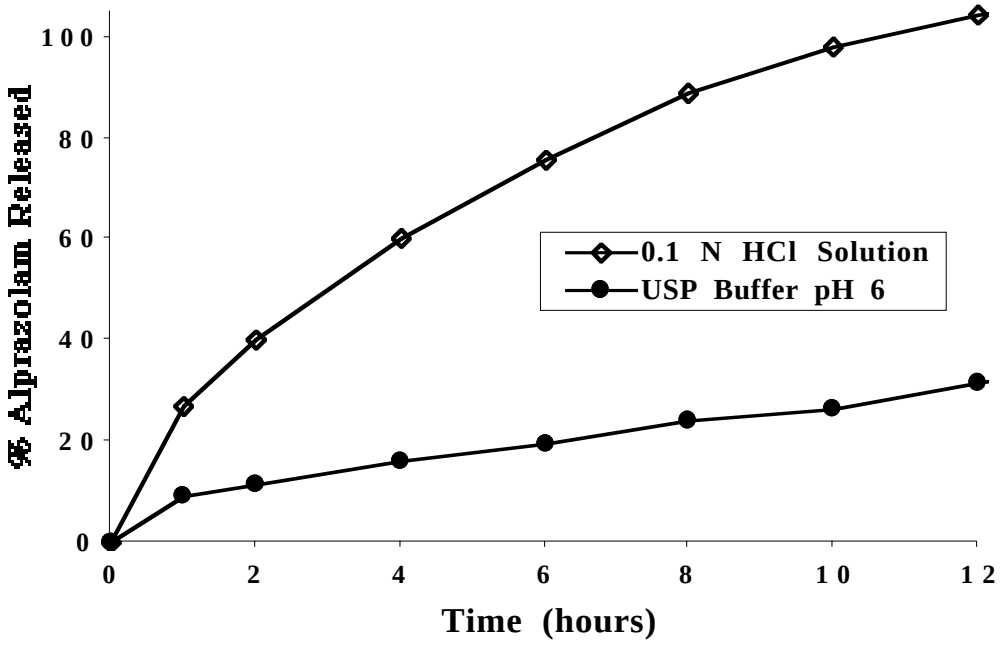


Figure 3.20 Effect of dissolution medium on ALP release from a matrix tablet (2.5 %w/w ALP, 37 %w/w HPMC K4MP, 20 %w/w MCC, 0.5 %w/w Mg stearate, 0.5 %w/w silicon dioxide, lactose qs.)

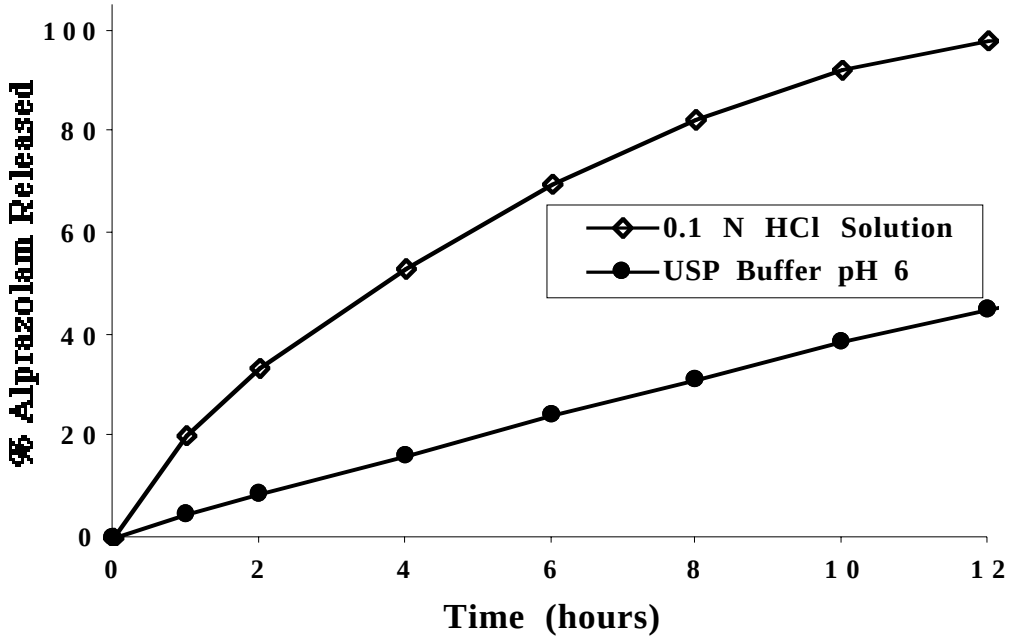


Figure 3.21 Effect of dissolution medium on ALP release from a matrix tablet (2.5 %w/w ALP, 45 %w/w HPMC K100LVP, 20 %w/w MCC, 0.5 %w/w Mg stearate, 0.5 %w/w silicon dioxide, lactose qs.)

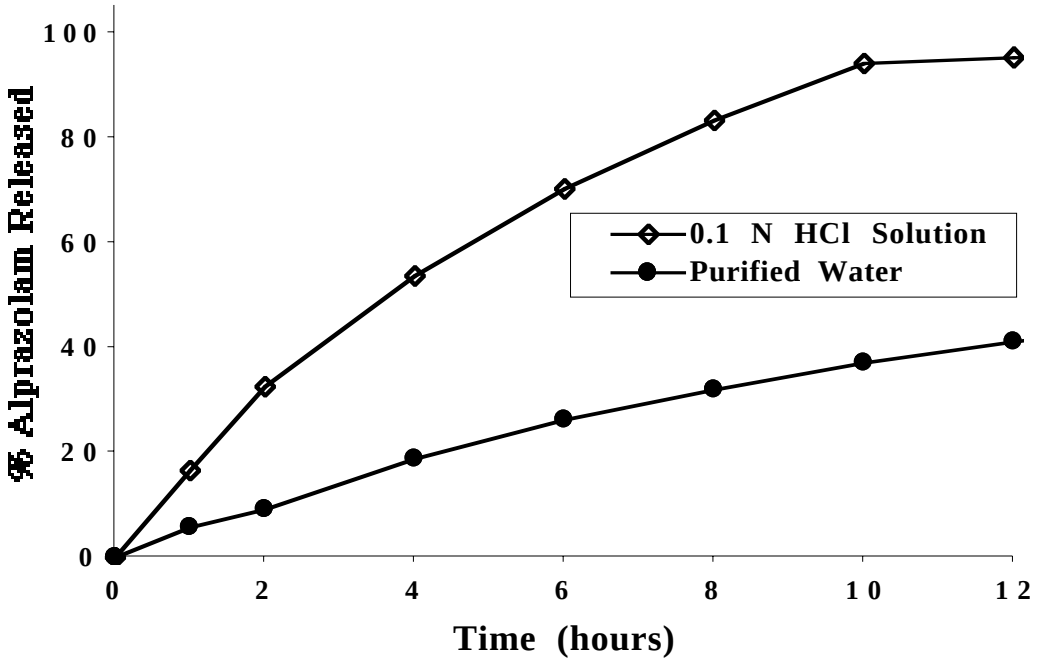


Figure 3.22 Effect of dissolution medium on ALP release from a matrix tablet (2.5 %w/w ALP, 40 %w/w of HPMC K100LVP, 20 %w/w MCC, 0.5 %w/w Mg stearate, 0.5 %w/w silicon dioxide, dicalcium phosphate qs.)

Stability Study of Matrix Tablets

Two clinical tablet formulations containing different molecular weight types of HPMC, HPMC K4M-42 (lot M0009) and K100LV-27 (lot M0010), were packaged in HDPE bottles with PP cap (foamed PE and pressure sensitive liner), and stored under different stability conditions, according to recommended ICH guidelines. At the conclusion of each stability condition, tablets from each formulation were tested for *in vitro* dissolution and statistically evaluated for differences using the similarity factor as previously defined. Additionally, a composite assay of 10 tablets and a HPLC analysis were conducted to determine the potency of the tablets and to investigate any possible degradation of ALP during storage. Stability studies were carried out to ensure the stability and safety of the tablet dosage forms during clinical study such that the tablets remained stable for at least one stability period following the completion of the clinical study, as mandated by clinical study requirements.

Table 3.12 summarizes the dissolution results of the two formulations at different storage conditions. Dissolution profiles at each stability condition are shown in Figure 3.23. In comparison to initial dissolution results, the dissolution results from each storage condition are well within the initial release specification. At each storage condition, dissolution profiles of the two clinical formulations were similar or equivalent with an f_2 factor ranging from 68-91 (only 2-5 %average difference, Table 3.13).

Dissolution profiles of K100LV-27 and K4M-42 formulations at different storage conditions, compared with the initial storage condition (time zero), are

shown in Figures 3.24 and 3.25, respectively. For each tablet formulation, the f_2 factor was calculated by a comparison of the dissolution profiles at each storage condition with the control at the initial condition. Results of f_2 factor ranging from 76-95 (2-5 %average difference) are shown in Table 3.14. Therefore, *in vitro* dissolution profiles of both tablet formulations remain unchanged for at least 6 months at 40˚C/75% relative humidity and 12 months at 25˚C/65% relative humidity.

In addition to the dissolution profiles, tablet potency results for all stability conditions as shown in Table 3.13 were within 90-110% of label claim. No degradation peaks were observed during HPLC analysis of tablets from all storage conditions. Table 3.15 shows the average tablet hardness of both formulations at different storage conditions compared to initial results obtained following tablet manufacturing. Results indicate that tablets tend to become slightly softer (lower hardness) when expose to a high temperature and humidity condition (i.e. 40˚C/75%RH). At the 25˚C/60%RH storage condition, average tablet hardness remained unchanged for at least 12 months. Tablets stored at 40˚C/75%RH condition may absorb some moisture from the environment and become softer over time. However, no swelling or hydration was observed from tablets stored at different storage conditions.

Overall, results from the stability studies indicated that tablets from both formulations were physically and chemically stable for at least 6 months at 40˚C/75%RH and 12 months at 25˚C/65%RH. Both tablet batches manufactured

under cGMP were within specification and could be released for *in vivo* clinical study.

Table 3.12 Summary of Dissolution Study of Two ALP Matrix Tablet Formulations Containing Different Molecular Weight Types of HPMC at Different Storage Conditions

Formulation K4M-42 (Lot M0009)

Time (hour)	K4M-42 (Lot M0009)															
	Initial		40 C, 1 mo.		40 C, 2 mo.		40 C, 3 mo.		40 C, 6 mo.		25 C, 3 mo.		25 C, 6 mo.		25 C, 12 mo.	
Assay date	6/13/00	SD	7/14/00	SD	8/13/00	SD	9/14/00	SD	12/22/00	SD	9/17/00	SD	12/23/00	SD	5/11/01	SD
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	24.81	2.75	22.79	0.27	20.88	1.12	23.53	2.29	22.28	2.55	26.42	2.66	23.90	2.04	22.03	2.30
2	38.22	2.83	36.65	0.35	35.22	3.02	36.11	3.58	35.35	3.54	40.25	3.78	38.09	3.11	40.10	3.20
4	58.03	4.22	59.32	0.47	54.05	4.68	56.95	6.26	55.48	5.52	60.08	5.61	59.08	4.96	60.06	4.96
6	72.47	4.99	71.79	0.53	68.26	5.05	68.46	6.37	69.69	6.23	74.39	6.04	73.52	5.05	75.43	5.45
8	82.93	4.75	81.72	0.58	79.06	5.87	79.11	6.38	80.16	6.13	86.37	5.29	83.25	4.75	86.82	5.46
10	91.42	4.06	90.41	0.63	87.90	5.51	88.77	6.03	87.99	5.39	93.79	5.95	90.74	4.08	95.12	5.11
12	97.06	3.21	95.92	0.66	92.46	3.80	94.97	4.92	93.27	4.47	98.84	4.34	95.65	3.44	100.47	4.25
14	102.06	3.47	100.39	0.68	96.60	3.05	99.03	4.22	96.43	3.58	102.67	3.57	98.64	2.67	104.31	3.69
16	102.78	1.41	103.19	0.70	99.61	2.77	102.62	3.40	99.13	2.40	105.24	3.30	100.90	1.74	106.77	3.30

Formulation K100LV-27 (Lot M0010)

Time (hour)	K100LV-27 (Lot M0010)															
	Initial		40 C, 1 mo.		40 C, 2 mo.		40 C, 3 mo.		40 C, 6 mo.		25 C, 3 mo.		25 C, 6 mo.		25 C, 12 mo.	
Assay date	6/14/00	SD	7/20/00	SD	8/14/00	SD	9/15/00	SD	12/21/00	SD	9/16/00	SD	12/24/00	SD	5/10/01	SD
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	24.14	2.11	23.62	2.38	22.63	3.39	25.81	2.90	22.06	2.40	24.32	5.43	25.81	1.53	22.60	2.99
2	38.01	3.64	38.76	4.63	37.42	4.96	40.97	3.15	35.68	3.06	35.45	0.47	38.57	2.80	36.21	3.78
4	58.35	5.94	59.33	5.25	56.82	5.13	60.06	3.42	55.90	3.93	55.05	0.65	57.53	4.56	55.47	1.68
6	72.92	4.09	74.44	4.36	70.85	4.35	73.58	3.42	70.53	3.62	70.34	0.57	72.19	5.11	70.00	2.15
8	84.31	3.40	86.23	3.31	81.56	3.53	84.48	2.44	82.09	2.46	82.16	0.71	83.08	5.21	83.41	6.83
10	93.69	3.60	95.89	3.35	89.92	2.67	92.18	1.45	90.05	1.67	91.87	0.74	91.21	4.52	90.64	2.52
12	99.51	2.74	101.74	1.83	95.54	2.54	98.17	0.78	95.76	0.86	98.68	1.19	97.27	3.10	97.66	2.44
14	102.65	1.54	104.84	1.60	97.88	2.68	100.56	0.44	98.81	1.03	101.99	1.73	100.39	2.24	102.37	2.35
16	102.95	2.05	105.79	1.26	98.60	3.43	101.27	0.71	99.85	1.24	103.64	2.01	101.30	2.23	103.95	2.13

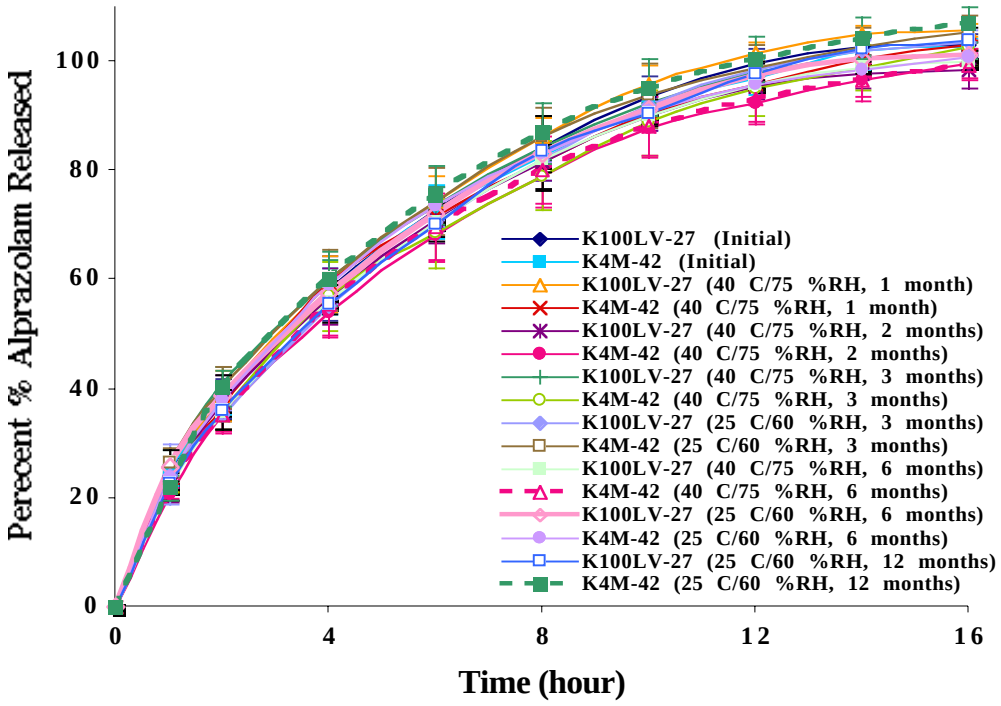


Figure 3.23 Dissolution profiles of two ALP matrix tablet formulations containing different molecular weight types of HPMC at different storage conditions

Table 3.13 Stability Study of ALP Matrix Tablet Formulations Containing different Molecular Weight Type of HPMC

Description	K100LV-27 (Lot M0010) Tablet potency (% Label)							
		40 ˚C/75 %RH				25 ˚C/60 %RH		
	Initial	1 mo.	2 mo.	3 mo.	6 mo.	3 mo.	6 mo.	12 mo.
Content uniformity	94.82	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Composite assay of 10 tablets	101.04	100.11	100.35	101.10	103.57	100.15	102.75	100.21
Similarity factor (f_2)*	91	78	80	68	90	68	91	70
% Average difference	2	5	5	5	2	5	2	5

Description	K4M-42 (Lot M0009) Tablet potency (% Label)							
		40 ˚C/75 %RH				25 ˚C/60 %RH		
	Initial	1 mo.	2 mo.	3 mo.	6 mo.	3 mo.	6 mo.	12 mo.
Content uniformity	101.67	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Composite assay of 10 tablets	105.58	105.56	101.35	102.14	102.58	102.01	103.15	105.09
Similarity factor (f_2)*	91	78	80	68	90	68	91	70
% Average difference	2	5	5	5	2	5	2	5

Note: * Calculated based on percent label claim between K4M-42 and K100LV-27 formulations at the same stability condition.

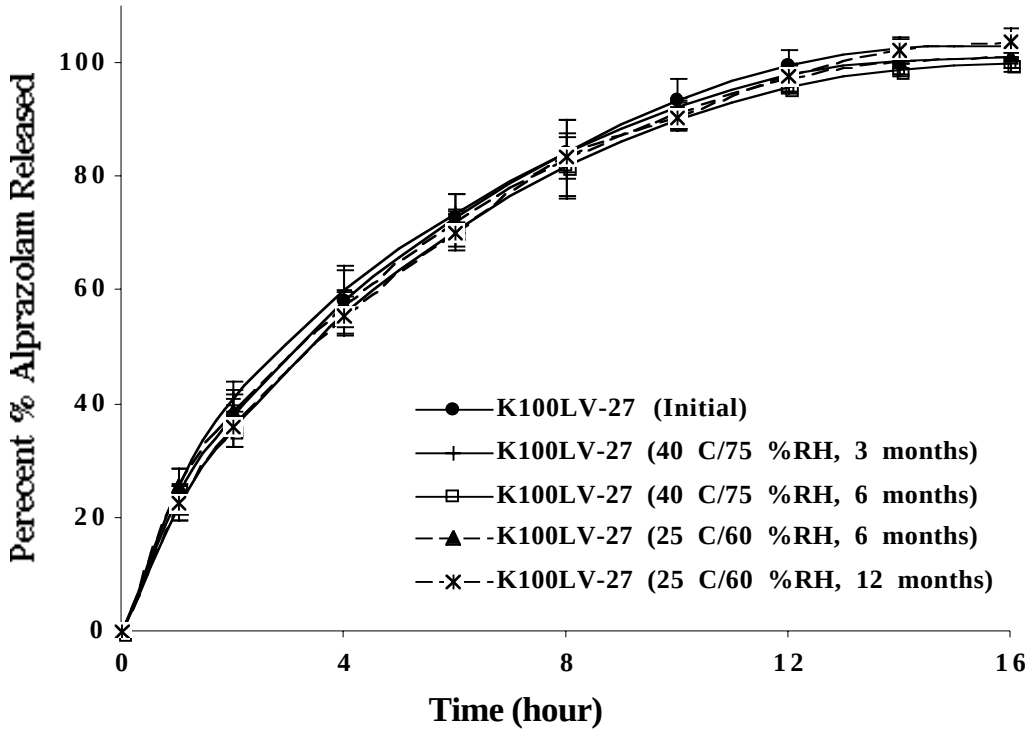


Figure 3.24 Dissolution profiles of ALP matrix tablets at different storage condition (formulation K100LV-27: 2.5 %w/w ALP, 45 %w/w HPMC K100LVP, 20 %w/w MCC, 0.5 %w/w Mg stearate, 0.5 %w/w silicon dioxide, lactose qs.)

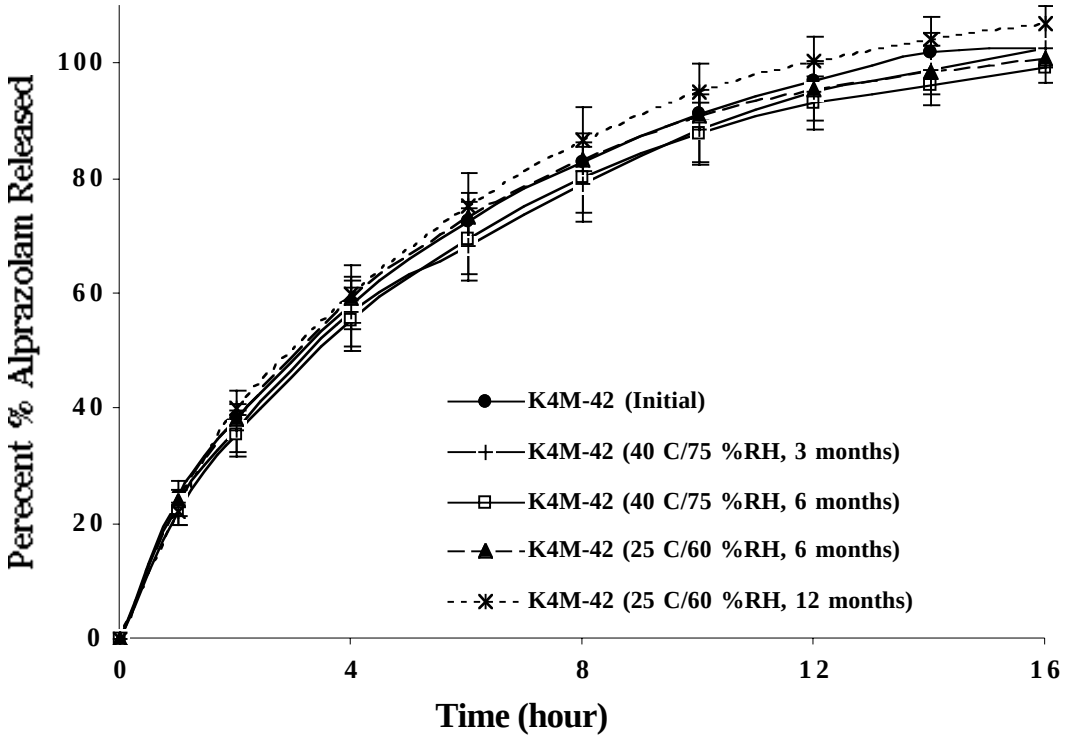


Figure 3.25 Dissolution profiles of ALP matrix tablets at different storage condition (formulation K4M-42: 2.5 %w/w ALP, 37 %w/w HPMC K4MP, 20 %w/w MCC, 0.5 %w/w Mg stearate, 0.5 %w/w silicon dioxide, lactose qs.)

Table 3.14 Similarity Factor (f_2) of ALP Matrix Tablet Dissolution Profiles between Initial Condition and Each Stability Condition

Stability Condition	**Initial, 0 month**			
	K4M-42 (Lot M0009)		**K100LV-27 (Lot M0010)**	
	f_2 factor	**% Avr. difference**	**f_2 factor**	**% Avr. difference**
40 ˚C/75 %RH, 3 mo.	77	5	85	2
40 ˚C/75 %RH, 6 mo.	76	5	78	5
25 ˚C/60 %RH, 6 mo.	95	2	88	2
25 ˚C/60 %RH, 12 mo.	76	5	80	5

Table 3.15 Tablet Hardness of ALP Matrix Tablets at Different Stability Conditions

Formulation	Stability Condition	Hardness (kg) Avr ± SD
K100LV-27 (Lot M0010)	Initial	6.13 ± 0.70
	12 mo., 25 C/60%RH	6.16 ± 1.03
	12 mo., 40 C/75%RH	5.36 ± 0.86
K4M-42 (Lot M0009)	Initial	6.46 ± 0.61
	12 mo., 25 C/60%RH	6.15 ± 0.36
	12 mo., 40 C/75%RH	4.58 ± 0.62

3.1.4 *In Vivo* Clinical Study

The *in vivo* clinical study in human subjects was completed in collaboration with Robert L. Talbert, Pharm.D. and his colleagues at GCRC, VA hospital, San Antonio, according to the testing protocol, previously approved by the Institutional Review Board (IRB) of the University of Texas Health Science Center.

Ten healthy volunteers participated throughout the study. The gender ratio of male:female subjects was 6:4. The range of age was 18-58 years old with an average age of 33.5±12.9 years old. The average body weight of the subjects was 83.4±11.9 kg.

A validated reverse-phase HPLC method was previously developed for quantification of ALP in plasma samples collected throughout the sampling schedule. Figures 3.26 and 3.27 displays the HPLC chromatograms of a control sample and a blood sample collected from a subject, respectively. Sharp peaks with good separations are shown in each chromatogram. The linearity of the calibration curve was excellent with a correlation coefficient (r^2) of no less than 0.994.

The assessments of the data collected throughout the study can be separated into two parts: Pharmacokinetics and Pharmacodynamics.

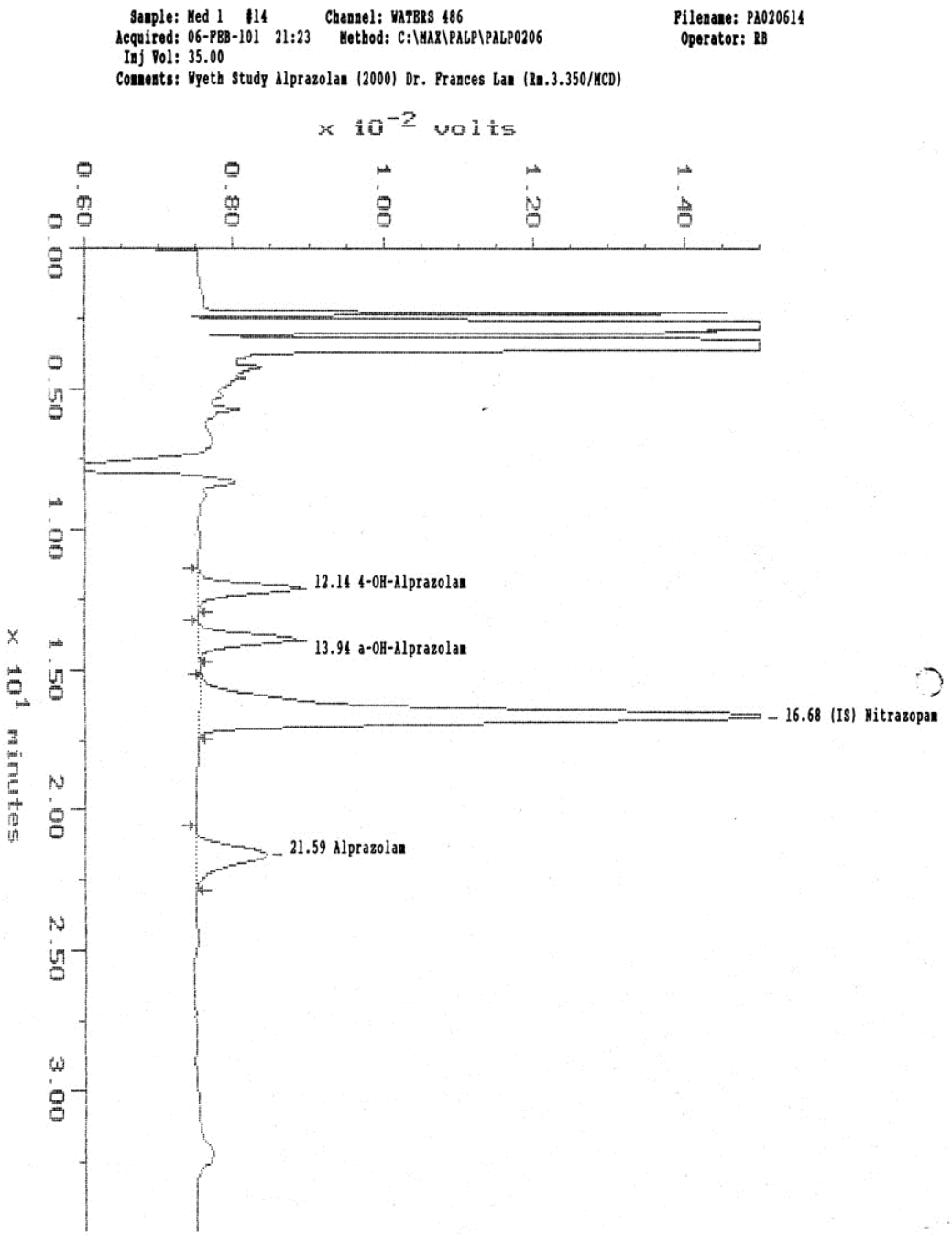


Figure 3.26 HPLC chromatogram of a control sample

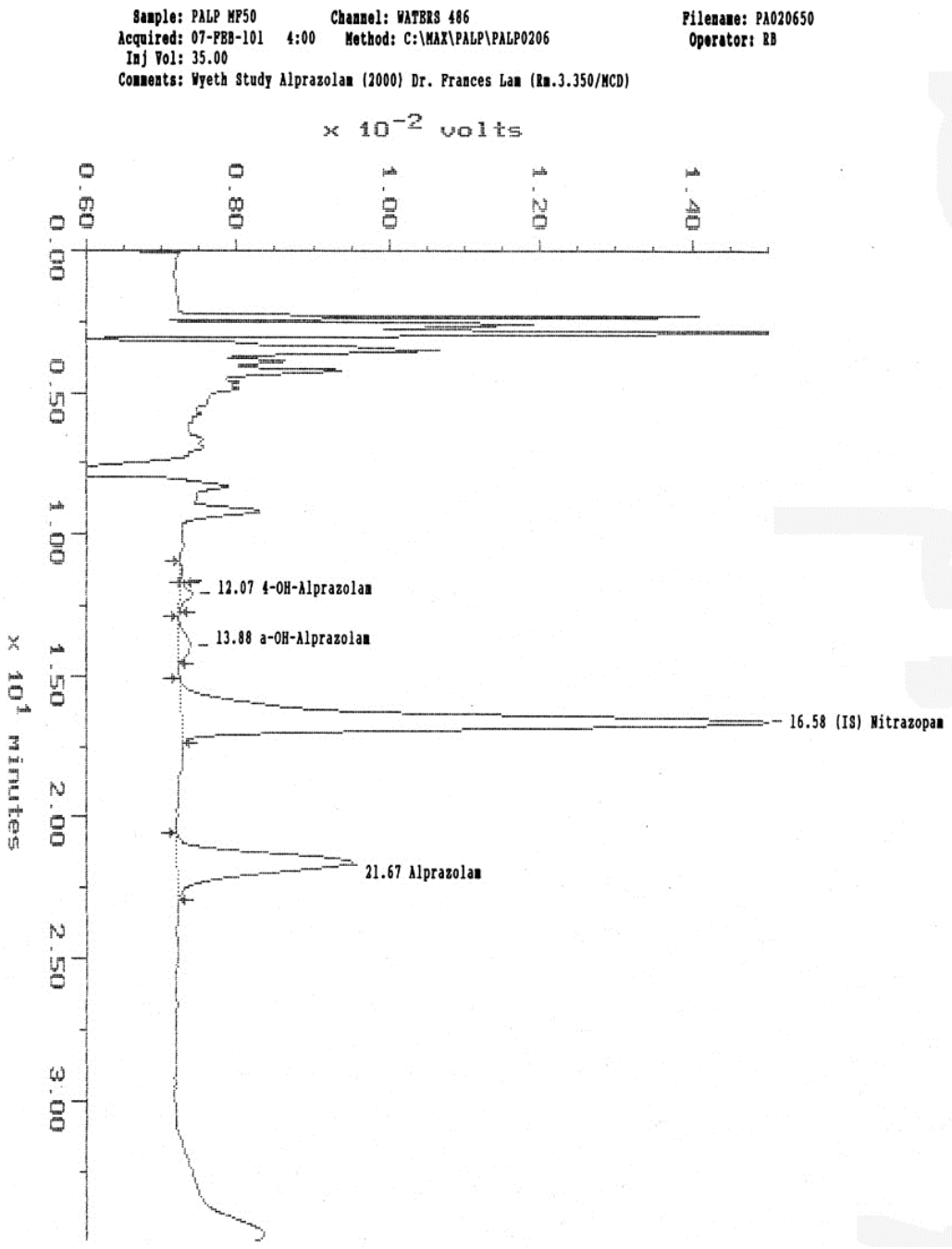


Figure 3.27 HPLC chromatogram of a blood sample collected from a subject

Pharmacokinetic Assessments

As shown in Figure 3.19, equivalent *in vitro* dissolution profiles were obtained from tablets containing different MW types (nominal viscosities) of HPMC (Initial dissolution: f_2 = 91, 2 %average difference). Additionally, *In vitro* dissolution profiles of both tablet formulations remained unchanged for at least 6 months at 40°C/75%RH and 12 months at 25°C/60%RH (f_2 = 67-91, 2-5 %average difference). This indicated that both tablet formulations stored at ambient conditions at the study site remained stable throughout the time period required for *in vivo* clinical study.

Figure 3.28 shows the plots of the mean plasma concentrations of ALP in each tablet formulation over time at different dosing conditions (i.e. fasted and fed states). For all conditions investigated, the mean plasma concentration of ALP (Cp) rapidly increased after an oral administration and then reached the maximum concentration (Cmax). Peak plasma concentrations at all conditions occurred 9 to 17.8 hours after oral administration, for all subjects. After reaching the peak plasma concentrations (Cmax), the Cp of ALP gradually declined, which corresponded to the drug elimination phase. From Figure 3.28, the absorption of ALP was delayed for 3 hours (3 hour lag period), when ALP tablets were taken during the fed state, with the presence of a high fat diet (i.e. 1000 kcal, 50% fat) within the stomach. This was similar to results reported in prior research. Drug absorption was delayed when ALP was taken after a fed state than a fasted state, but total absorption remained unchanged. High fat diets may have a potential for drug-food interactions and may alter drug absorption [United States

Pharmacopeial Convention, 1999; FDA, 1996; Greenblatt and Wright, 1993; Charman, 2000].

Table 3.16 summarizes the pharmacokinetic parameters, including $AUC_{0-\infty}$, Tmax and Cmax, of both tablet formulations in fasted and fed states. For each parameter, the plots of both tablet formulations containing different molecular weight type polymers in fasted and fed states were compared in Figures 3.29, 3.30, and 3.31. The wide range for Tmax from 9.0-17.8 hours was obtained from all conditions investigated. This may due to the small subject size used in the study. However, overall results indicated that the $AUC_{0-\infty}$, Tmax, and Cmax were insignificantly different between two tablet formulations containing different MW types (nominal viscosities) of HPMC (HPMC-K4MP and HPMC-K100LVP) in the fed and fasted states. Therefore, MW types of HPMC did not influence *in vitro* or *in vivo* performance of controlled release tablets.

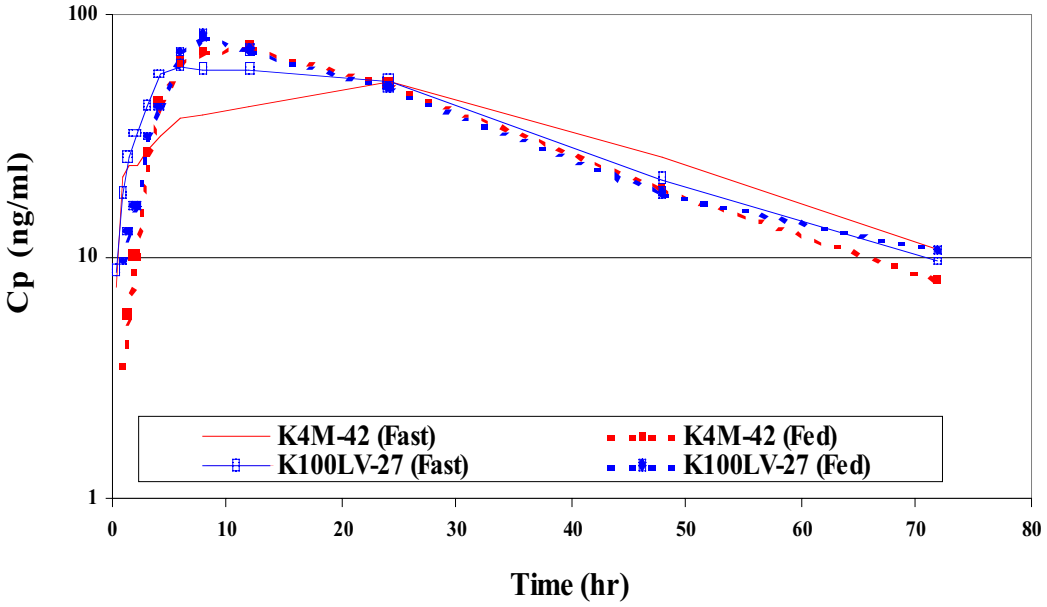


Figure 3.28 Plots of mean plasma concentrations over time of different formulations and dosing conditions

Table 3.16 Pharmacokinetic Parameters in Fasted and Fed States of ALP in Matrix Tablet Formulations Containing Different Molecular Weight Types of HPMC Polymer (i.e. HPMC-K4MP and HPMC-K100LVP)

State	**Fasted**		**Fed**	
Parameters	**K4MP**	**K100LVP**	**K4MP**	**K100LVP**
$AUC_{0-\infty}$ (ng/ml.hr)	2625	2678	2590	2683
P-Value	0.82		0.90	
Tmax (hr)	17.8	9.6	9.0	9.2
P-Value	0.2		0.5	
Cmax (ng/ml)	56.2	69.4	80.4	82.9
P-value	0.28		0.66	

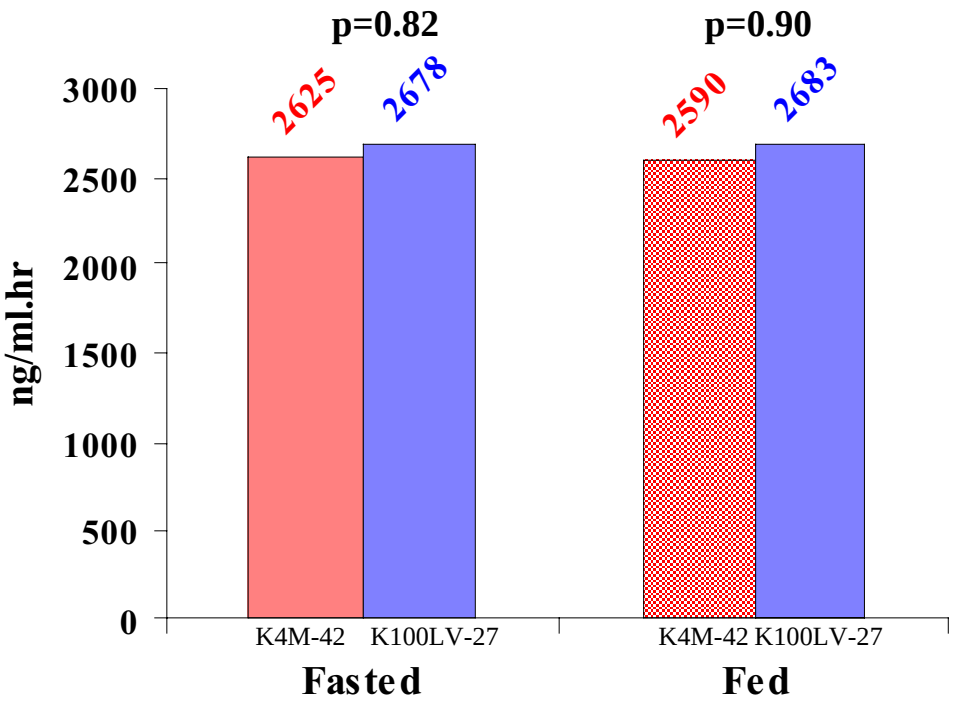


Figure 3.29 $AUC_{0-\infty}$ (ng/ml.hr) in fasted and fed states of ALP in Matrix Tablet Formulations Containing Different Molecular Weight Types of HPMC Polymer (i.e. HPMC-K4MP and HPMC-K100LVP)

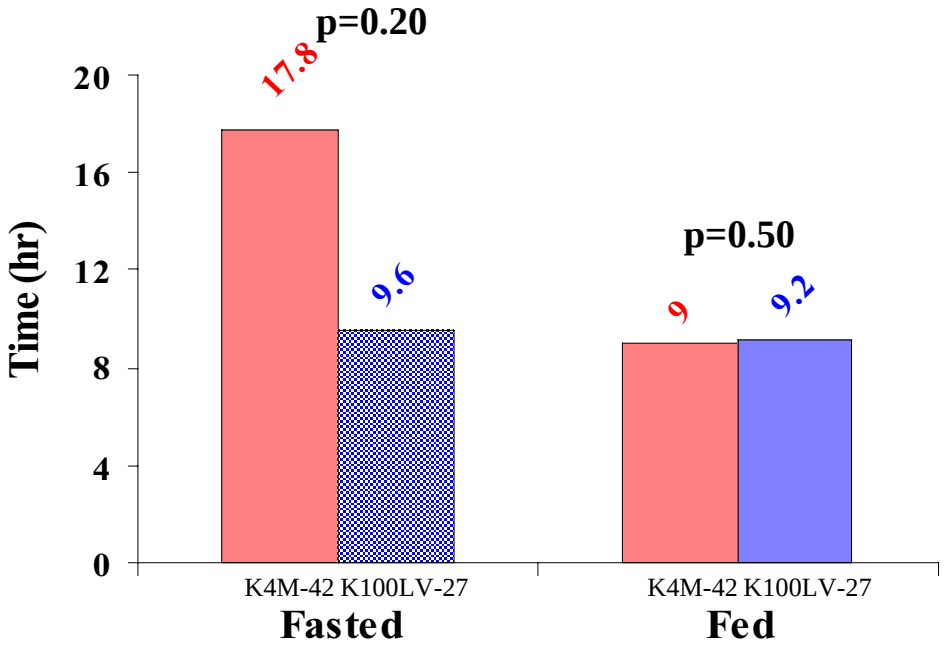


Figure 3.30 Tmax (hr) in fasted and fed states of ALP in Matrix Tablet Formulations Containing Different Molecular Weight Types of HPMC Polymer (i.e. HPMC-K4MP and HPMC-K100LVP)

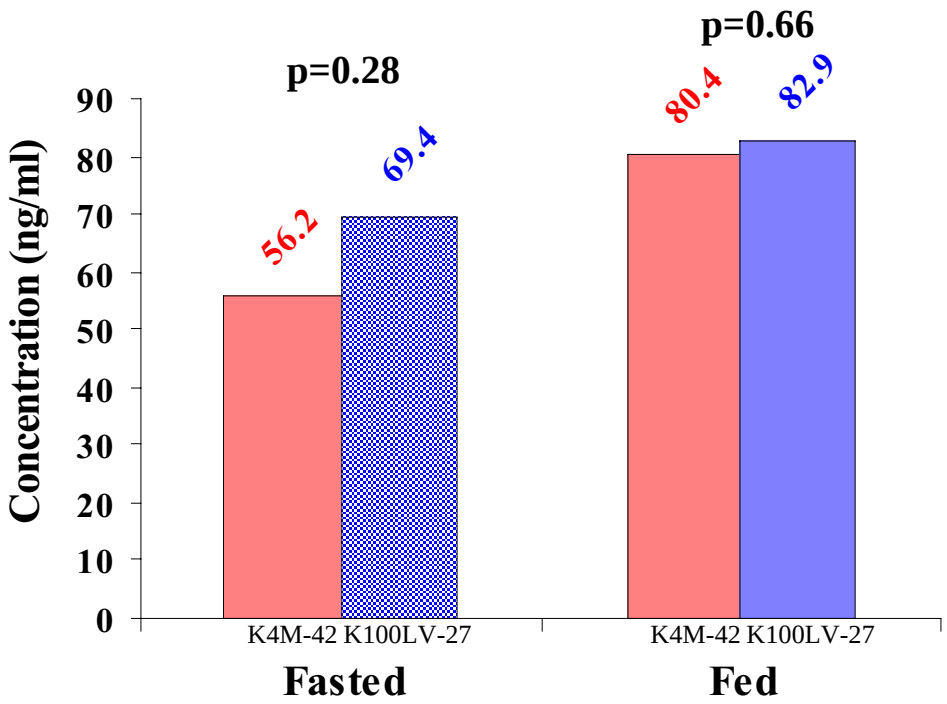


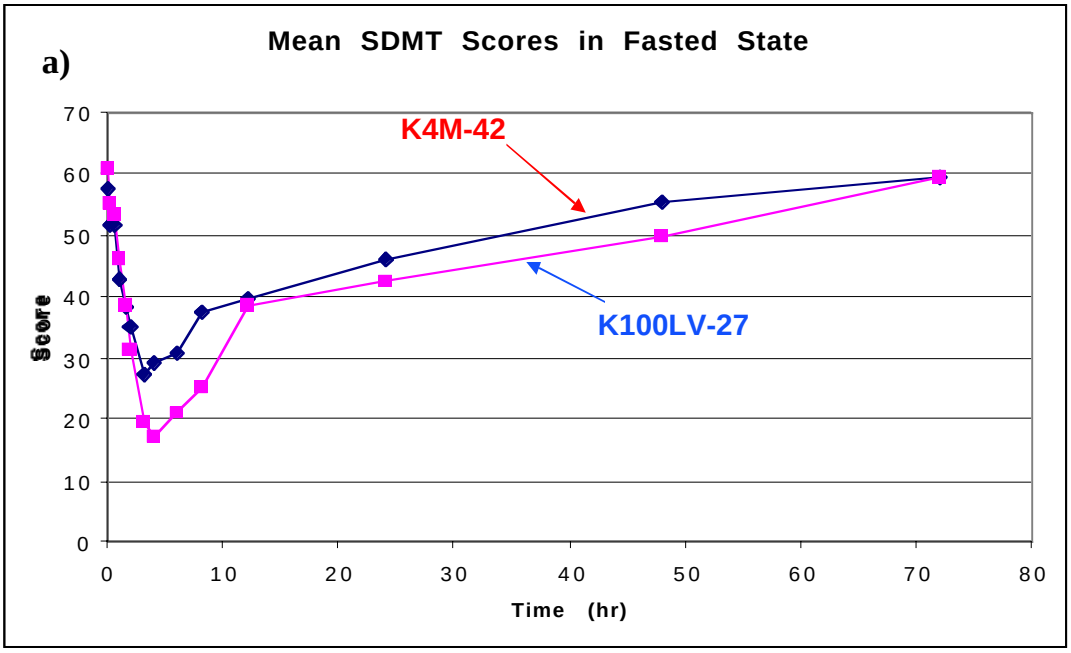
Figure 3.31 Cmax (ng/ml) in fasted and fed states of ALP in Matrix Tablet Formulations Containing Different Molecular Weight Types of HPMC Polymer (i.e. HPMC-K4MP and HPMC-K100LVP)

Pharmacodynamic Assessments

Pharmacodynamic assessments obtained from each blood sample included Visual Analog Scale (VAS) for wakefulness and Symbol Digital Matching Test (SDMT), which is matching time over 90 seconds where different forms were used for each time period,. For SDMT, the symbol digit substitution test assessed concentration and psychomotor speed, where the number correct in 90 seconds was recorded (See Appendix A for SDMT worksheet used during the study).

Pharmacodynamic assessments during fasted and fed states are shown in Figures 3.32a and 3.32b, respectively. During the fasted state, although the formulation containing HPMC-K100LVP polymer produced slightly greater sedation at 4 hours, but the difference was not statistically significant. The Tmax for effect was slightly earlier with the formulation containing HPMC-K4MP polymer (3 vs. 4 hours). Large SD in SDMT scores was seen for both formulations containing different MW types of HPMC polymer from hour 1 through hour 12. Additionally, at hour 4, the SD was approximately 2/3 of the mean value (24.2±16.5). The rate of recovery was similar between the two formulations containing different MW types of HPMC polymer.

During the fed state, no significant differences were observed in onset, peak effect or duration for sedation rating when compared the formulation containing HPMC-K4MP with the formulation containing HPMC-K100LVP. The presence of a high fat meal (i.e. 1000 kcal, 50% fat) delayed the absorption of ALP and lengthened the time of maximal sedation, based on the SDMT scores, compared with the fasted state.



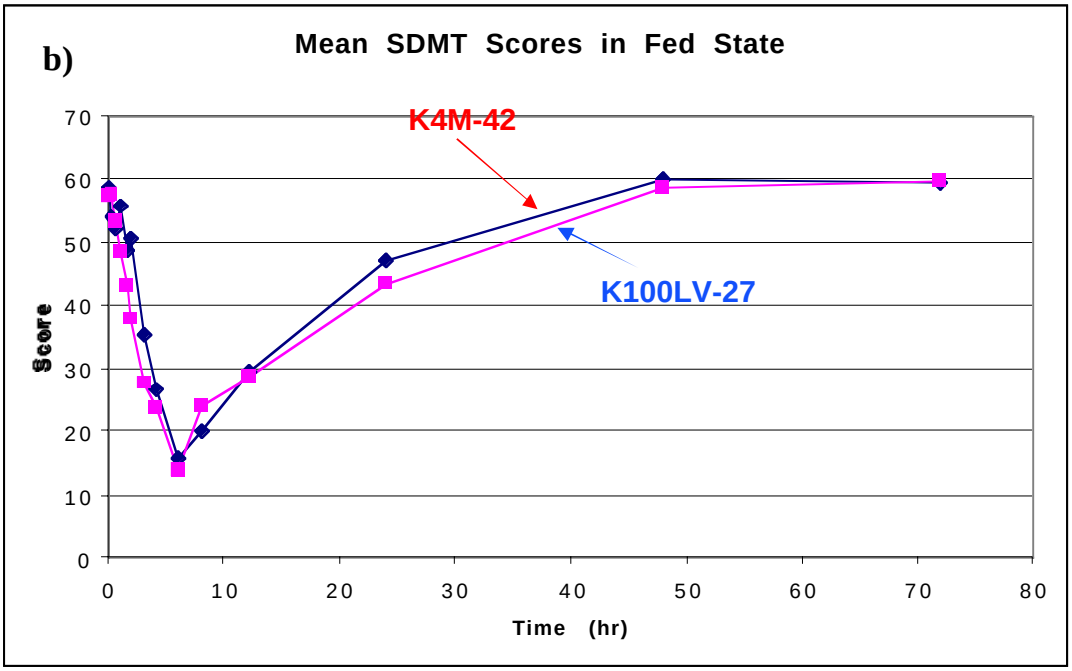


Figure 3.32 Mean SDMT scores for HPMC-K4MP and HPMC-K100LVP polymers in a) fasted state and b) fed state

Figure 3.33 displays the reverse relationship between SDMT scores and the mean plasma concentrations of ALP (Cp). The Cp of ALP rapidly increased after oral administration and then reached the maximum concentration (Cmax) at Tmax of 9 hours (for subject 2). The SDMT scores decreased dramatically, when the Cp of ALP approached the Cmax. This was due to high degree of sedation that occurred during first 9 hours following oral administration. After 9 hours, the Cp of ALP gradually decreased, while the SDMT scores of the subject were improved due to less degree of sedation. In other words, time-dependent effects occurred during the oral administration of ALP tablets. Specifically, less sedation at the same or greater plasma concentrations later in time was observed.

Figure 3.34 shows the counter-clockwise hysteresis that was apparent in both fasted and fed states. This also indicated that acute tolerance occurred. Additionally, a lag phase for onset of sedation was observed in the fed state.

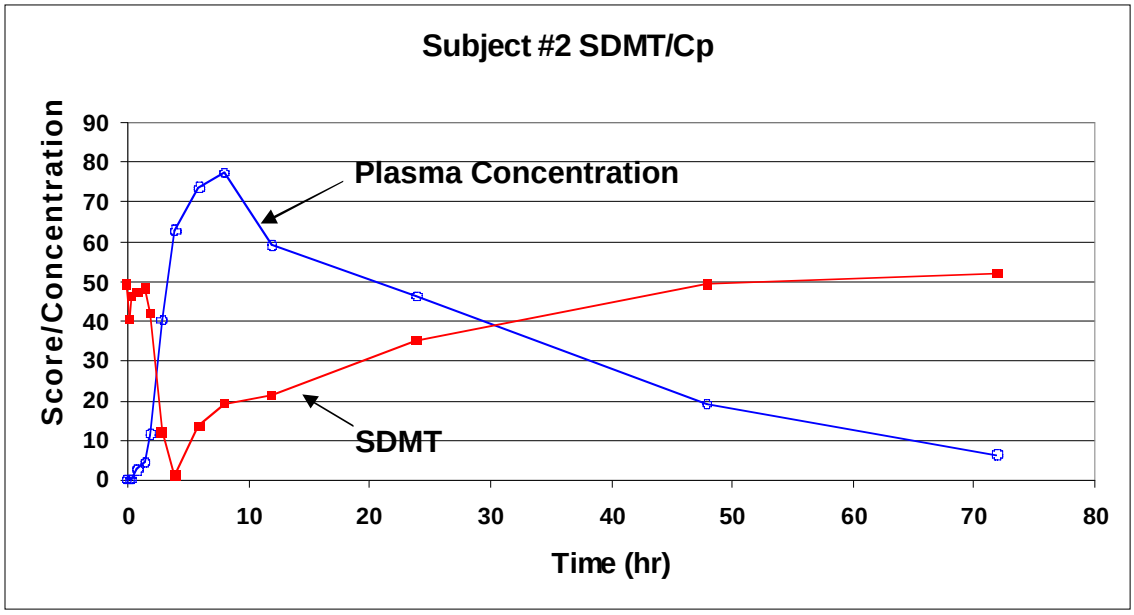


Figure 3.33 Relationship between SDMT scores and plasma concentration of ALP in each subject

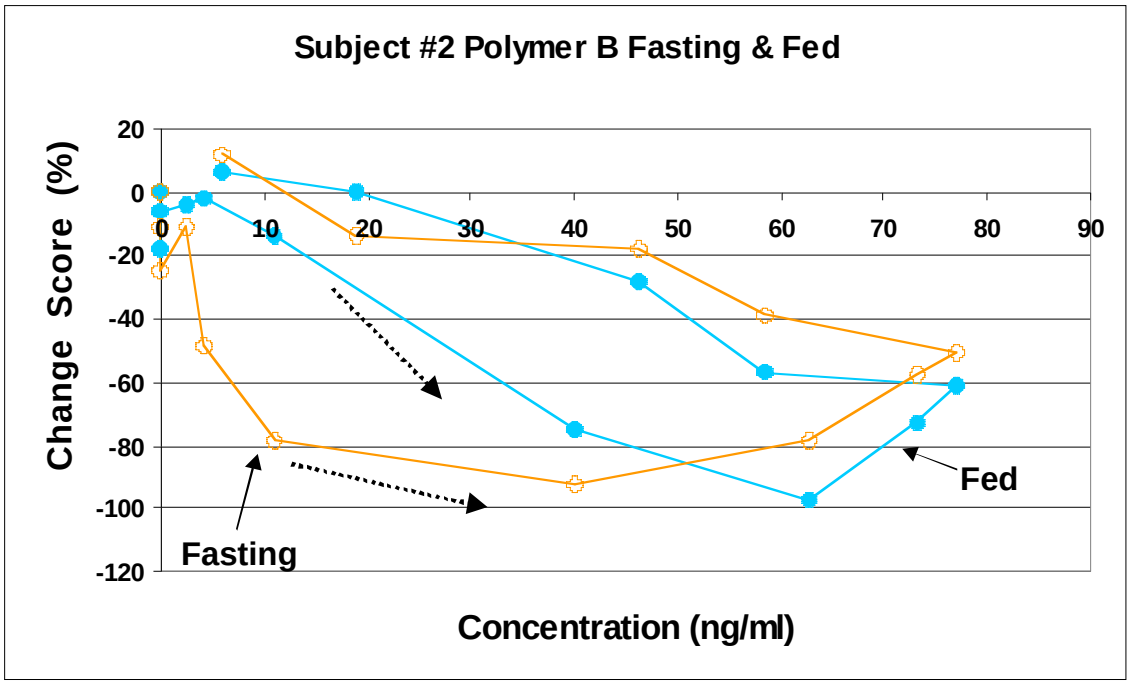


Figure 3.34 Counter-clockwise hysteresis of the formulation containing HPMC-K100LVP polymer (K100LV-27 formulation) in fasted and fed states

3.2 MULTIPARTICULATE SYSTEM (FILM-COATED BEADS)

Influence of processing parameters on drug release from cellulose ether coated matrix bead formulations.

3.2.1 Uncoated Matrix Beads

Uncoated matrix beads of CPM and theophylline were prepared by an extrusion/spheronization technique using purified water as a binder. Dried beads sized between 16 and 20 mesh were collected for further coating. Dissolution of each active drug from uncoated beads was determined using the appropriate media as previously described in section 2.2.2, to ensure an immediate release pattern. As is shown in Figure 3.35, the release profile of each uncoated bead formulation displays an immediate release behavior. Specifically, the release of CPM from uncoated beads in purified water was nearly 100% within the first 20 minutes, whereas the release of theophylline from uncoated beads in buffer pH 3.0 was nearly 100% within 60 minutes. However, the release of theophylline from uncoated beads was slower than the release of CPM, even though the matrix beads contained the same excipient, microcrystalline cellulose. This was due to the differences in physical properties between active drug substances, such as their aqueous solubilities as well as the level of drug loading within each type of bead formulation (i.e. 15% CPM loading and 40% theophylline loading). Uncoated matrix beads prepared with microcrystalline cellulose displayed a strong physical structure that did not easily break or became damaged during fluidized bed coating.

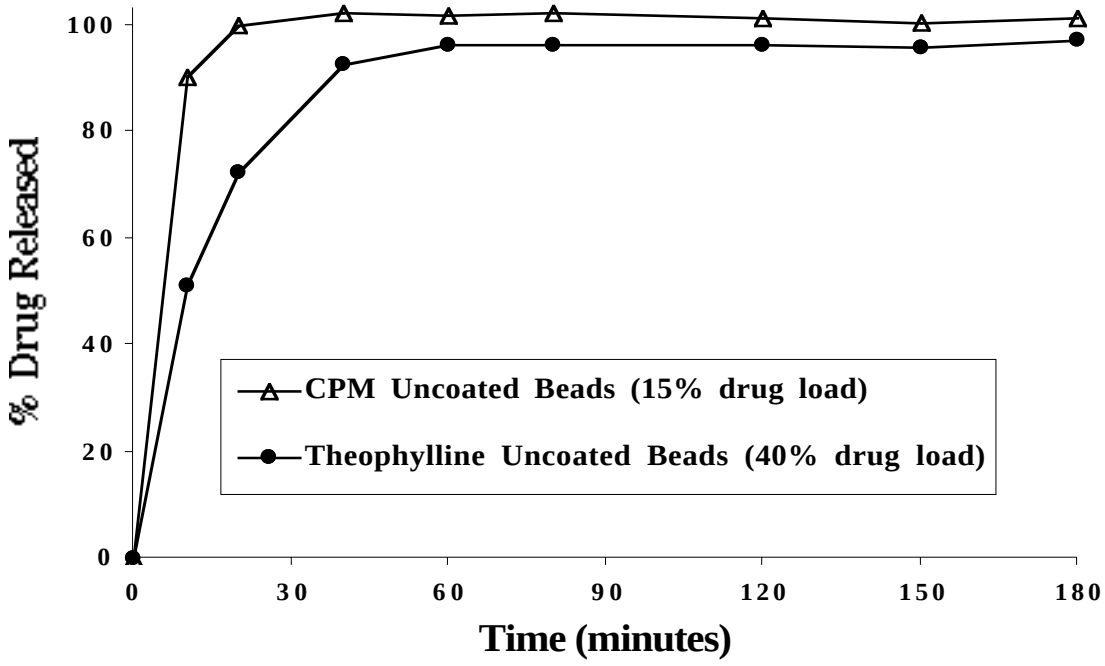


Figure 3.35 Dissolution profiles of uncoated beads

3.2.2 Coated Matrix Beads

Uncoated beads of each drug type were utilized for different coating studies. The influence of processing parameters, including curing conditions, plasticization, and the incorporation of a water-soluble additive, on drug release from EC coated matrix bead formulations was investigated. Dissolution study, dissolution profile comparisons using similarity factor (f_2), and SEM were used as tools during this investigation.

This research study was divided into three sections in order to investigate the impact of each processing parameter used during EC coating on drug release from the matrix beads.

3.2.2.1 Curing Conditions

Following the coating process, EC coated beads containing either a water-soluble drug, CPM, or a slightly water-soluble drug, theophylline, were oven-cured at different temperatures (40˚C, 60˚C, or 80˚C) for up to 72 hours in order to determine the optimum conditions for complete film coalescence and to stabilize the amount of drug release. Bead samples were taken at different curing times and analyzed using dissolution studies. Generally, the curing process results in a reduction of drug release when compared to drug release from uncured dosage forms [Lippold et al., 1989; Gilligan and Li Wan Po, 1991; Bodmeier and Paeratakul, 1991a; Schmidt and Niemann, 1993; Hutchings et al., 1994a; Bodmeier and Paeratakul, 1994; Guma et al., 1997; Amighi and Moes, 1997; Sakr et al., 1998; Frohoff-Hulsmann et al., 1999a].

For CPM coated beads, a higher percent weight gain or coating level, up to 36%, is necessary to achieve sustained release, because of its high aqueous solubility. Figure 3.36 shows the effect of different curing times at 60˚C on the amount of CPM release from beads coated with an EC dispersion (35% theoretical coating level), plasticized with 30%w/w water miscible plasticizer, TEC, for 2 hours. The rate of CPM release was slower when coated beads were exposed to 60˚C for at least 2 hours. However, the slowest rate of drug release was obtained from coated beads cured for 12 hours at 60˚C, indicating more complete film coalescence at this condition. When comparing dissolution profiles of coated beads cured for 2 and 12 hours at 60˚C, the amount of CPM release was significantly reduced for the samples cured for 12 hours with an f_2 of 27 (greater than 20% average difference between both profiles). Interestingly, coated beads cured for 18 hours at 60˚C showed slightly higher drug release when compared to coated beads cured for 12 hours at the same temperature. Similar results obtained from beads cured for various times at 80˚C are shown in Figure 3.37. The slowest drug release rate was obtained from coated beads cured for 1 hour at 80˚C. However, the amount of CPM release tended to increase when coated beads were exposed to a longer curing time of 12 hours. When comparing the dissolution profiles of coated beads cured at 60˚C and 80˚C for 12 hours in Figure 3.38, the curing temperature of 80˚C was more efficient for film coalescence, resulting in a reduction in the amount of drug release from the coated beads. When a higher curing temperature used, the time to achieve complete film formation is shorter because the high temperature facilitates the coalescence of the film. In other

words, the curing rates of coated beads are higher with higher storage temperatures. Figure 3.39 shows the influence of the coating levels on the amount of CPM release from the same coated beads formulation cured at 80˚C for 2 hours. As expected, the amount of CPM release was reduced when the higher coating level was applied to the uncoated beads. The theoretical coating level of 24% was sufficient to obtain a sustained release profile of CPM coated beads. However, this only applies when coated beads are cured at 80˚C for 2 hours. When an efficient curing condition is used (80˚C for 2 hours in this case), the amount of coating solution and time can be significantly reduced, while a sustained release profile is maintained. When the coating level was increased from 28 to 30%, both dissolution profiles were similar with an f_2 of 78 (5% average difference). The maximum capability of the coating system to sustain the drug release may be reached at a 28% theoretical coating level. Coating levels higher than 28% were not necessary to provide more sustained release of CPM.

Beads that were coated with the EC dispersion (35% theoretical coating level) plasticized with 24 %w/w water insoluble plasticizer, AMG, for 24 hours, showed a reduction in the amount of CPM release when the coated beads were cured for at least 2 hours at 60˚C (Figure 3.40). The slowest release rate of CPM was obtained from coated beads cured for 6 hours. However, if coated beads were cured for 24 hours at the same temperature, the amount of CPM release was significantly increased. Similar to the previous system, a longer curing time does not show any benefits to facilitate film formation process.

Figure 3.41 shows the influence of coating level and curing time at 60˚C on the release of CPM from matrix beads coated with an EC dispersion (20-35% theoretical coating levels), plasticized with 24 %w/w water insoluble plasticizer, DBS, for 24 hours. Similar to the systems previously described, the amount of CPM release was delayed when the higher coating level was applied to the uncoated beads. Additionally, the coated beads cured for 24 hours at 60˚C displayed higher amounts of CPM release compared to coated beads cured for only 6 hours at the same temperature. However, this result is more pronounced when a lower coating level is applied. Specifically, the amount of CPM release was significantly increased when coated beads at 20% weight gain were cured for 24 hours, whereas the amount of drug release was slightly increased when coated beads at 35% weight gain were cured for 24 hours. Similar results were observed in all systems investigated, even though different plasticizers, plasticization times, and coating levels were used in each formulation. These findings were further investigated in studies to follow.

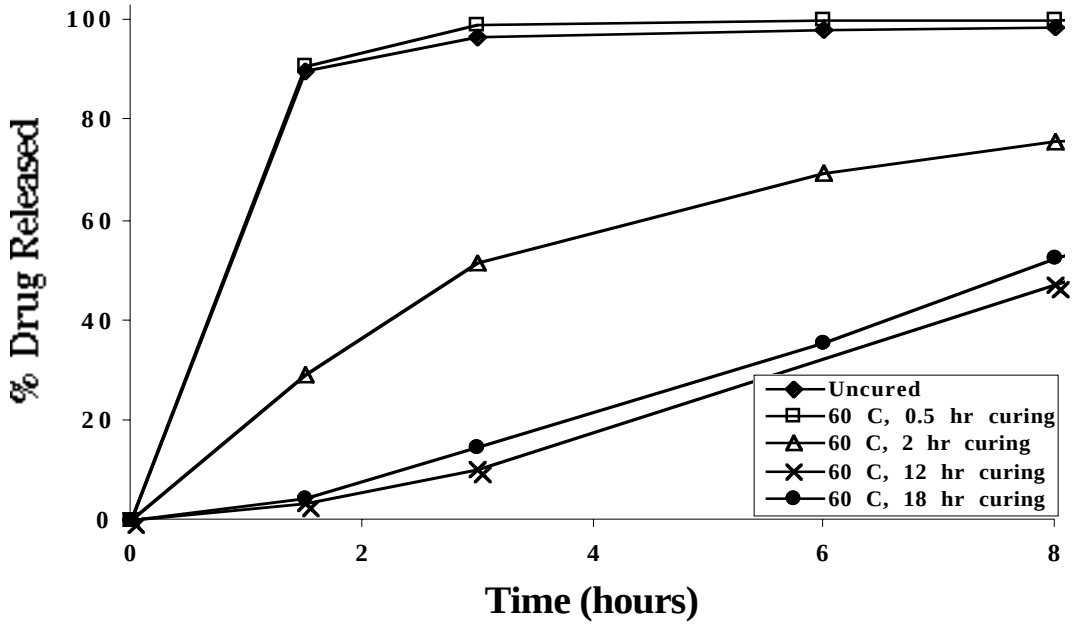


Figure 3.36 Influence of curing time at 60˚C on the release of CPM from matrix beads coated with EC dispersion plasticized with 30 %w/w of TEC for 2 hours (35 % theoretical weight gain)

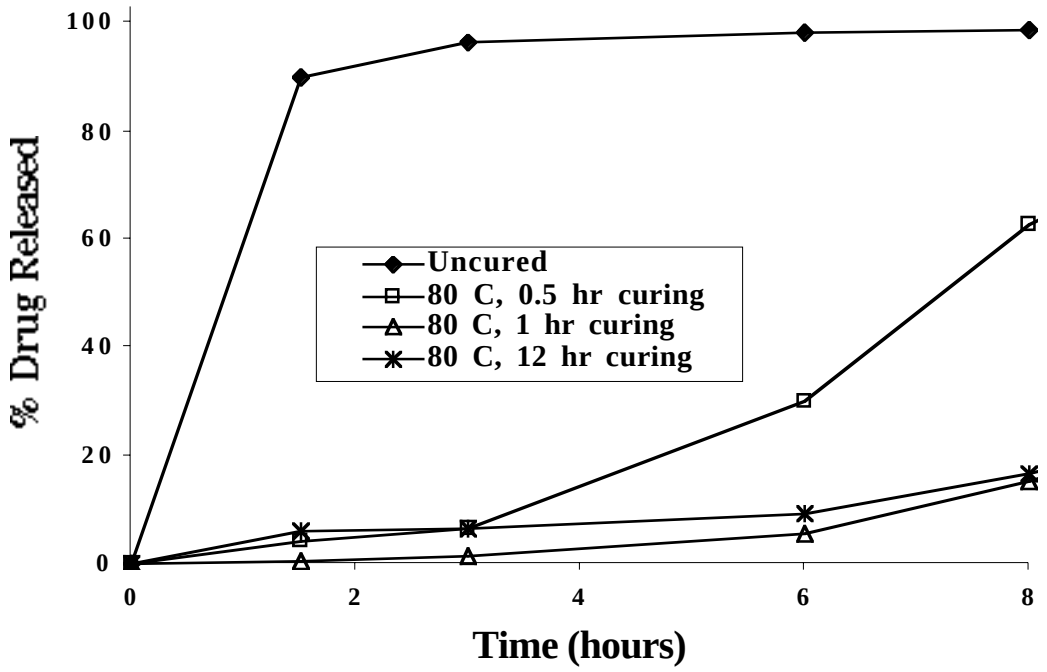


Figure 3.37 Influence of curing time at 80˚C on the release of CPM from matrix beads coated with EC dispersion plasticized with 30 %w/w of TEC for 2 hours (35 % theoretical weight gain)

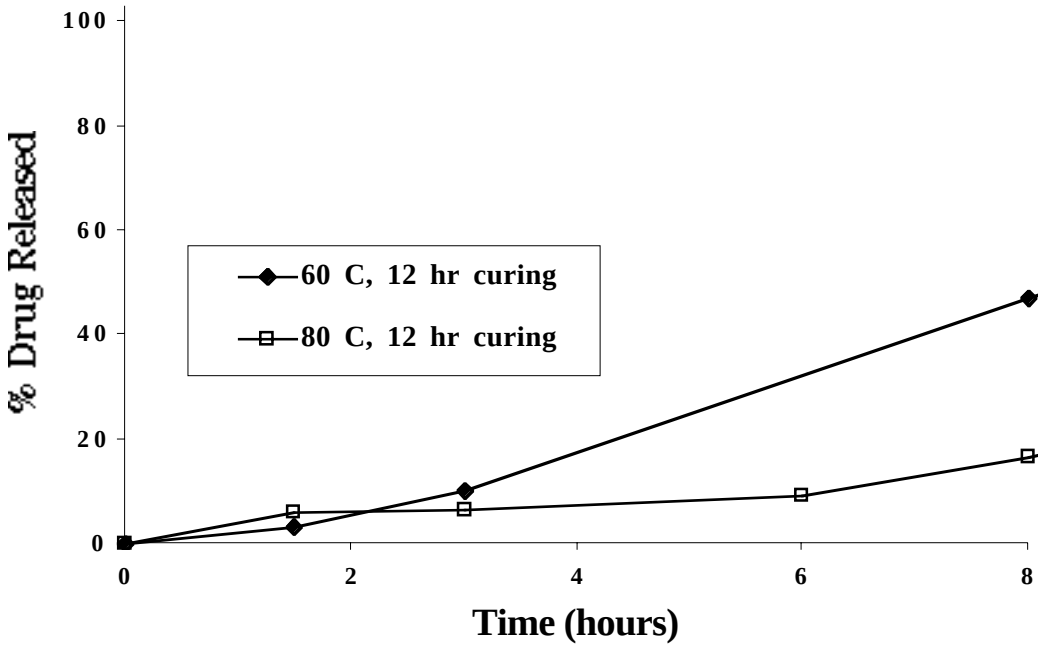


Figure 3.38 Influence of curing temperature on the release of CPM from matrix beads coated with EC dispersion plasticized with 30 %w/w of TEC for 2 hours (35 % theoretical weight gain)

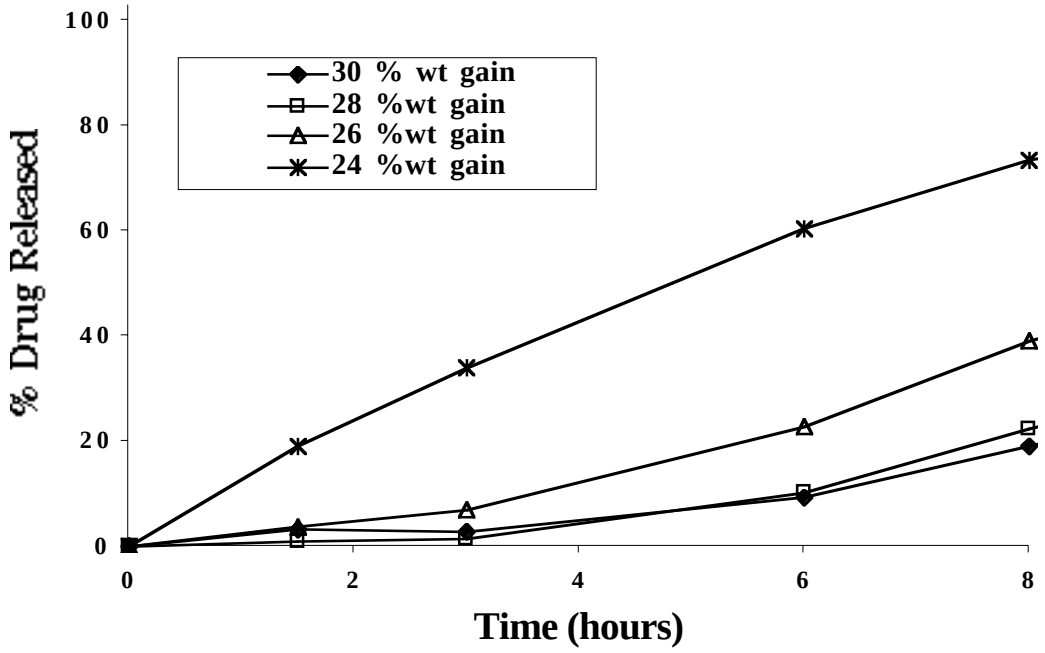


Figure 3.39 Influence of coating level (percent weight gain) on the release of CPM from matrix beads coated with EC dispersion plasticized with 30 %w/w of TEC for 2 hours and cured at 80˚C for 2 hours

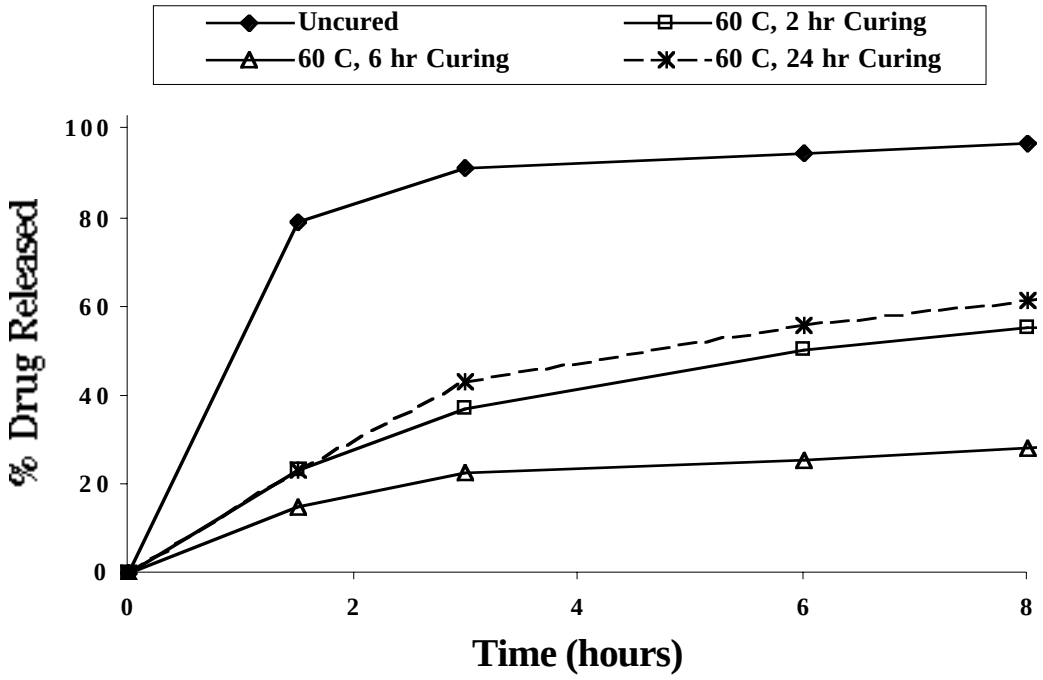


Figure 3.40 Influence of curing time at 60˚C on the release of CPM from matrix beads coated with EC dispersion plasticized with 24 %w/w of AMG for 24 hours (35 % theoretical weight gain)

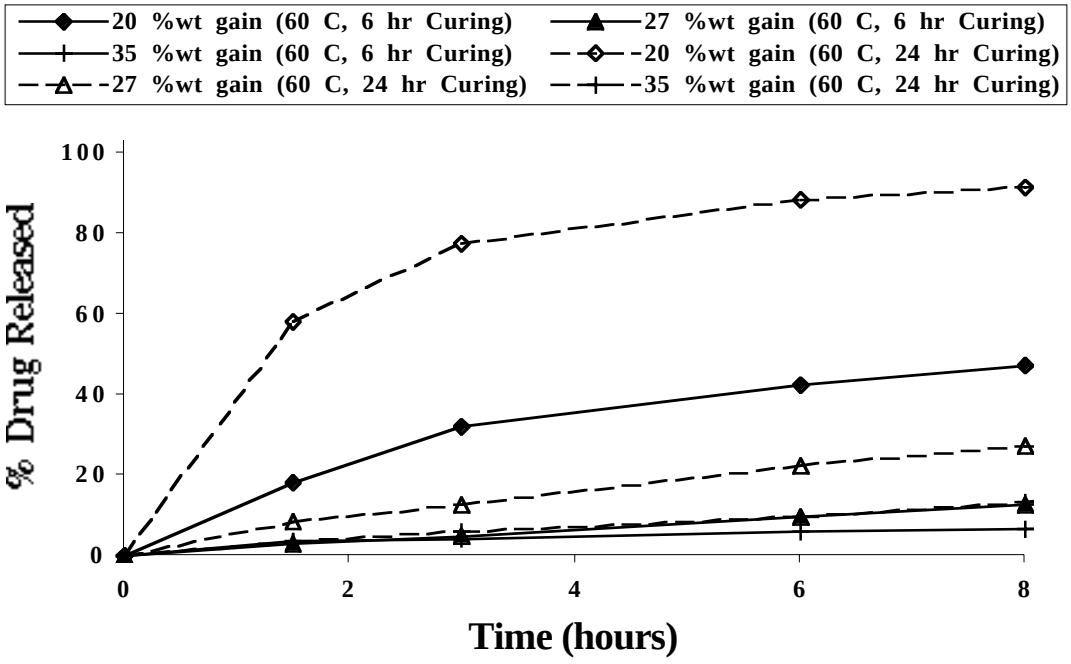


Figure 3.41 Influence of curing time at 60˚C on the release of CPM from matrix beads coated with EC dispersion plasticized with 24 %w/w of DBS for 24 hours (20-35 % theoretical weight gain)

Following the studies on curing time and temperature, further studies were designed to elucidate the cause of increased drug release when coated beads were cured at a longer time. In order to slow down the amount of drug release from beads cured at longer times, a subcoating solution of HPMC E5, plasticized with 2 %w/w PEG 400 for 2 hours, was applied to the uncoated CPM beads at a 2% theoretical coating level prior to the application of the EC dispersion. Application of HPMC subcoat should not have an impact on the amount of drug release from the beads since it is only used as a protective agent. Figure 3.42 shows the comparison of release profiles of uncoated and subcoated beads. Both release profiles were nearly identical, indicating an immediate release behavior. Additionally, the dissolution profiles of CPM coated beads at a 35% theoretical weight gain, with and without a 2 %w/w HPMC-E5 subcoat, were almost identical (Figure 3.43). The subcoating application had no impact on drug release from the final coated beads.

Figure 3.44 shows the influence of curing time at 60˚C on the release of CPM from matrix coated beads with 2% weight gain of subcoating solution, and 36% weight gain of EC dispersion, plasticized with 30 %w/w TEC for 2 hours. The amount of CPM release was delayed when coated beads were cured at 60˚C for a longer time up to 12 hours. If beads were cured for longer than 12 hours, the amount of drug release was increased. These results were similar to the previous studies of the coated beads without a protective subcoating application. Similarly, the rate of CPM release was slowest when coated beads were cured at 60˚C for 12 hours.

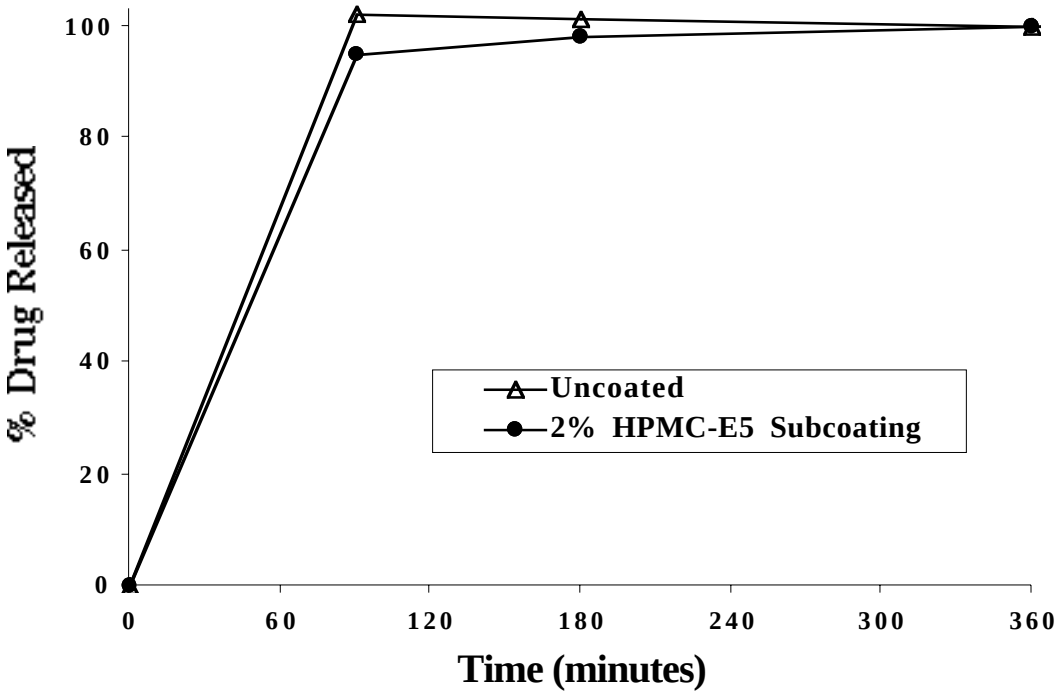


Figure 3.42 Dissolution profiles of CPM uncoated beads and subcoated beads (coated with 7.5 %w/w of HPMC-E5 plasticized with 2 %w/w of PEG 400 for 30 minutes at 2 % coating level)

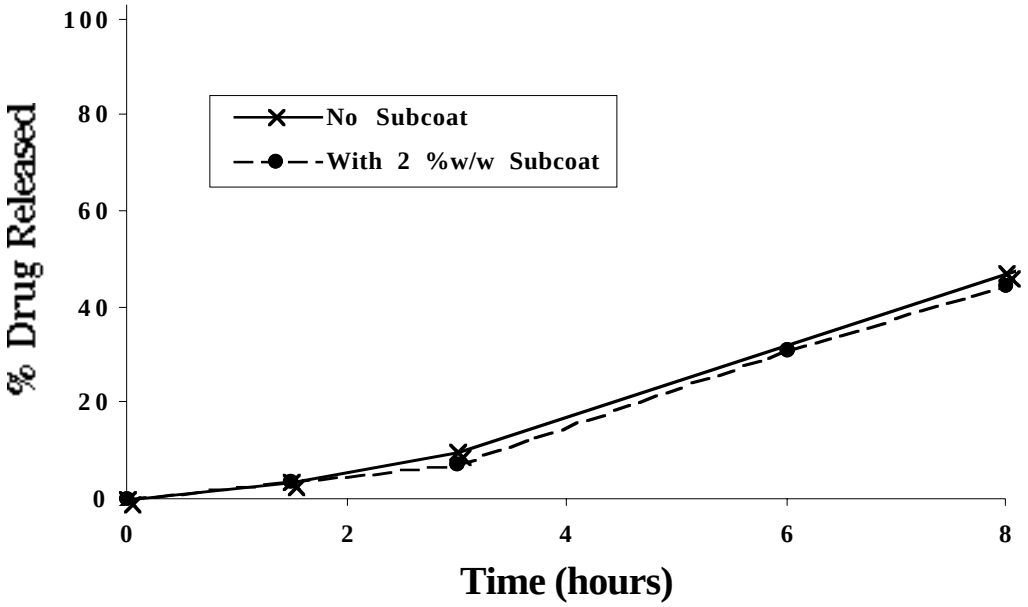


Figure 3.43 Comparison of dissolution profiles of CPM beads without and with 2 %w/w subcoat (7.5 %w/w of HPMC-E5 plasticized with 2 %w/w of PEG 400 for 30 minutes) prior to EC dispersion (plasticized with 30 %w/w of TEC for 2 hours) at 35 % theoretical weight gain and cured at 60˚C for 12 hours.

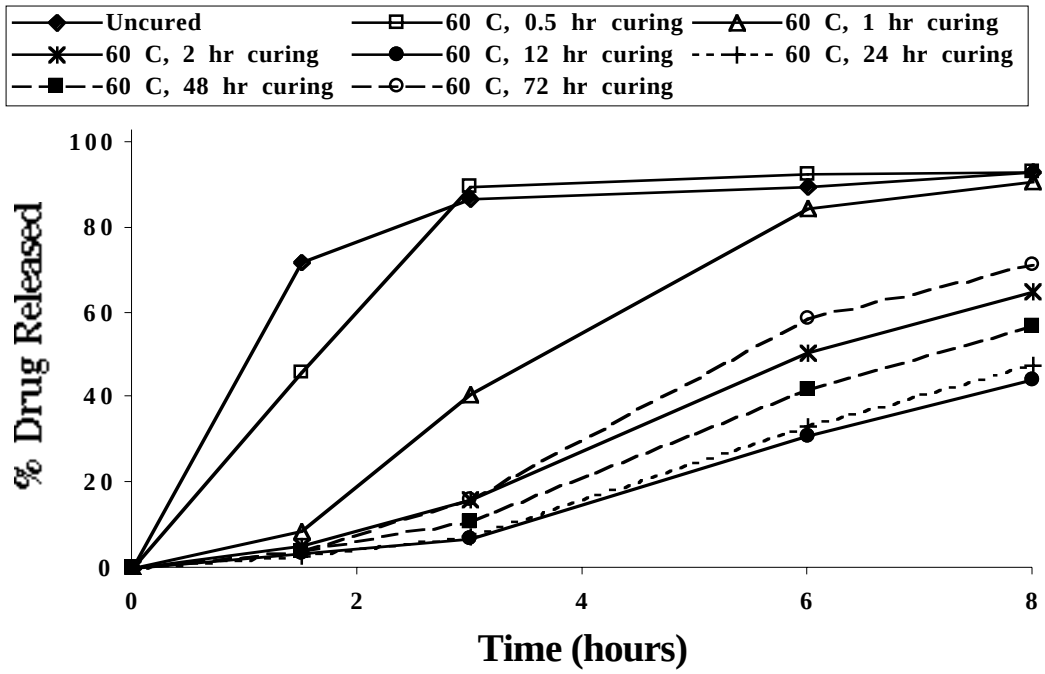


Figure 3.44 Influence of curing time at 60˚C on the release of CPM from matrix beads coated with 2% HPMC-E5 subcoating and EC dispersion plasticized with 30 %w/w of TEC for 2 hours (36 % theoretical weight gain)

The influence of curing conditions on the release of CPM from the same coated beads formulation (36% coating level) is shown in Figure 3.45. Two curing temperatures, 40˚C and 60˚C, were used to cure the EC coated beads with an HPMC-E5 subcoat at different curing times. At 40˚C, a longer curing time is necessary to complete the film formation of the coated beads. However, the amount of drug release from the coated beads cured at 40˚C from 24 to 72 hours remains unchanged. The release of CPM was not sustained when cured at 40˚C, even though a longer curing time was used. This indicates that the completion of film coalescence is a function of both curing temperature and curing time. The curing temperature of 40˚C, which is close to the bed temperature during the coating process, is not sufficient to complete film coalescence of the EC coated beads. Furthermore, this temperature is too close to the glass transition temperature of the plasticized EC. Generally, the optimum curing temperature should be higher than the glass transition temperature of the polymeric material to accelerate the film formation process and to avoid aging problems of the coated products [Ghebre-Sellassie et al., 1988; Lippold et al., 1989; Gilligan and Li Wan Po, 1991; Bodmeier and Paeratakul, 1991a; Wesseling and Bodmeier, 1999b]. At 60˚C curing, the slowest rate of CPM release from the EC coated beads with an HPMC-E5 subcoat was obtained when beads were cured for 12 hours. This is similar to previous results in other systems. In another words, complete film coalescence was obtained when coated beads were cured at 60˚C for 12 hours.

Similar to the 36% theoretical coating level, an increase in the amount of CPM release was observed from beads coated with the EC dispersion at different

levels (with 2% HPMC-E5 subcoat) and cured at 60˚C for 24 hours (Figure 3.46). However, this result was less pronounced at higher coating levels. In this coating system, at least a 24% theoretical coating level was necessary to obtain a sustained release profile of CPM.

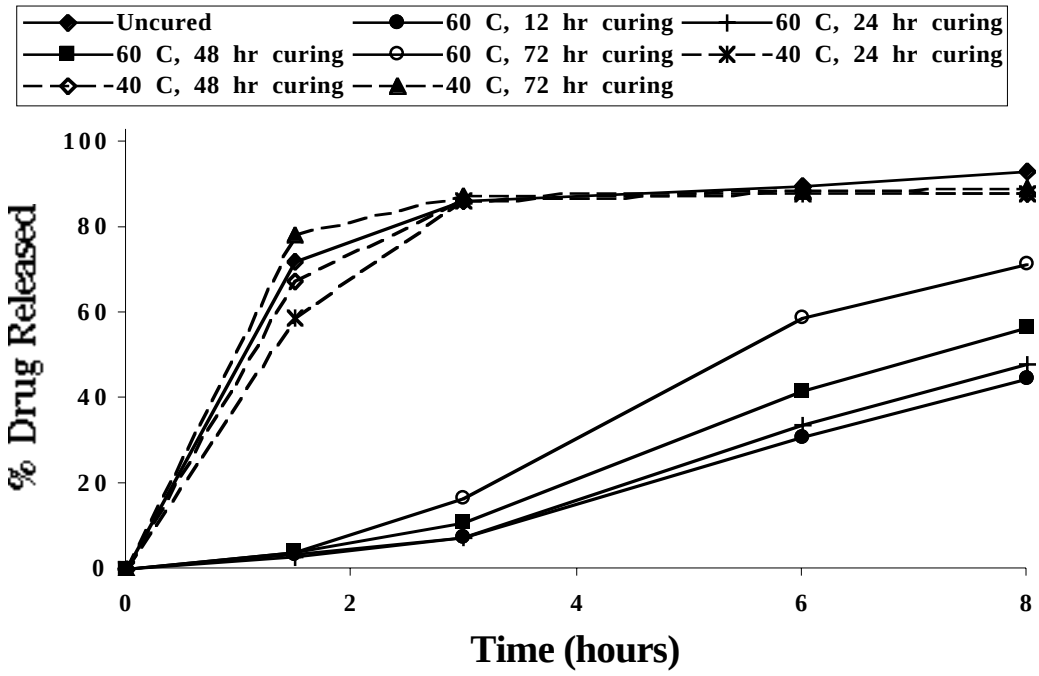


Figure 3.45 Influence of curing conditions on the release of CPM from matrix beads coated with 2% HPMC-E5 subcoating and EC dispersion plasticized with 30 %w/w of TEC for 2 hours (36 % theoretical weight gain)

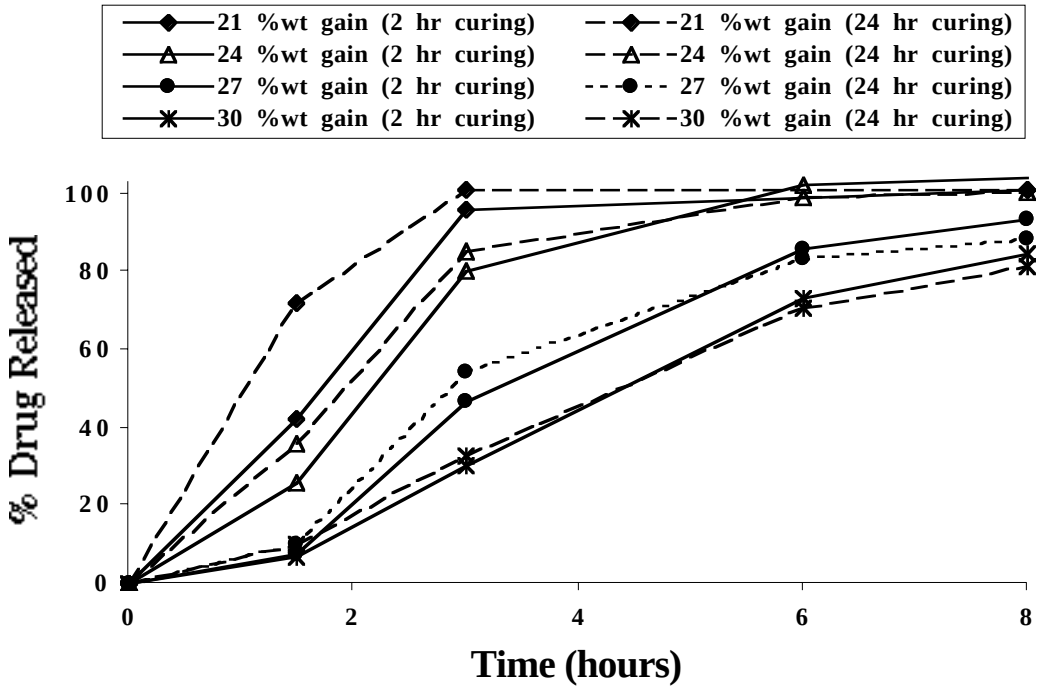


Figure 3.46 Influence of curing time at 60˚C on the release of CPM from matrix beads coated with 2% HPMC-E5 subcoating and EC dispersion plasticized with 30 %w/w of TEC for 2 hours (21-30 % theoretical weight gain)

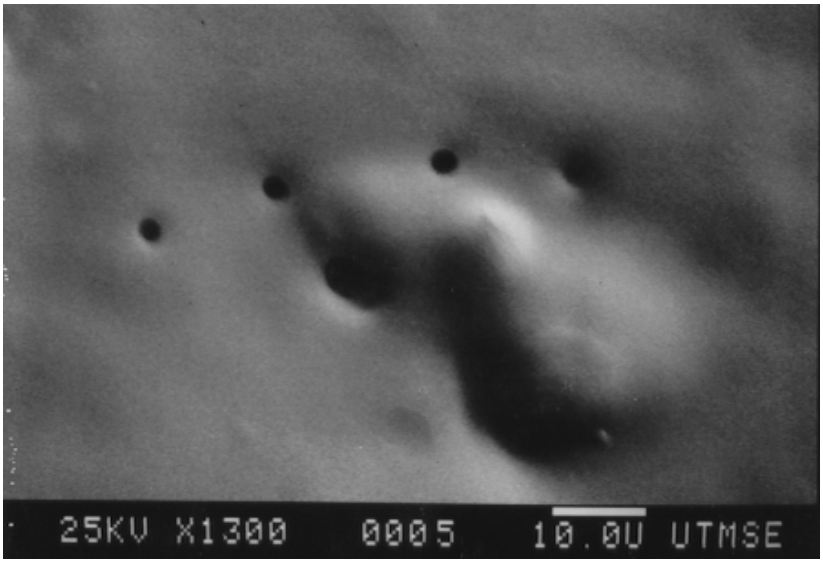
SEM is an effective tool for evaluating film coatings and revealing the surface morphology of the beads [Mehta and Jones, 1985]. SEM micrographs shown in Figure 3.47 compare the surface morphology of beads coated with EC dispersion at 35% weight gain and cured at 60˚C for 24 hours, with and without an HPMC-E5 subcoat. The surface of the coated beads without an HPMC-E5 subcoat is smoother, but more porous than the surface of the coated beads with an HPMC-E5 subcoat. Pores on the surface of the beads could be the result of the high aqueous solubility of CPM such that it could leach from the matrix core. When uncoated beads were coated with HPMC-E5, many of those pores were filled with the subcoating solution. However, these pores may be responsible for the faster dissolution obtained from the coated beads, with and without subcoating, cured at 60˚C for longer than 12 hours.

The surface morphology of CPM beads, coated with a 2% HPMC-E5 subcoat and 36% EC dispersion followed by curing at 60˚C from 0 (uncured) to 72 hours, is shown in Figure 3.48. The surface of coated beads was rough, especially when the coated beads were cured for short periods of time. Even though the coated film became smoother and more completely coalesced when cured for longer periods of time (48 and 72 hours), a higher number of pores or film disruptions were observed (Figures 3.48 and 3.49). The disruption of the coated film caused a faster release of the CPM from the coated beads. When comparing between the SEM micrographs in Figure 3.48 and the release profiles of CPM from the coated beads shown in Figure 3.44, the results suggested that the

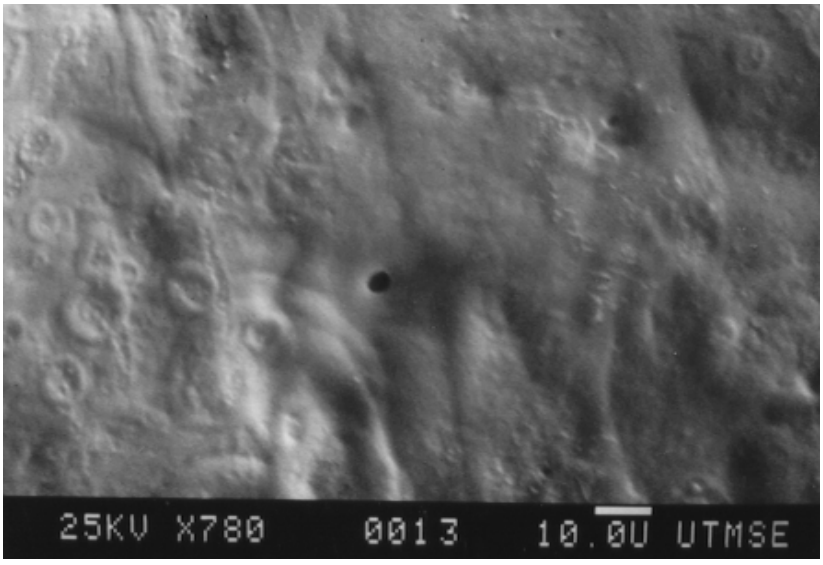
optimum curing condition without film disruption for CPM coated beads should be 60˚C for 12 hours.

Results indicate that an additional application of HPMC-E5 subcoat does not help by slowing down the amount of drug release from beads cured at longer periods of time. The influence of curing conditions on CPM release from the coated beads is independent of coating level and subcoating application.

In the following study, the influence of different drug type on the curing conditions was investigated. Theophylline anhydrous was selected as a lipophilic model drug, which had a different aqueous solubility when compared to CPM in the previous study.

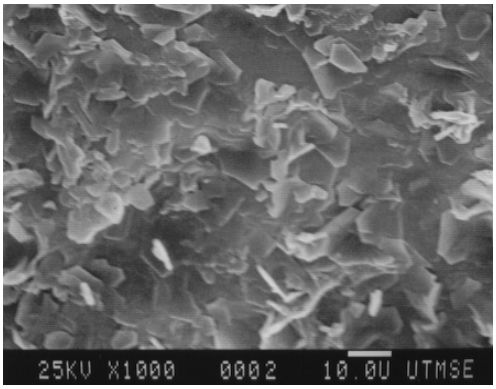


without HPMC-E5 Subcoat

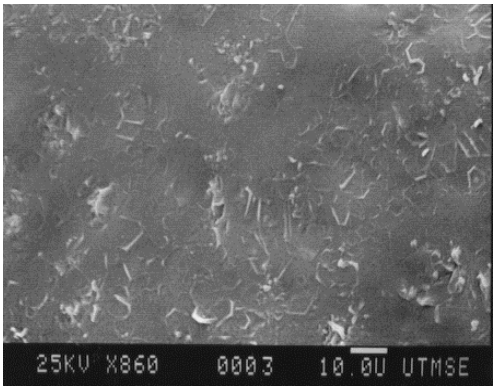


with HPMC-E5 Subcoat

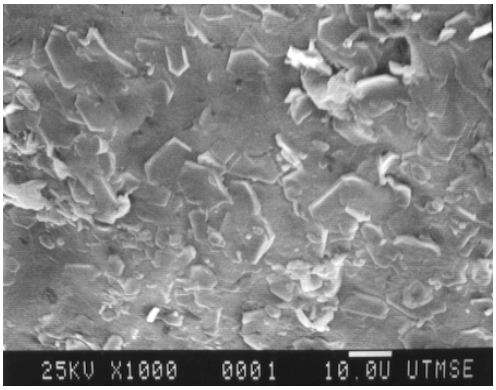
Figure 3.47 Comparison of Surface morphology of CPM beads with and without application of HPMC E5 subcoating prior to EC dispersion (plasticized with 30 %w/w of TEC for 2 hours, 35 % theoretical weight gain) and cured at 60˚C for 24 hours



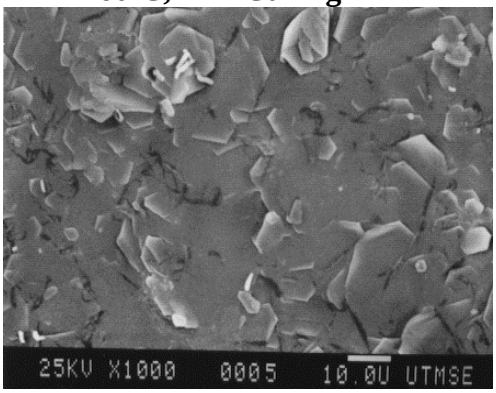
Uncured Beads



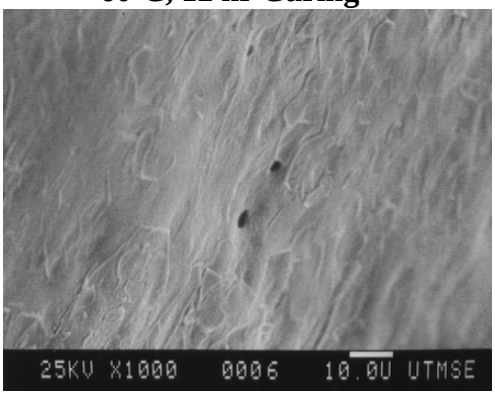
60˚C, 2 hr Curing



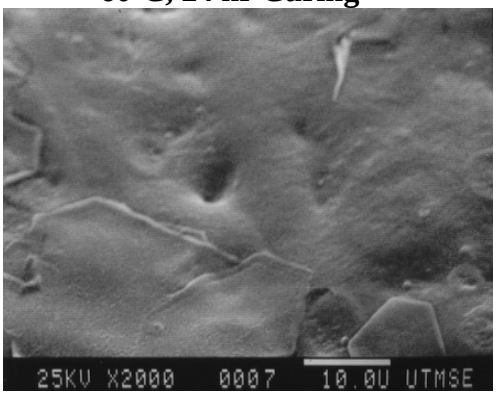
60˚C, 12 hr Curing



60˚C, 24 hr Curing



60˚C, 48 hr Curing



60˚C, 72 hr Curing

Figure 3.48 Surface morphology of CPM beads coated with 2% HPMC-E5 subcoating and EC dispersion plasticized with 30 %w/w of TEC for 2 hours (36 % theoretical weight gain)

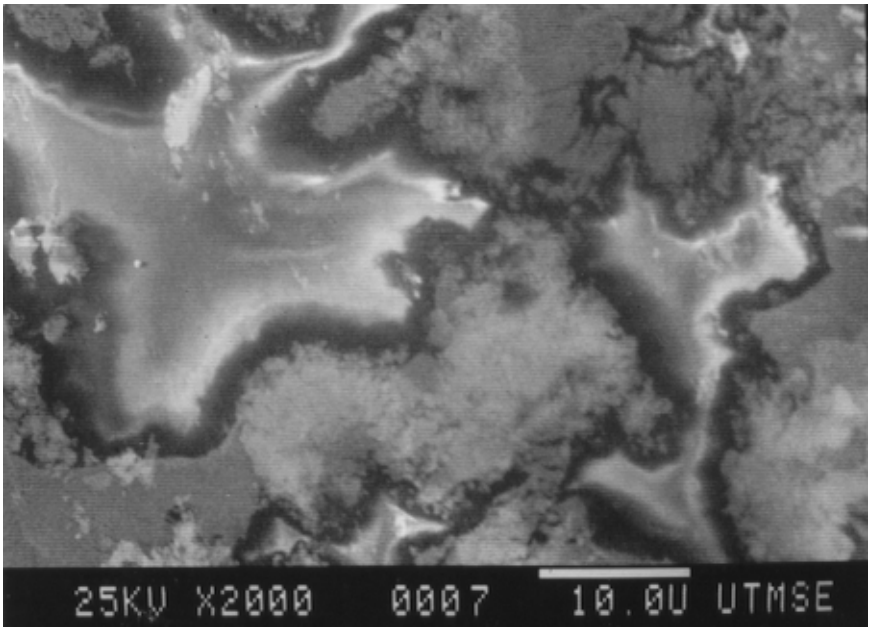


Figure 3.49 Surface morphology of CPM beads coated with 2% HPMC-E5 subcoating and EC dispersion plasticized with 30 %w/w of TEC for 2 hours (36 % theoretical weight gain), and cured at 60˚C for 72 hours.

A coating study to investigate the influence of curing conditions on the release of theophylline from EC coated beads was carried out. Uncoated theophylline beads were coated with 7-19.72% EC dispersion, plasticized with 24 %w/w water insoluble plasticizer, DBS, for 24 hours and then oven-cured at either 60˚C or 80˚C for different periods of time. Due to the limited aqueous solubility of theophylline, a lower coating level of 9-11% was sufficient to obtain a sustained release profile. Dissolution studies were conducted in pH 3.0 buffer for the first 3.5 hours followed by adjustment to pH 7.4 for the remainder of the dissolution.

The influence of curing time at 60˚C on the release of theophylline from the matrix beads coated with 19.72% EC dispersion is shown in Figure 3.50. When the curing time was increased from 0.5 to 2 hours, the amount of theophylline release was significantly reduced, due to higher film coalescence. However, the faster drug release was observed when the coated beads were exposed to a high temperature of 60˚C for longer periods of time, such as 24, 48 or 72 hours. These results were similar to previous studies on CPM beads. This may due to a loss of film integrity when coated beads were exposed to extreme curing conditions. The results shown in Figure 3.51 shows more pronounced differences when the coated beads were cured at either 40˚C or 60˚C for longer than 24 hours. The results in Figure 3.51 also indicated that the curing rate of beads exposed to 60˚C was faster than the curing rate of beads exposed to 40˚C. This was because, at 60˚C the coated beads were held above the T_g of the plasticized EC polymer.

The influence of coating levels and curing time at 60˚C and 80˚C, on theophylline release, is shown in Figures 3.52 and 3.53. Similar to CPM, slower drug release was observed, when the coating level was increased. For both curing temperatures, the rate of theophylline release was faster when the coated beads were cured for 24 hours. This indicated that the 24-hour period at 60˚C or 80˚C was not a suitable curing condition for the EC coated beads, since the film may be disrupted, resulting in a faster release. The effect curing temperatures at 60˚C and 80˚C on drug release was compared in Figure 3.54. A slightly faster curing rate was obtained when the coated beads were exposed to 80˚C for 2 hours. The curing rate is a function of the curing temperature rather than the coating levels. SEM micrographs, shown in Figure 3.55, review the surface morphology of theophylline beads coated with an 11% EC dispersion and cured at 80˚C for 24 hours. When cured at 80˚C for 24 hours, film disruptions or pores were found on the surface of the theophylline coated beads. This indicated that a faster drug release from the coated beads exposed to the extreme curing conditions was caused by a disruption of the film.

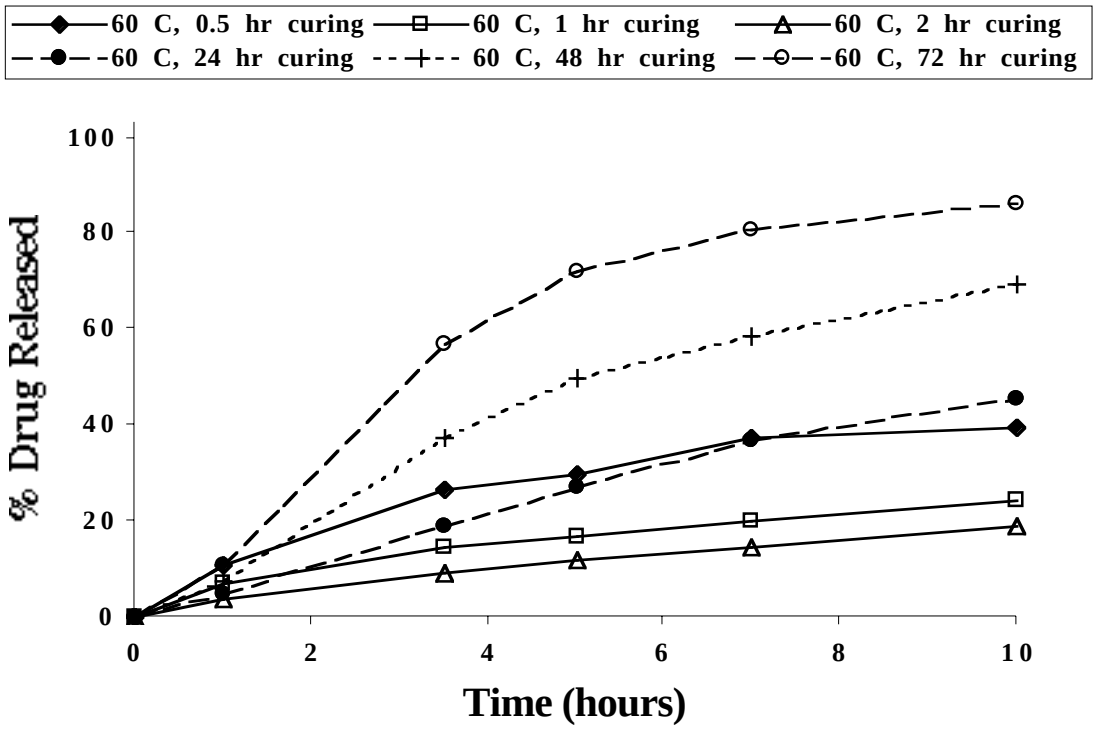


Figure 3.50 Influence of curing time at 60˚C on the release of theophylline from matrix beads coated with EC dispersion plasticized with 24 %w/w of DBS for 24 hours (19.72 % theoretical weight gain)

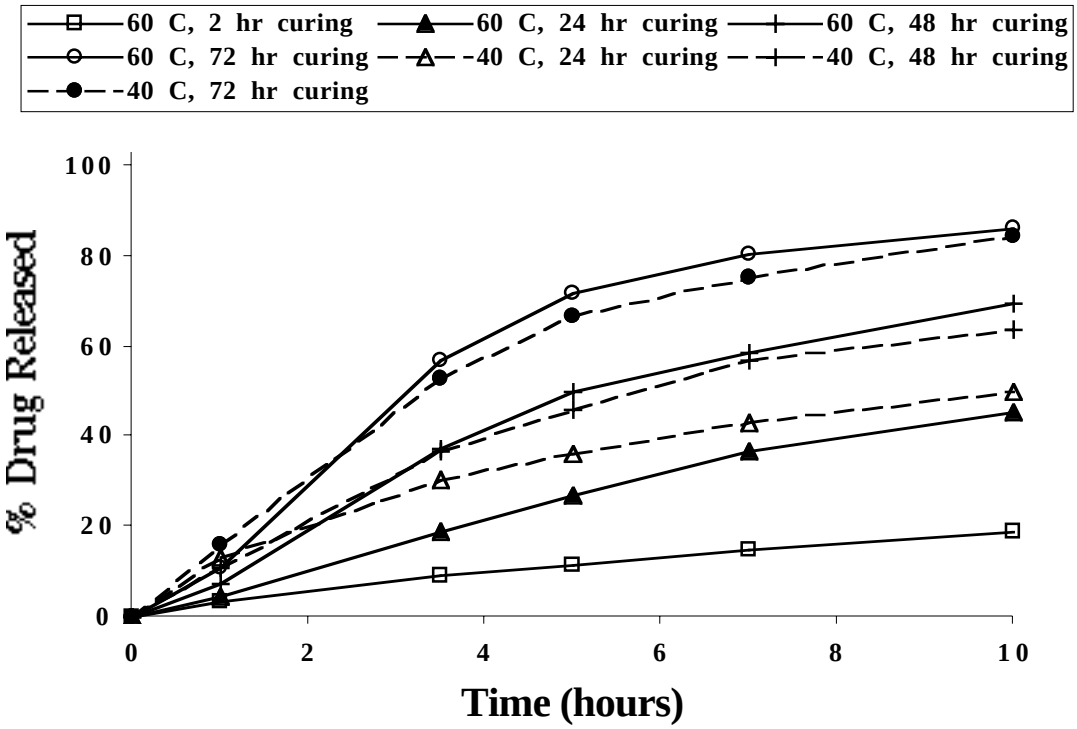


Figure 3.51 Influence of curing condition on the release of theophylline from matrix beads coated with EC dispersion plasticized with 24 %w/w of DBS for 24 hours (19.72 % theoretical weight gain)

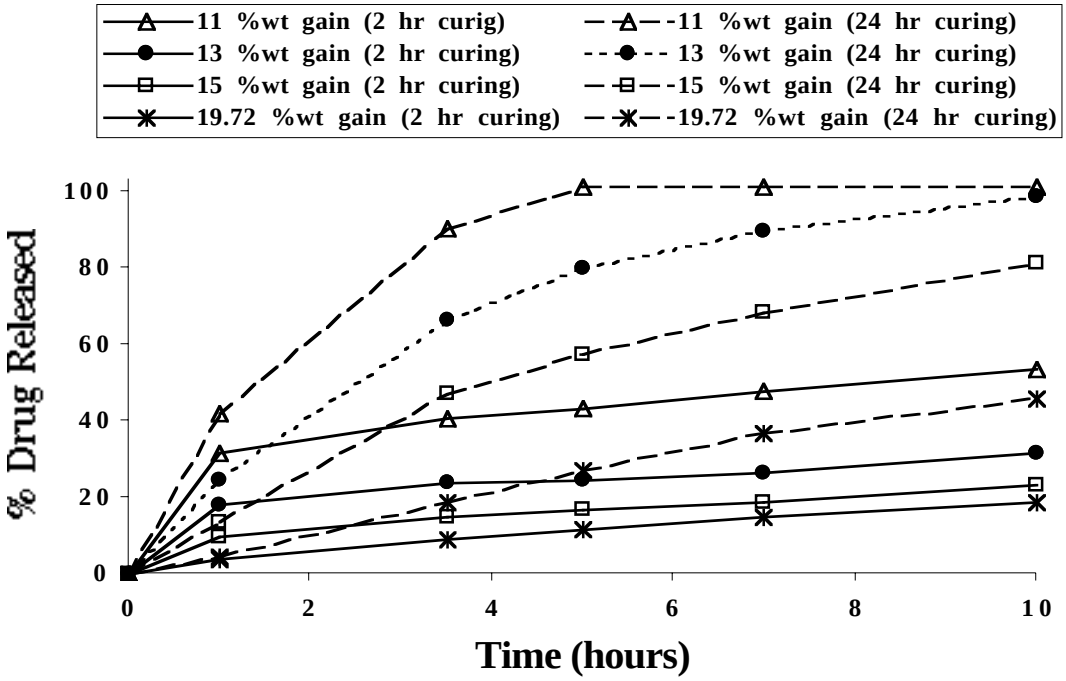


Figure 3.52 Influence of curing time at 60˚C on the release of theophylline from matrix beads coated with EC dispersion plasticized with 24 %w/w of DBS for 24 hours (11-19.72 % theoretical weight gain)

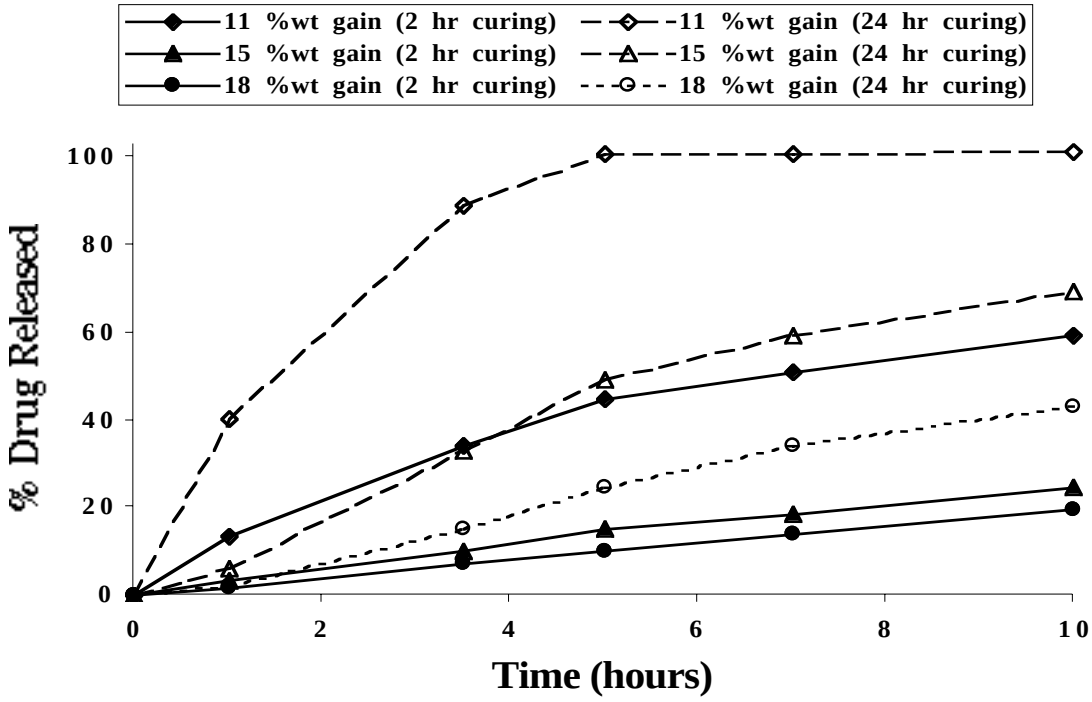


Figure 3.53 Influence of curing time at 80˚C on the release of theophylline from matrix beads coated with EC dispersion plasticized with 24 %w/w of DBS for 24 hours (11-18 % theoretical weight gain)

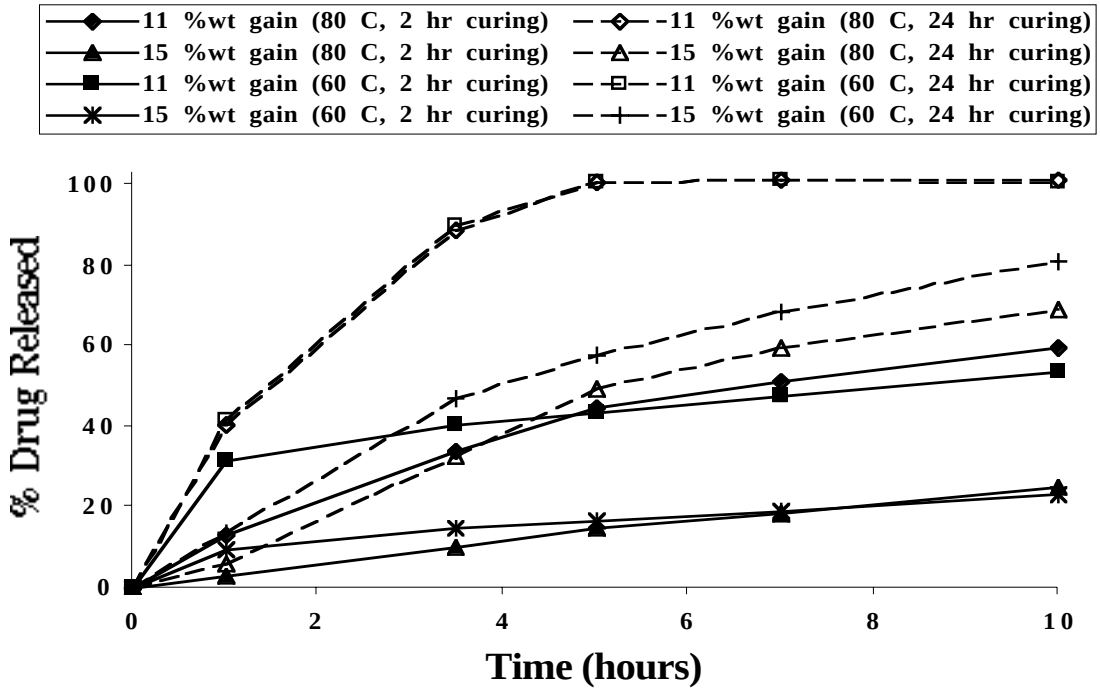


Figure 3.54 Influence of curing condition on the release of theophylline from matrix beads coated with EC dispersion plasticized with 24 %w/w of DBS for 24 hours (11 and 15 % theoretical weight gain)

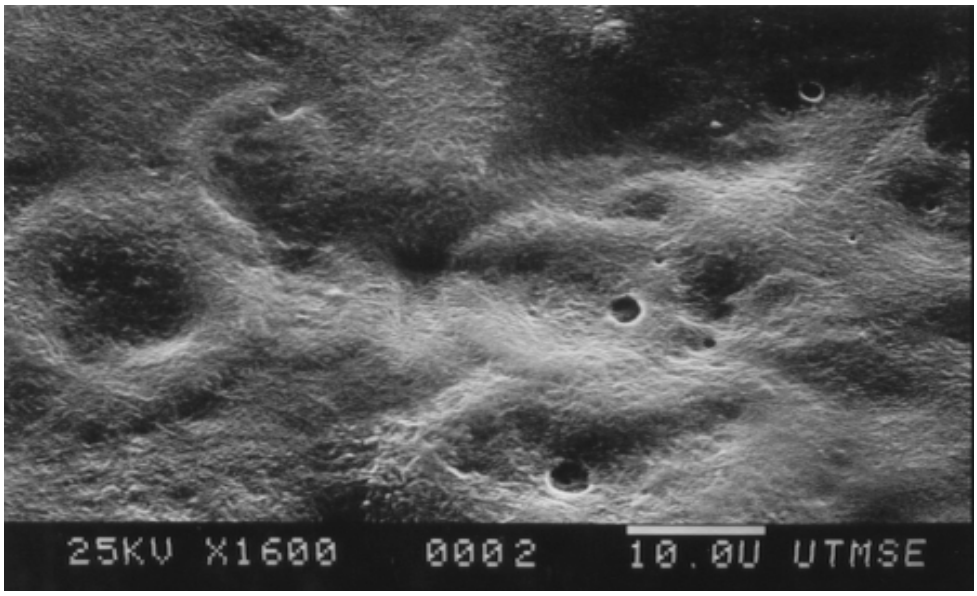


Figure 3.55 Surface morphology of theophylline beads coated with EC dispersion plasticized with 24 %w/w of DBS for 24 hours (11% theoretical weight gain) and cured at 80˚C for 24 hours

In another coating study of theophylline, a different type of plasticizer, AMG, was used to plasticize the EC dispersion. The influence of curing time at 60˚C on the release of theophylline from the EC-AMG coated beads is shown in Figure 3.56. Similar to the previous coating system, when DBS was used as a plasticizer, a faster release was observed when the coated beads were exposed to 60˚C for 24 hours. Similar results were observed at all coating levels. When the coating level was higher than 7%, sustained release profiles were obtained from the coated beads cured at 60˚C for 6 hours. As was shown by this investigation, the influence of curing conditions on theophylline release was independent of the coating level and the plasticizer type.

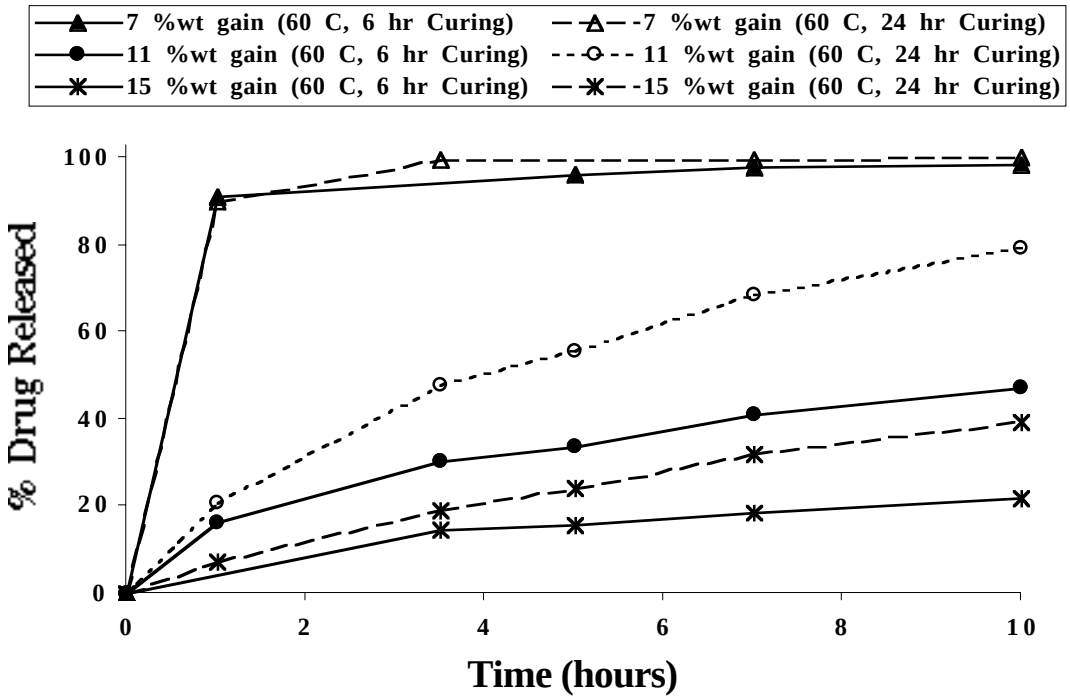


Figure 3.56 Influence of curing time at 60˚C on the release of theophylline from matrix beads coated with EC dispersion plasticized with 24 %w/w of AMG for 24 hours (7-15 % theoretical weight gain)

Overall, the results of the curing study indicated that the curing time and temperature influenced release of both water-soluble and slightly water-soluble drugs from matrix beads coated with an aqueous EC dispersion. When an elevated curing temperature was used, a shorter curing time was needed to complete the film formation. The recommended curing conditions, which would ensure complete film coalescence without disrupting film integrity of coated beads, were either 6 to 12 hours at 60˚C or 1 to 2 hours at 80˚C. Faster drug release profiles were obtained for coated beads cured for long periods of time, especially at a high curing temperature. Additionally, the SEM micrographs showed a loss of film integrity (i.e. pores) for the coated beads exposed to those extreme curing conditions. From the previous study reported in the literature, the curing step was shown to have no influence on the drug release from beads coated with another EC dispersion, Surelease®. This may be due to the differences in coating composition and preparation between Aquacoat® ECD and Surelease® and the differences in film formation mechanism [Shah et al., 1994; Wesseling and Bodmeier, 1999b]. Aquacoat® ECD dispersion contains EC polymer, cetyl alcohol (stabilizer), and sodium lauryl sulfate (stabilizer/emulsifier). At those extreme curing conditions used in this study, these stabilizers, especially cetyl alcohol, may not be stable or efficiently functioned as a stabilizer for the EC polymer. Cetyl alcohol within the film may start melting and creating the pores when the coated beads were exposed to a higher temperature than its melting point of 49˚C [Budavari et al., 1996], especially when the beads were cured for longer periods of time. The squeezing out of cetyl alcohol and sodium lauryl

sulfate from the microcapsules coated with Aquacoat® ECD dispersion plasticized with 19.4% DBS after post-treatment of 68˚C for 1 hour and storage time of 3-4 months was also reported [Lippold et al., 1990].

The influence of curing conditions on drug release from the dosage forms was independent of coating level, subcoating application, plasticization, or drug type.

3.2.2.2 Plasticization

The influence of plasticizer type and plasticization time was investigated in this study for their effect on the release of water-soluble and slightly water-soluble drugs from coated beads. Plasticizers, including water miscible (i.e. TEC) and water-insoluble (i.e. AMG and DBS) types, were plasticized for either 2 or 24 hours with the EC dispersion prior to application onto the uncoated beads containing CPM or theophylline. The coated beads were cured at 60˚C for 6 hours as recommended in section 3.2.2.1. Dissolution studies were carried out to determine the influence of plasticization on drug release.

For CPM beads, the influence of plasticization time of 24 %w/w AMG on drug release from coated beads is shown in Figure 3.57. Dissolution profiles of beads containing different coating levels indicated that the plasticization time had a significant influence on the amount of CPM release from the coated beads. Specifically, when a 24-hour mixing time was used to plasticize AMG with the EC dispersion, the release of CPM was slower. A longer plasticization time for AMG and EC dispersion was necessary to achieve a sustained release profile for CPM. Therefore, the coating level and processing time could be reduced while maintaining similar sustained release profiles. Figure 3.58 shows the effect of the coating level, ranging from 25-35%, on the release of CPM from the same coating formulation previously described. Similar to other studies, when the coating level was increased, the amount of drug release was significantly decreased. In this coating system, at least 30% coating level was necessary in order to obtain a sustained release profile for CPM.

In another coating study, a separate plasticizer, DBS, was used at the same level as AMG and plasticized with the EC dispersion for 24 hours. A long plasticization time was recommended for DBS to permeate completely into the polymer network to lower the film forming temperature and enhance the flexibility of the film. The high solubility value of EC in DBS determined at 20˚C was greater than 10%, which was in agreement with the similar solubility parameters of EC ($21.1(J/cm^3)^{1/2}$) and DBS ($18.8\ (J/cm^3)^{1/2}$) [Lippold et al., 1990; Lippold et al., 1999]. The influence of coating level on the release of CPM from beads, plasticized with DBS for 24 hours, is shown in Figure 3.59. At a coating level between 20-25%, the rate of CPM release was extremely slow, when compared to the release of the system containing AMG as a plasticizer. For a coating system containing AMG, at least 30% coating level was required for a 10-hour release product; whereas less than 20% coating level was required for a coating system containing DBS (Figure 3.60). This indicated that DBS was more efficient than AMG in terms of plasticization with the EC polymer.

In addition, CPM within the matrix of the beads may function as a plasticizer due to its high solubility in the film. This plasticization behavior of CPM has been reported for Eudragit®RS30D. The T_g of Eudragit®RS30D polymer decreased with increasing levels of CPM in the film. CPM was soluble in the film, where it was incorporated into the polymer network, functioning as a plasticizer. Finally, it helped promote particle deformation and coalescence of the film upon drying [Wu and McGinity, 1999].

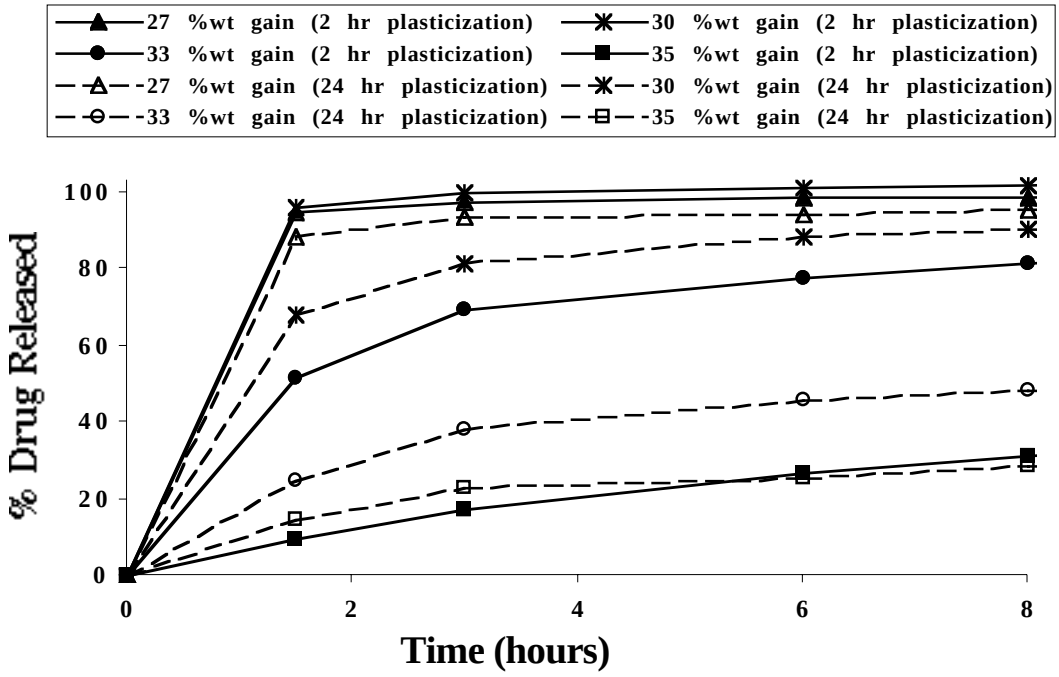


Figure 3.57 Influence of plasticization time of 24 %w/w AMG with EC dispersion on the release of CPM from matrix coated beads cured at 60˚C for 6 hours (27-35 % theoretical weight gain)

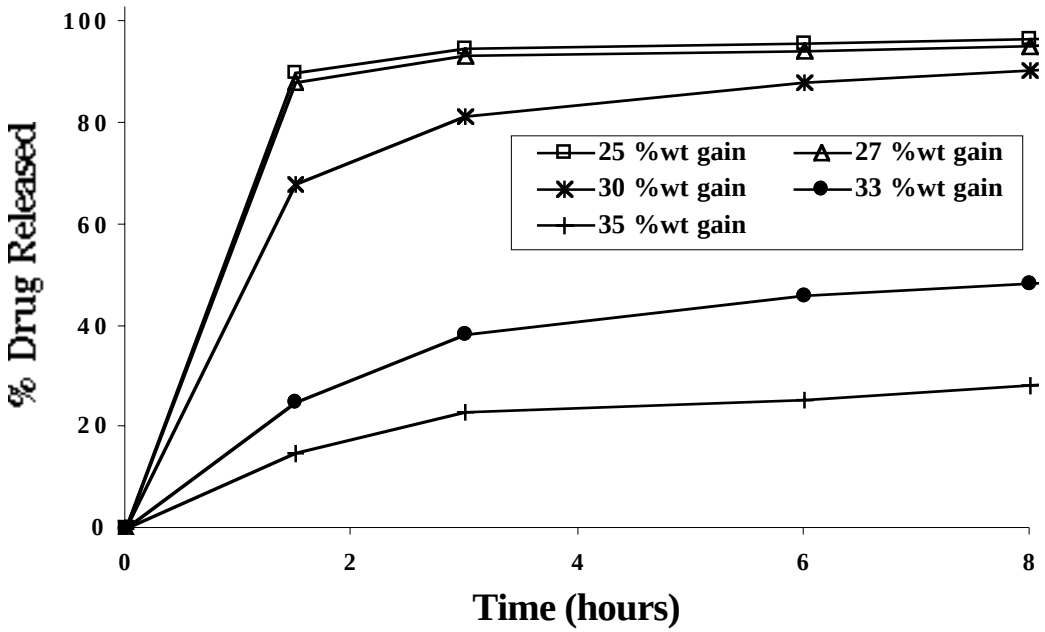


Figure 3.58 Influence of coating level on the release of CPM from matrix beads coated with EC dispersion plasticized with 24 %w/w AMG for 24 hours and cured at 60˚C for 6 hours (25-35 % theoretical weight gain)

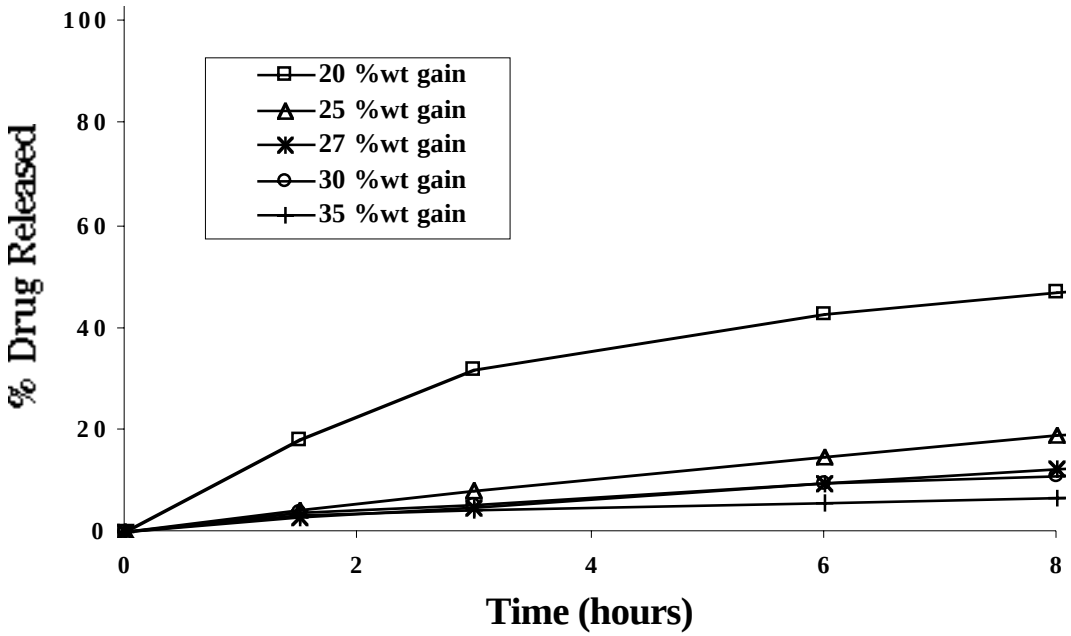


Figure 3.59 Influence of coating level on the release of CPM from matrix beads coated with EC dispersion plasticized with 24 %w/w DBS for 24 hours and cured at 60˚C for 6 hours (20-35 % theoretical weight gain)

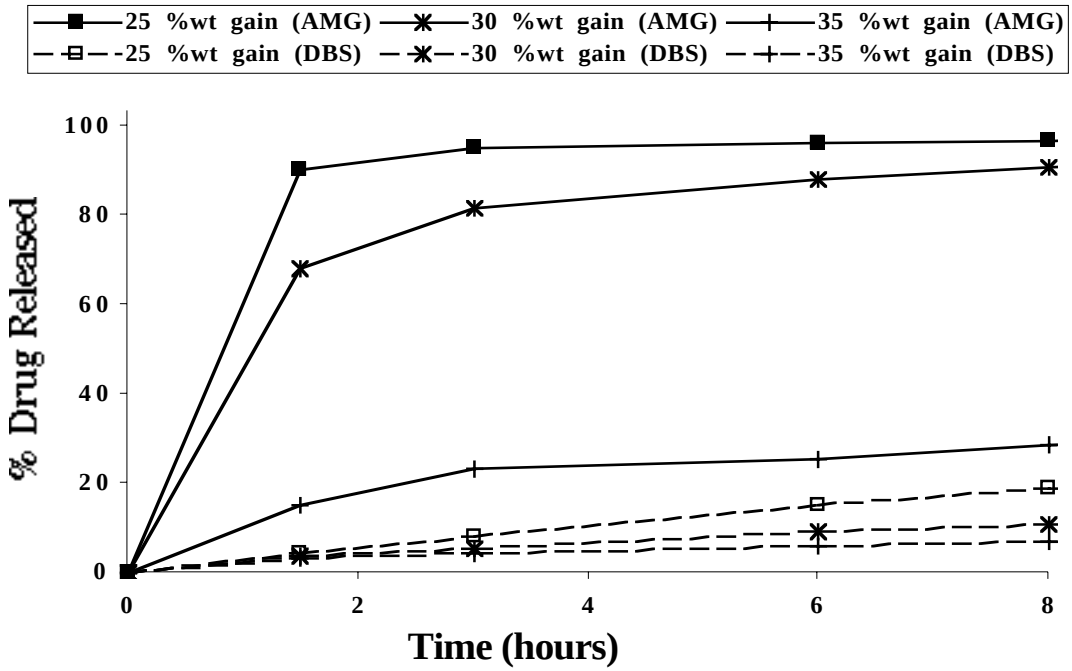


Figure 3.60 Influence of plasticization type on the release of CPM from matrix beads coated with EC dispersion plasticized for 24 hours and cured at 60˚C for 6 hours (27-35 % theoretical weight gain)

For theophylline beads, the coating level necessary to obtain a sustained release profile was significantly lower than CPM beads as previously described in the results of the curing study. In the coating formulation containing 24% AMG plasticized with the EC dispersion for 24 hours, a coating level between 7 and 11% was necessary to sustain the release of theophylline from the coated beads, as shown in Figure 3.61. If the same coating formulation was used to coat CPM matrix beads, a coating level of at least 30% was necessary to obtain similar release profiles (Figure 3.58). Therefore, the type of drug substance used to prepare the core beads has a major impact on the release of the drug from a multiparticulate system. Specifically, the release of drug from the system mainly depends on the aqueous solubility of the drug.

The effect of plasticization time of 2 or 24 hours on the release of theophylline from coated beads is shown in Figure 3.62. Unlike the CPM release profiles shown in Figure 3.57, a slower release of theophylline was obtained from beads coated with an EC dispersion, plasticized with 24% AMG for only 2 hours. When a plasticization time of 24 hours was used, faster drug release was obtained. This result was similar for all coating levels. Therefore, the 2-hour mixing time of AMG with the EC dispersion was sufficient to plasticize the EC polymer and was used in further studies of theophylline coated beads.

Finally, another type of plasticizer, TEC, was used at 24% to plasticize the EC dispersion for 2 hours. Due to the miscibility of TEC and the aqueous EC dispersion, a plasticization time of 2 hours was sufficient to incorporate the plasticizer into the polymer chains. The results shown in Figure 3.63 indicated

that at least an 11% coating level was necessary to obtain a 10-hour release profile of theophylline. From the dissolution profiles of previous systems containing AMG, shown in Figures 3.62 and 3.64, a coating level of less than 11% was sufficient to obtain a similar release profile for theophylline. This indicated that AMG was more efficient as a plasticizer for the EC dispersion. Therefore, 24% AMG was used to plasticize the EC dispersion for 2 hours in further studies of theophylline coated beads.

Overall, the results of the plasticization study indicated that the plasticizer type and plasticization time influenced release of both water-soluble and slightly water-soluble drugs from matrix beads coated with an aqueous EC dispersion. Different types of plasticizer used in the coating formulation appeared to influence the release rate of the drug, by altering the water permeability of the film [Saettone et al., 1995]. A suitable plasticizer type as well as the optimum plasticization time were dependent on each coating system, and were primarily dependent on the nature of the drug substance. The influence of plasticization on drug release from the dosage forms was independent of coating level.

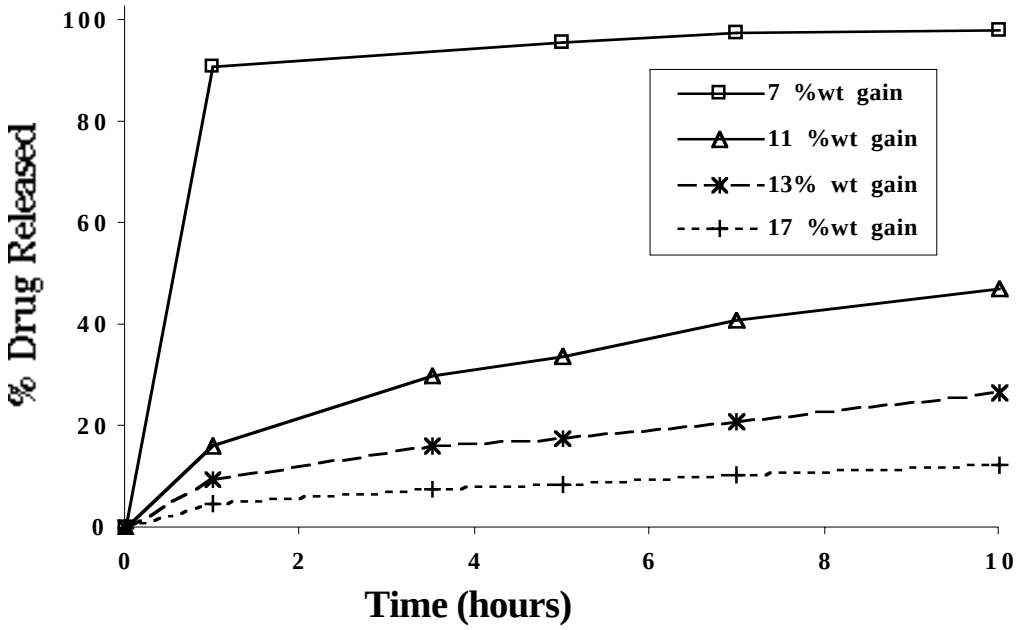


Figure 3.61 Influence of coating level on the release of theophylline from matrix beads coated with EC dispersion plasticized with 24 %w/w AMG for 24 hours and cured at 60˚C for 6 hours (7-17 % theoretical weight gain)

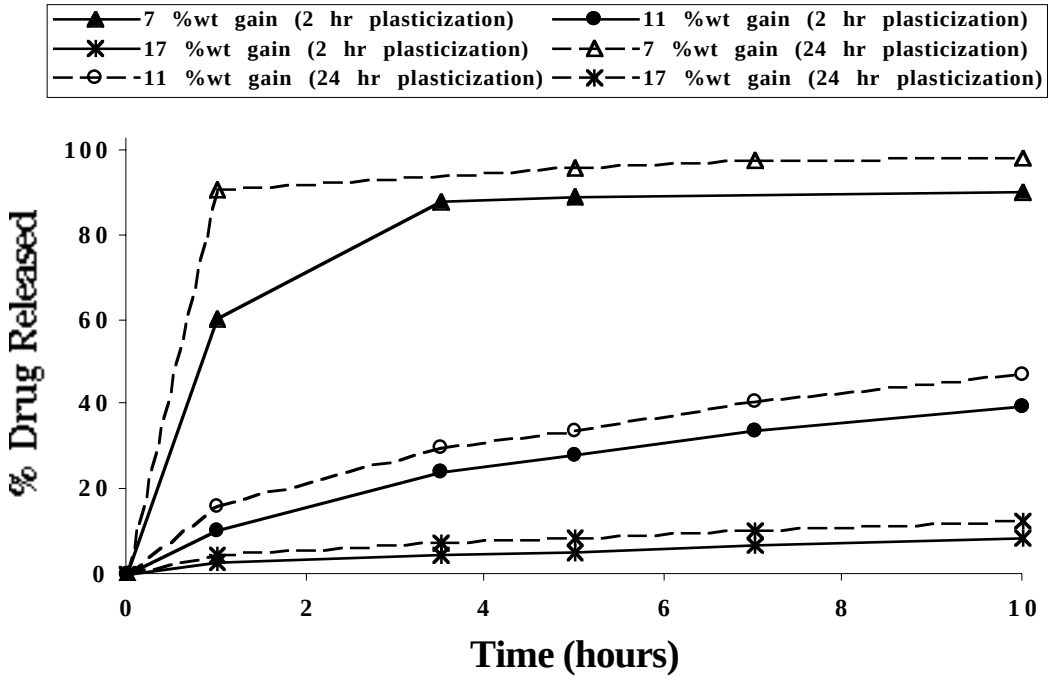


Figure 3.62 Influence of plasticization time of 24 %w/w AMG with EC dispersion on the release of theophylline from matrix coated beads cured at 60˚C for 6 hours (7-17 % theoretical weight gain)

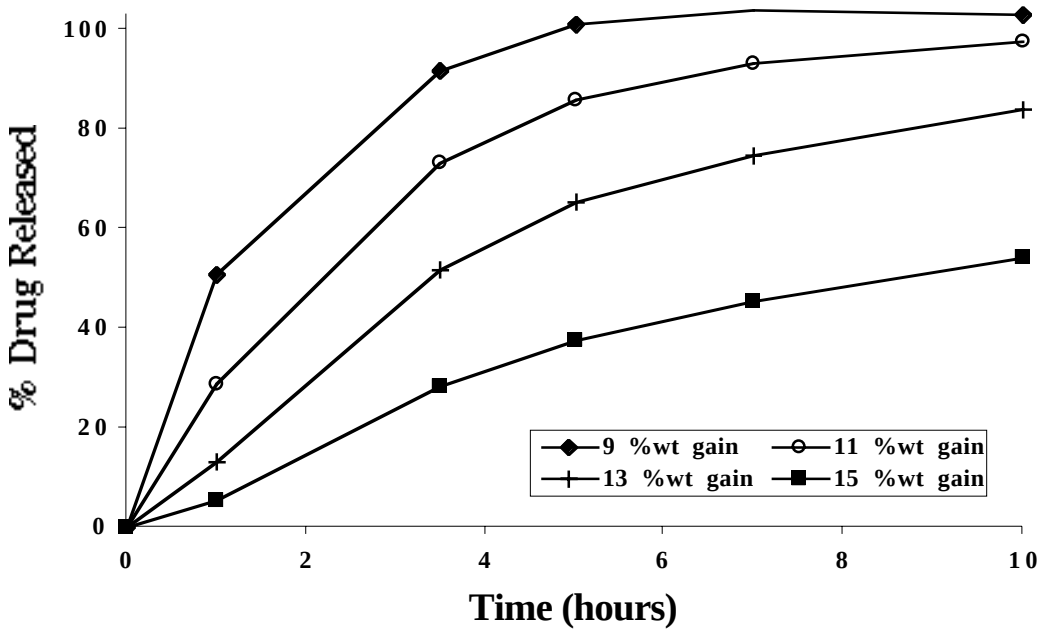


Figure 3.63 Influence of coating level on the release of theophylline from matrix beads coated with EC dispersion plasticized with 24 %w/w TEC for 2 hours and cured at 60˚C for 6 hours (9-15 % theoretical weight gain)

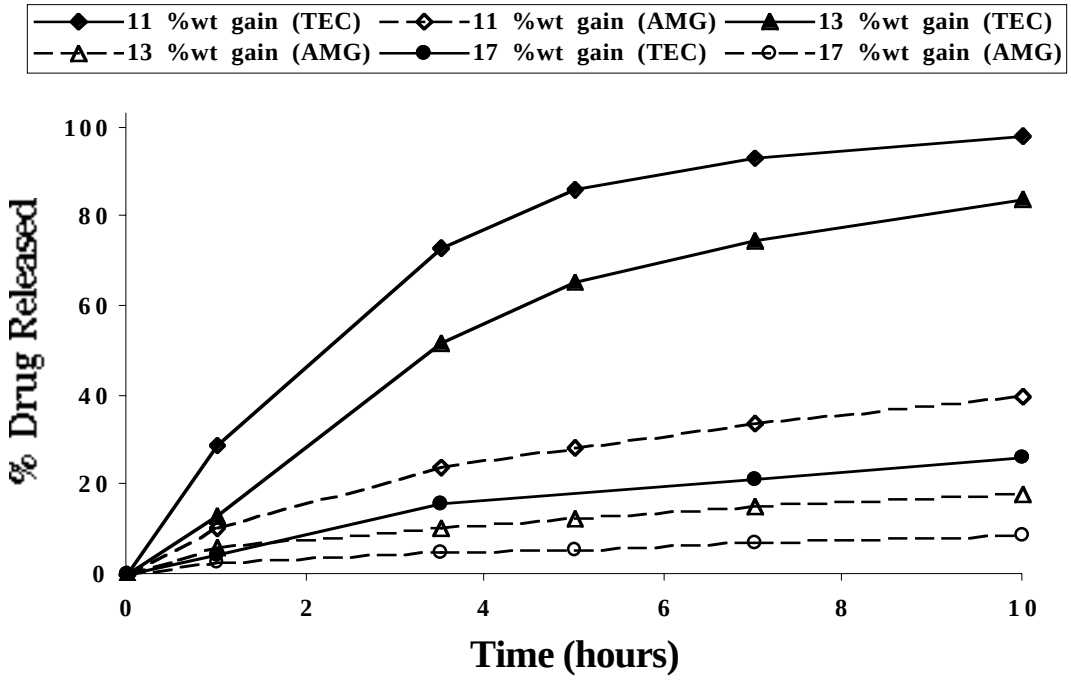


Figure 3.64 Influence of plasticization type on the release of theophylline from matrix beads coated with EC dispersion plasticized for 2 hours and cured at 60˚C for 6 hours (11-17 % theoretical weight gain)

3.2.2.3 Water Soluble Additives

As was shown from previous results, the rate of theophylline release from beads coated at high coating levels was very slow. This was due to the limited solubility of theophylline during dissolution. In this study, the influence of water-soluble additives on the release of a slightly water-soluble drug, theophylline, from EC coated beads, was investigated. Theophylline uncoated matrix beads were coated with an EC dispersion containing a plasticizer and a water-soluble additive. After coating, the coated beads were cured at 60˚C for 6 hours as recommended in section 3.2.2.1. Dissolution studies were carried out to determine the influence of the water-soluble additive on drug release.

Figure 3.65 shows the effect of incorporation of a water-soluble additive on the rate of theophylline release from coated beads. A water-soluble additive, HPMC-E5, was added at a level of 5% to the EC dispersion, plasticized with 24% AMG for 2 hours. When comparing the dissolution profiles of coated beads with and without the incorporation of HPMC-E5, the amount of drug release from beads containing theophylline was increased by the addition of HPMC-E5. This result was more noticeable at low coating levels (11 and 13%). However, when the coating level was increased to 17%, the incorporation of HPMC-E5 had no effect on the release of theophylline. This could be due to the level of HPMC-E5 incorporated in the coating dispersion was not sufficient to enhance the drug release. The influence of coating levels on theophylline release from matrix beads coated with the same coating formulation and the incorporation of 5% HPMC-E5, is shown in Figure 3.66. Similar to other studies, when the coating

level was increased, the amount of theophylline was significantly decreased. When HPMC-E5 was added to the coating formulation, at least a 9% coating level was necessary to obtain a sustained release profile. At higher coating levels, a higher level of HPMC-E5 may be required to enhance the amount of theophylline release from the coated beads. The influence of 20 %w/w HPMC-E5 incorporated into the coating formulation is shown in Figure 3.67. When the level of HPMC-E5 was increased to 20 %w/w, the rate of theophylline release drastically increased. At an 11% coating level, the rate of theophylline release was significantly slower. At the same coating level, the use of 20 %w/w HPMC-E5 in the coating formulation caused dose dumping and lack of sustained release of theophylline. The dissolution profiles of theophylline coated beads with the incorporation of 5 and 20 %w/w of HPMC-E5 are compared in Figure 3.68. With an increase in HPMC-E5 concentration, the coating became more permeable and more porous upon exposure to water (dissolution medium), therefore dramatically increasing the release rate of drug from the coated beads [Thombre et al., 1989]. Similar results were reported for beads coated with an EC dispersion containing HPMC (Pharmacoat®603) and TEC or DEP. The drug release rates increased with increasing levels of HPMC from 10 to 30% [Frohoff-Hulsmann et al., 1999a].

The extent of drug release from the coated beads was dependent on the level of HPMC-E5 incorporated into the formulation.

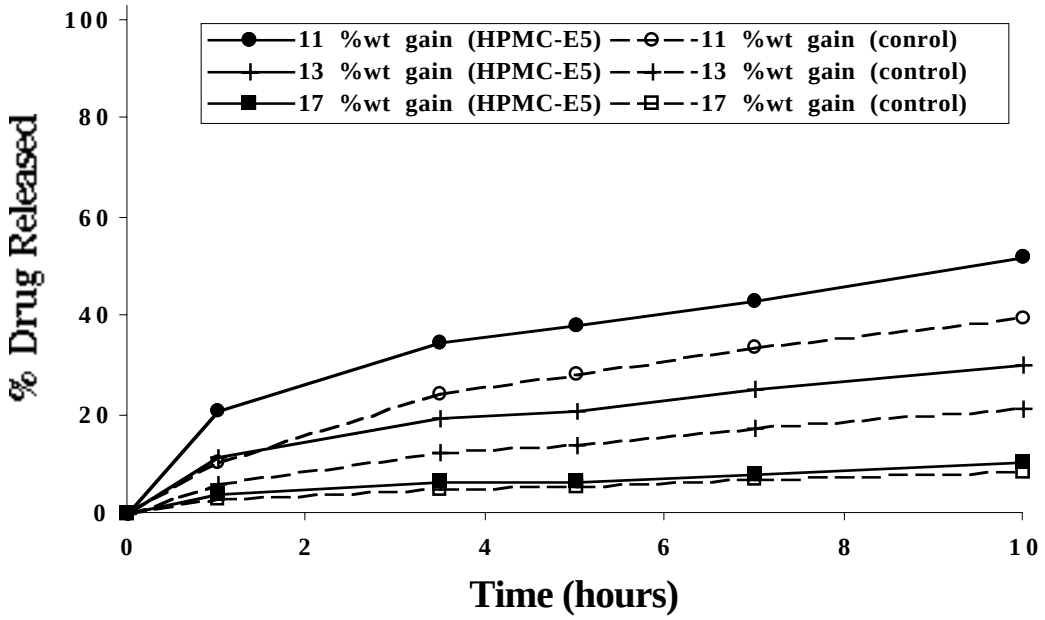


Figure 3.65 Influence of coating levels on the release of theophylline from matrix beads coated with EC dispersion plasticized with 24 %w/w AMG for 2 hours and 5 %w/w HPMC-E5, and cured at 60˚C for 6 hours (11-17% theoretical weight gain)

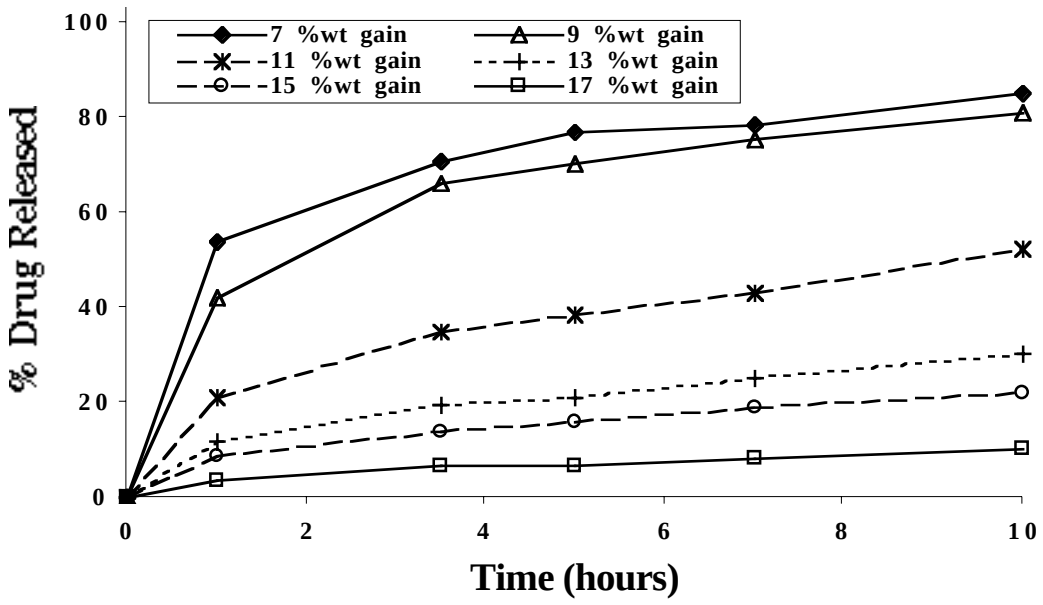


Figure 3.66 Influence of HPMC-E5 on the release of theophylline from matrix beads coated with EC dispersion plasticized with 24 %w/w AMG for 2 hours and 5 %w/w HPMC-E5, and cured at 60˚C for 6 hours (11-17 % theoretical weight gain)

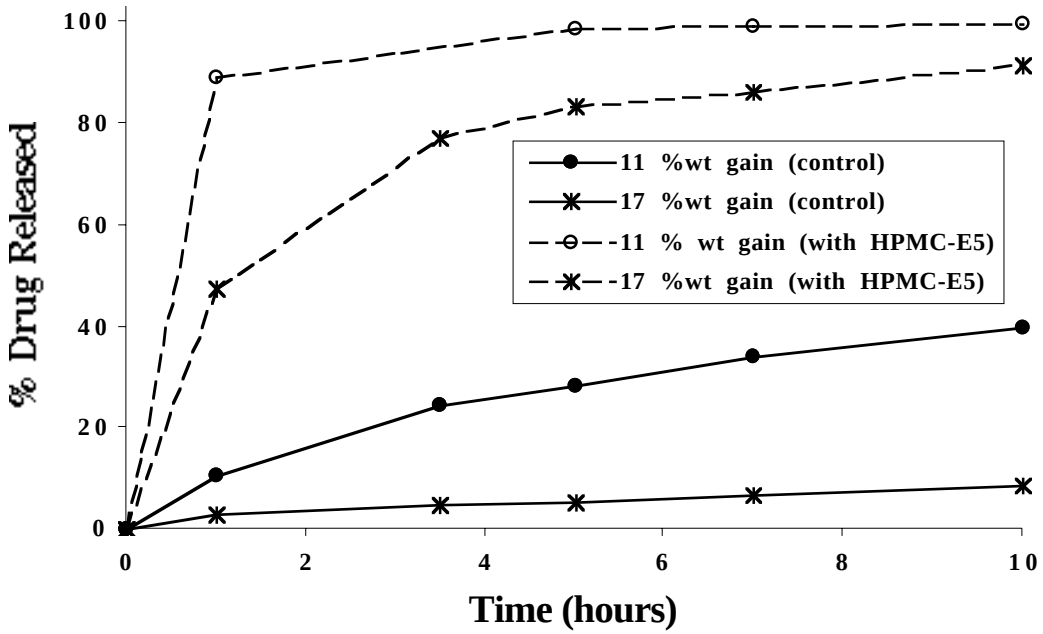


Figure 3.67 Influence of HPMC-E5 at 20 %w/w on the release of theophylline from matrix beads coated with EC dispersion plasticized with 24 %w/w AMG for 2 hours and cured at 60˚C for 6 hours (11 and 17% theoretical weight gain)

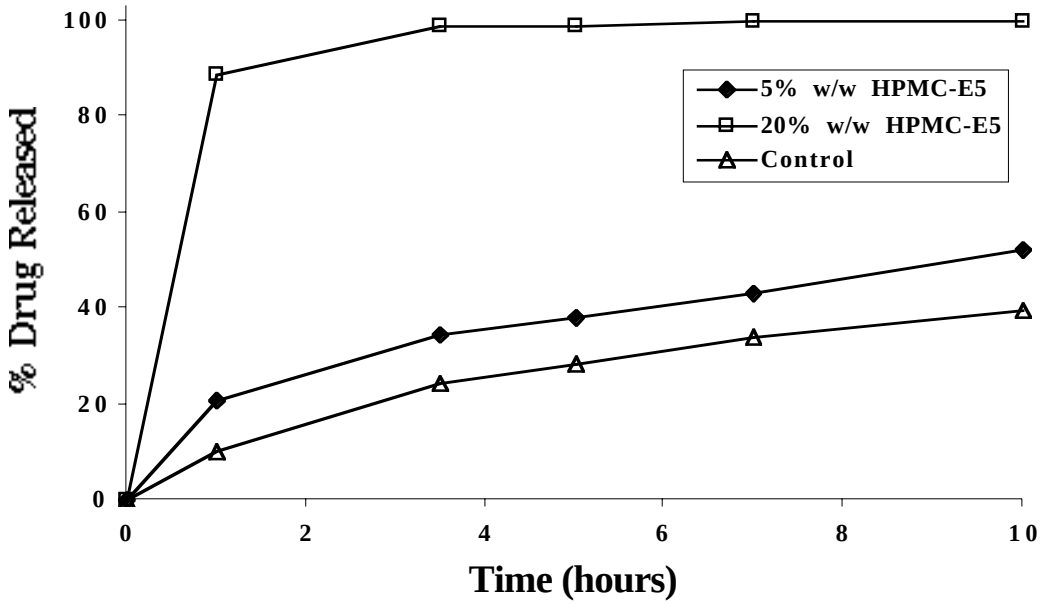


Figure 3.68 Influence of HPMC-E5 levels on the release of theophylline from matrix beads coated with EC dispersion plasticized with 24 %w/w AMG for 2 hours and cured at 60˚C for 6 hours (11% theoretical weight gain)

The influence of the types of water-soluble additives, at 5 %w/w, on the release of theophylline is shown in Figure 3.69. At a 9% coating level, EC coated beads containing PEG 8000 had a higher rate of theophylline release than EC coated beads containing other water-soluble additives, including HPMC-E5, sucrose and mannitol. Similar results were also observed at other coating levels. Therefore, PEG 8000 functioned as an effective water-soluble additive in the formulation, at a low level. In order to obtain a sustained release profile, a higher coating level was necessary when PEG 8000 was used as an additive in the formulation.

The influence of plasticizer type on the release of theophylline from beads containing 5 %w/w PEG 8000 as an additive is compared in Figure 3.70. For both 13 and 15% coating levels, the coated beads containing DBS as a plasticizer had a slower rate of drug release, even though 5 %w/w of PEG 8000 was incorporated into the coating formulations to enhance the drug release. In order to enhance the dissolution of theophylline from the coated beads, a higher level of PEG 8000 than was needed.

Theophylline coated beads with DBS or AMG as a plasticizer and PEG 8000 as a water-soluble additive showed two-phased release profiles, similar to the results reported in the literature. During the first phase of the release profile, the release was fast and characterized by drug diffusion through water-filled pores created after the migration of the water-soluble additive. During the second phase, those pores gradually closed or the permeability of the coating significantly decreased due to the dramatic reduction in the free volume between the polymer

chains. Therefore, the slower drug release was obtained during the second phase of the release profile [Gunder et al., 1995; Lippold et al., 1989; Frohoff-Hulsmann et al., 1999a; Frohoff-Hulsmann et al., 1999b].

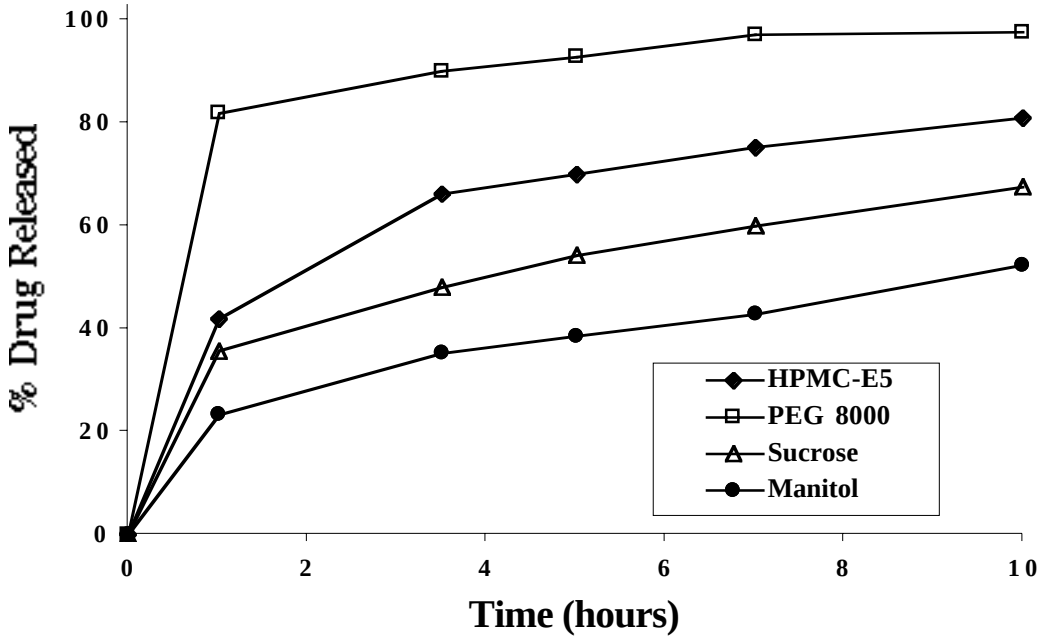


Figure 3.69 Influence of water soluble additive type on the release of theophylline from matrix beads coated with EC dispersion plasticized with AMG for 2 hours and 5 %w/w water soluble additive, and cured at 60˚C for 6 hours (9% theoretical weight gain)

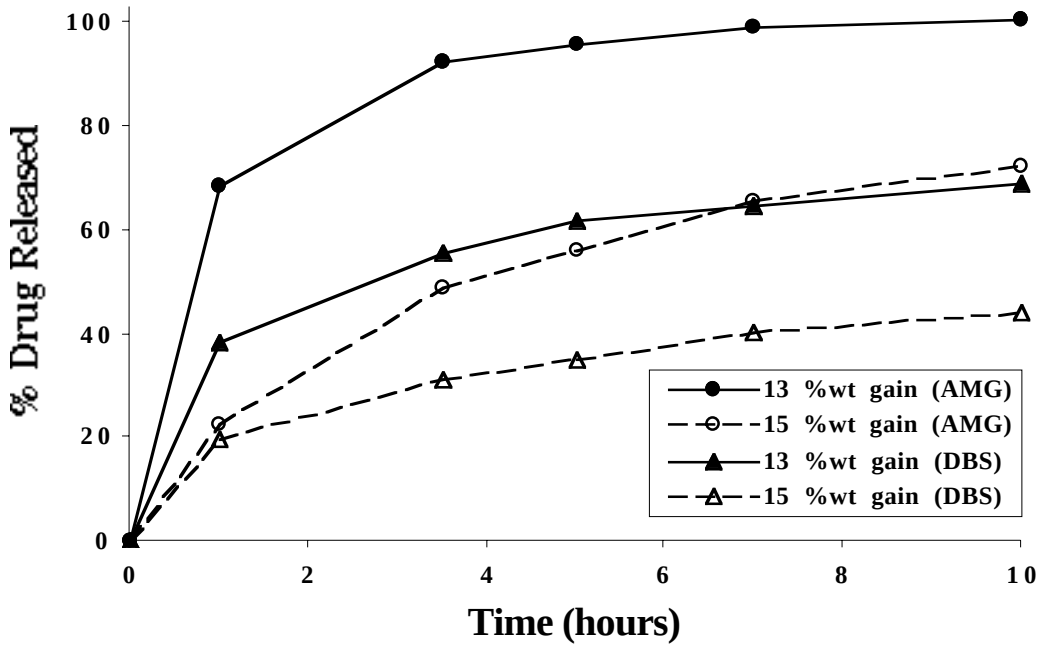


Figure 3.70 Influence of plasticization on the release of theophylline from matrix beads coated with EC dispersion plasticized with 24 %w/w AMG for 2 hours or 24 %w/w DBS for 24 hours and 5 %w/w PEG 8000, and cured at 60˚C for 6 hours (13 and 15% theoretical weight gain)

The results of this study showed that enhanced release of a slightly water-soluble drug (i.e. theophylline) was achieved by the inclusion of a water-soluble additive, which rapidly dissolved in the dissolution medium leaving small channels or pores for the drug to pass through, thus increasing the permeability of the membrane and modifying the dissolution rate. Therefore, the incorporation of these additives into the EC coating dispersion can be used to modify the dissolution rate of drug from solid dosage forms. The amount of drug release from EC coated beads was influenced by the water-soluble additive type and level.

The influence of the water-soluble additive on the film formation of EC was explained by Miller and Vadas. When a water-soluble additive was introduced into the EC aqueous dispersion, it was distributed throughout the continuous aqueous phase. Following film drying, the water-soluble additive was deposited on the interfaces between latex particles and may interfere with the coalescence of the film. Therefore, when high levels of these additives were used in the coatings, the initial coalescence could be incomplete and further gradual coalescence may be time dependent [Miller and Vadas, 1984].

The mechanism of the water-soluble additive's ability to enhance the drug release can be explained by a rapid dissolution of a water-soluble additive after exposure of the coated beads to an aqueous dissolution medium. The dissolution medium or solvent penetrated into the beads to dissolve the water-soluble additive, which then migrated out and left pores in the coated film. At the same time, the dissolution of the drug within the matrix was initiated. Finally, the

dissolved drug diffused through the EC film into a dissolution medium, especially via the water-filled pores previously created by the water-soluble additive [Frohoff-Hulsmann et al., 1999a; Lippold et al., 1989].

CHAPTER 4

SUMMARY AND CONCLUSIONS

The use of cellulose ether polymers in oral controlled release dosage forms, including matrix tablets and multiparticulate dosage forms was investigated. Hydroxypropyl methylcellulose (HPMC) and ethylcellulose (EC) polymers were used to formulate and control the release of active ingredients from the hydrophilic matrix tablets and film coated beads, respectively. Formulations and processing parameters were developed and optimized in order to achieve desired rate of drug release from each drug delivery system.

For the matrix tablet delivery system, alprazolam (ALP), a lipophilic drug, was used as a model active ingredient. The preformulation studies for ALP were carried out to investigate its physiochemical properties. The studies included drug solubility, thermal properties, particle size and particle size distribution, surface morphology, and crystallinity. An approximate aqueous solubility of ALP determined at 37±0.5˚C was 44 µg/ml (1 part of ALP per 22727 parts of water), indicating a water-insoluble nature of the drug. The solubility of ALP was pH dependent. Particularly, ALP had a higher solubility in an acidic pH solution than in an alkaline media. Solubility results also helped determine sink conditions, which are an important experimental parameter that must be controlled during dissolution studies, of ALP in different dissolution media. For the dissolution studies of ALP matrix tablets, 0.1 N HCl solution (pH 1.1) was used as a

dissolution medium because ALP had a higher solubility and sink conditions for ALP release could be achieved in this medium. In contrast, purified water or alkaline media should not be used for dissolution studies of ALP, since ALP dissolution did not occur under sink conditions, due to its low solubility. DSC results demonstrated a sharp endothermic peak for ALP at 232-233˚C, which corresponded to its melting point. Results also indicated the crystalline nature of the drug and an irreversible melting process. The average Particle size of ALP, determined by laser light scattering and SEM, was in the range of 2-9 µm. Similar to DSC results, SEM micrographs and powder X-ray diffraction patterns indicated the crystalline structure of ALP. Analytical methods including ultraviolet spectroscopy and chromatographic analysis for ALP quantitation were developed. For UV analysis, a method was developed for quantitation of ALP in solution and in dissolution media at a maximum wavelength of 264 nm. The linearity of the calibration curve in the range of 0.001-0.020 mg/ml was excellent with a correlation coefficient (r^2) of 0.999. For chromatographic analysis, a reverse-phase HPLC method at 222 nm was developed for quantification of ALP contained in matrix tablet formulations. The linearity of the calibration curve in the range of 0.005-0.06 mg/ml was excellent with a correlation coefficient (r^2) of 0.999. The precision of the both methods was less than 1%RSD.

Lipophilic drugs, such as ALP, are difficult to completely extract and quantitate from tablets containing HPMC polymer due to their highly lipophilic nature and the gelling properties of the HPMC polymer. An efficient method to achieve complete recovery of alprazolam from powder blends and tablets

containing different excipient types and different molecular weight types of HPMC was developed and qualified. The method consisted of using hot water to swell the HPMC polymer followed by the addition of cold water to completely dissolve HPMC, and then adding a strong solvent (ACN) to dissolve the alprazolam and extract the drug from the HPMC solution. This method may be useful to recover other lipophilic drugs from hydrophilic matrix tablets containing HPMC.

For controlled release tablet formulations, the influence of different formulation parameters on the release of ALP from an HPMC matrix tablet was investigated. Formulation parameters, including tablet size, drug loading, polymer levels, excipient type and level, molecular weight type of HPMC, and dissolution media, were optimized during screening and formulation development of the matrix tablets. *In vitro* dissolution studies and similarity factor assessments were used as tools during formulation development.

Variations in tablet size influenced both the amount and extent of ALP release from a matrix tablet as well as the amount of HPMC necessary in the formulation to maintain a sustained release profile. A high level of HPMC was necessary for smaller tablets to obtain a desirable sustained release profile. When the tablet size was increased, resulting in an increased surface area for drug release, the rate of drug release was slower due to the change in the surface area-to-volume ratios and the amount of initial gel formation. Th optimum tablet size of 11 mm was selected to prepare 400 mg tablets throughout formulation development.

The amount of drug loading in a matrix tablet did not have an impact on the amount of ALP release. Similar release profiles were obtained from tablets containing either 5 or 10 mg ALP. The 10-mg ALP was loaded into a 400-mg matrix tablet. However, obtaining content uniformity of each tablet prepared by direct compression was a challenge. Therefore, a blending method to achieve good content uniformity was developed. The content uniformity of 10 tablets was within 90-110% of label amount of ALP with a low magnitude of RSD, indicating that the blending method developed was efficient to obtain a uniform distribution of ALP in each tablet. Additionally, the HPMC level was shown to be the most important factor to control drug release from a matrix tablet. When the HPMC level in the formulation was increased, the amount and extent of drug release significantly decreased. This was due to an increase in polymer concentration resulting in an increased viscosity of the gel as well as the formation of a gel layer with a longer diffusional path.

While maintaining the HPMC and drug level constant in the controlled release tablet formulations investigated, it was found that the type and level of excipient influenced the rate and extent of ALP release. The similarity factor was useful to compare dissolution profiles of tablets containing different excipients. The percent average difference, based on f_2 values, between dissolution profiles of formulations containing a soluble excipient compared to formulations containing an insoluble excipient was in the range of 15-20%, indicating dissimilarities in the release profiles. The percent average difference between dissolution profiles of formulations containing a similar type of excipient (i.e. soluble or insoluble

excipients) was in the range of 5-10%, indicating similar profiles. The insoluble excipients, especially DCP, caused the drug to be released at a slower rate and to a lesser extent than the soluble excipients investigated. Intermediate release profiles were obtained when binary mixtures of LAC and DCP were used in the formulation. The release mechanism of ALP from each tablet formulation was described by either Hixson-Crowell cube root kinetics equation or Peppas'equation (non-Fickian (anomalous) diffusion). Differences in excipient type or level in the formulations did not have an impact on the release mechanism of ALP from the tablets.

The influence of two different molecular weight types of HPMC, including HPMC-K4MP and HPMC-K100LVP, on the release of ALP from a matrix tablet was investigated. The rate of ALP release from a tablet formulation containing a low molecular weight type HPMC, HPMC-K100LVP, was faster than the amount of ALP release from a similar tablet formulation containing a high molecular weight type HPMC, HPMC-K4MP. Even though both HPMC types possess a similar degree of methoxyl substitution and hydroxypropyl substitution and similar gelation rates, they are different in terms of their degree of polymerization resulting in different molecular weights, which is reflected in the viscosity of an aqueous solution. Specifically, HPMC-K4MP has a molecular weight or nominal viscosity about 40 times greater than HPMC-K100LVP.

To investigate the influence of dissolution media on the release of ALP from the matrix tablets, USP buffer pH 6.0 or purified water was used as a dissolution medium rather than 0.1 N HCl solution (pH 1.1). Drug release

profiles of the same tablet formulation in different media were compared. No dose dumping of ALP occurred at any pH, which may confirm safety for oral administration of ALP tablets during the *in vivo* clinical study. The extent of ALP release in either USP buffer pH 6.0 or purified water was significantly lower than the extent of drug release from the same tablet formulations in 0.1 N HCl solution. Additionally, the extent of drug release in buffer pH 6.0 and purified water was incomplete and less than 50% at 12 hours. This was because the dissolution of ALP in buffer pH 6.0 and purified water did not occur under sink conditions.

Screening and formulation development studies demonstrated that rate of ALP release from HPMC matrix tablets was influenced by tablet size, excipient type, polymer level and type (MW distribution), and pH of the dissolution medium. However, drug loading did not have an impact on the release of ALP from matrix tablets.

Finally, two controlled release tablet formulations containing different HPMC molecular weight types or nominal viscosities (i.e. formulations K100LV-27 and K4M-42) were developed. Tablet size, shape and hardness were identical for both formulations. The K4M-42 tablet formulation containing 37 %w/w of HPMC-K4MP had an equivalent *in vitro* dissolution with K100LV-27 tablet formulation containing 45 %w/w of HPMC-K100LVP. A clinical batch of each formulation was successfully prepared according to cGMP. Both clinical batches were tested for initial product release prior to conducting the *in vivo* clinical study. The characterization of ALP tablets in terms of weight and hardness

variations, content uniformity, batch composite, and *in vitro* dissolution, met the predetermined acceptance criteria. Stability studies following the recommended ICH guidelines indicated that *in vitro* dissolution profiles of both tablet formulations remained unchanged for at least 6 months at 40°C/75 %RH and 12 months at 25°C/60%RH (f_2 = 67-91, 2-5 %average difference). Tablet potency results for all stability conditions were within 90-110% of label claim. No degradation peaks were observed during HPLC analysis of tablets from all storage conditions. However, tablets tended to become slightly softer (lower hardness) when expose to a high temperature and humidity condition (i.e. 40˚C/75%RH). At 25˚C/60%RH, the average tablet hardness remained unchanged for at least 12 months. Overall results demonstrated that both tablet batches manufactured under cGMP were within predetermined specification and were stable for at least one stability period following the completion of the clinical study, as mandated by clinical study requirements. Therefore, these two clinical formulations, which were equivalent *in vitro* (Initial dissolution: f_2 = 91, 2 %average difference), were tested for bioequivalence during an *in vivo* clinical study.

In vivo clinical results indicated that molecular weight types of HPMC did not influence *in vitro* or *in vivo* performance of controlled release tablets containing lipophilic ALP. Series of sustained release tablets provided bioequivalent results in both fed and fasted states. *In vitro* dissolution conditions sufficiently mimicked *in vivo* dissolution conditions and produced similar relative release profiles for all formulations. Similar literature results, postprandial administration of SR tablets resulted in a decreased Tmax and an increased Cmax,

possibly due to an increase in polymer erosion of the HPMC matrix tablet resulting from mechanical attrition. During pharmcodynamic assessment, no significant differences in SDMT scores were noted for both tablet formulations containing different MW types of HPMC. Also, no gender effects were observed during the study. Food delayed absorption of ALP by approximately 3 hours.

In further studies, the erosion mechanism as well as the rate of erosion of the ALP matrix tablets should be investigated in more detail in order to explain the release mechanism of ALP from the matrix tablets. The pharmacokinetic and pharmacodynamic approaches of ALP in the controlled release matrix tablets should be carefully evaluated in order to obtain a better understanding of absorption, distribution, metabolism and elimination mechanisms of ALP in the human subjects. Studies on other lipophilic and hydrophilic drugs may be necessary to investigate if the similar formulation parameters have a similar impact on the release of the drug from HPMC matrix tablets. Additionally, the concept that different molecular weight types of HPMC have no impact on *in vitro* and *in vivo* performance of controlled release matrix tablets should be proven with other lipophilic drugs and hydrophilic drugs.

For the multiparticulate delivery system, chlorpheniramine maleate (CPM) and theophylline anhydrous were used as models for the water-soluble and slightly water-soluble drugs, respectively. Uncoated matrix beads containing either CPM or theophylline, and microcrystalline cellulose were prepared by an extrusion/spheronization technique using purified water as a binder. Immediate

released profiles were obtained from each type of uncoated beads. The rate of drug release was reduced when a higher coating level was applied to the uncoated beads. The influence of processing parameters on drug release from EC coated matrix bead formulations was investigated.

The curing temperature and curing time influenced release of both CPM and theophylline from beads coated with an aqueous EC dispersion. The curing process results in a reduction of drug release when compared to drug release from uncured dosage forms. However, a faster drug release was observed when the coated beads were exposed to a high temperature of 60˚C for longer periods of time, such as 24, 48 or 72 hours. Additionally, the SEM micrographs showed a loss of film integrity (i.e. pores) for the coated beads exposed to these extreme curing conditions. Therefore, the optimum curing conditions should be determined in order to ensure complete film coalescence without disrupting film integrity. The completion of film coalescence is a function of both curing temperature and curing time. The optimum curing temperature should be higher than the glass transition temperature of the polymeric material, to accelerate the film formation process and to avoid aging problems of the coated products. The curing rates of coated beads were higher with higher storage temperatures because the high temperature facilitates the coalescence of the film. Specifically, the curing rate of beads exposed to 60˚C was faster than the curing rate of beads exposed to 40˚C. This was because, at 60˚C the coated beads were held above the T_g of the plasticized EC polymer. The recommended curing conditions, which

would ensure complete film coalescence without disrupting film integrity of coated beads, were either 6 to 12 hours at 60˚C or 1 to 2 hours at 80˚C.

For CPM coated beads, a higher percent weight gain or coating level, up to 36%, is necessary to achieve sustained release, because of its high aqueous solubility. Similar results were obtained when an HPMC-E5 subcoat was applied to the uncoated beads prior to the EC dispersion application. For theophylline coated beads, a lower coating level of 9-11% was sufficient to obtain a sustained release profile, due to the limited aqueous solubility of theophylline. The type of drug substance used to prepare the core beads had a major impact on the release of the drug from a multiparticulate system. Specifically, the release of drug from the system mainly depended on the aqueous solubility of the drug.

The influence of curing conditions on drug release from the dosage forms was independent of coating level, subcoating application, plasticization, or drug type.

In addition to the curing conditions, the amount of drug release from EC coated matrix beads was also influenced by plasticizer type and mixing time. Plasticizers, including water miscible (i.e. TEC) and water-insoluble (i.e. AMG and DBS) types, were plasticized for either 2 or 24 hours with the EC dispersion prior to application onto the uncoated beads containing CPM or theophylline.

For CPM beads, plasticization time had a significant influence on the amount of CPM release from the coated beads. Specifically, when a 24-hour mixing time was used to plasticize AMG with the EC dispersion, the release of CPM was slower. A longer plasticization time for AMG was necessary to achieve

a sustained release profile for CPM. DBS was found to be more efficient than AMG in terms of plasticization with the EC polymer.

Unlike the CPM release profiles, a slower release of theophylline was obtained from beads coated with an EC dispersion, plasticized with 24% AMG for only 2 hours. When a plasticization time of 24 hours was used, faster drug release was obtained. The 2-hour mixing time of AMG with the EC dispersion was sufficient to plasticize the EC polymer and was used in further studies of theophylline coated beads. AMG was found to be more efficient as a plasticizer for the EC dispersion than TEC. Therefore, 24% AMG was used to plasticize the EC dispersion for 2 hours in further studies of theophylline coated beads.

Results of the plasticization study indicated that the plasticizer type and plasticization time influenced release of both water-soluble and slightly water-insoluble drugs from matrix beads coated with an aqueous EC dispersion. Different types of plasticizer used in the coating formulation appeared to influence the release rate of the drug, by altering the water permeability of the film. A suitable plasticizer type as well as the optimum plasticization time were dependent on each coating system, and were primarily dependent on the nature of the drug substance. The influence of plasticization on drug release from the dosage forms was independent of coating level.

Dissolution profiles for theophylline beads demonstrated that the rate of theophylline release from beads coated at high coating levels was extremely slow. This was due to the limited solubility of theophylline during dissolution. Enhanced release of a slightly water-soluble drug (i.e. theophylline) was achieved

by the inclusion of a water-soluble additive, which rapidly dissolved in the dissolution medium leaving small channels or pores for the drug to pass through, thus increasing the permeability of the membrane and modifying the dissolution rate. Therefore, the incorporation of these additives into the EC coating dispersion can be used to modify the dissolution rate of drug from solid dosage forms. Additionally, the amount of theophylline released from EC coated beads was manipulated by the inclusion of different types and levels of water-soluble additives.

The mechanism of the water-soluble additive's ability to enhance the drug release can be explained by a rapid dissolution of a water-soluble additive after exposure of the coated beads to an aqueous dissolution medium. The dissolution medium or solvent penetrated into the beads to dissolve the water-soluble additive, which then migrated out and left pores in the coated film. At the same time, the dissolution of the drug within the matrix was initiated. Finally, the dissolved drug diffused through the EC film into a dissolution medium, especially via the water-filled pores previously created by the water-soluble additive.

This model is also applicable for formulation scientists, in order to manipulate and control the release of a slightly water-soluble drug substance.

Overall, results demonstrated the amount of drug release from EC coated matrix beads was influenced by drug type, plasticization, water-soluble additives, and curing conditions. Further studies should include the investigation of the drug release mechanisms from the EC coated matrix beads with and without the incorporation of a water-soluble additive. Stability or aging studies of the EC

coated matrix beads should be carried out in order to determine the optimum storage conditions for maintaining the release of the drug over extended periods of time. Other aqueous EC dispersion products, such as Surelease®, may be used for sustained release coating. The influence of the similar processing parameters should be investigated to determine if similar results are obtained.

In conclusion, different molecular weight types of HPMC did not influence *in vitro* or *in vivo* performance of controlled release tablets containing lipophilic ALP. Controlled release tablets provided bioequivalent results in both fed and fasted states.

Drug release from the EC coated matrix beads containing either a water-soluble or slightly water-soluble model drug was influenced by plasticizer type, plasticization time, and curing conditions. The amount of theophylline released from EC coated beads was manipulated by the inclusion of different types and levels of water-soluble additives.

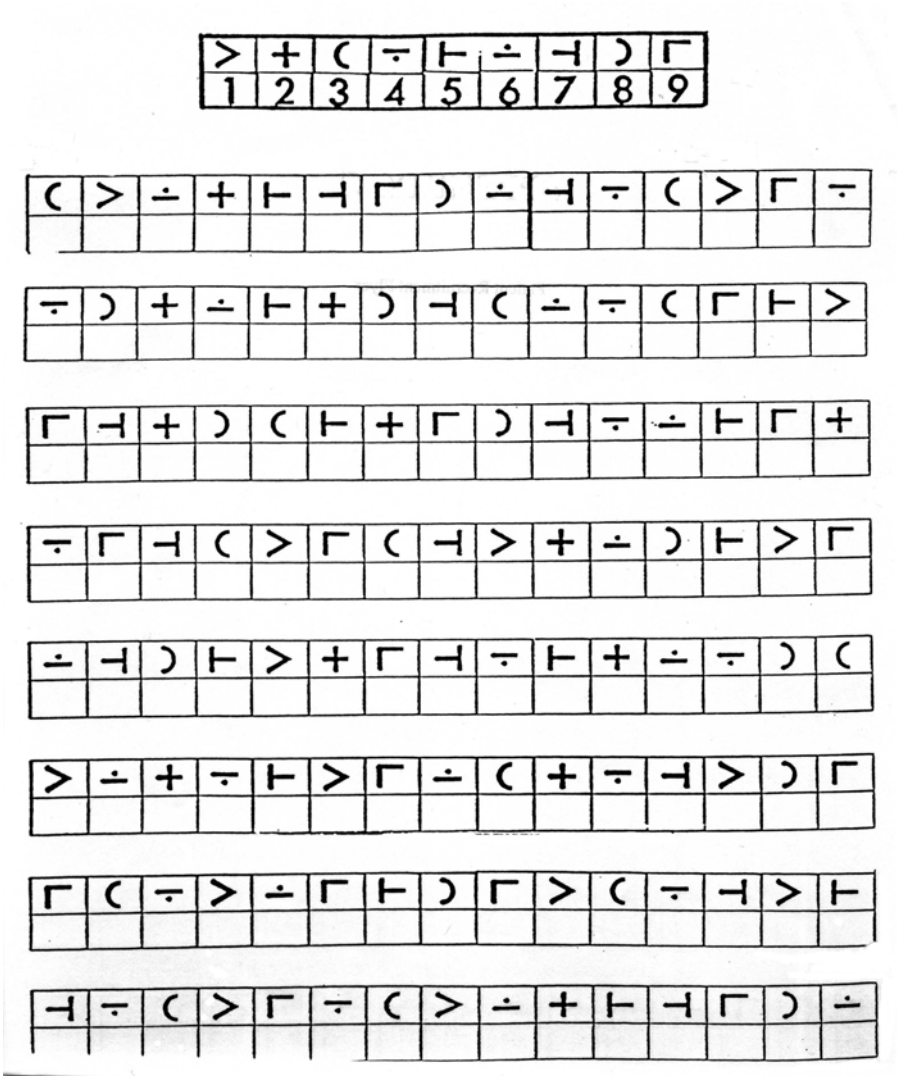
For both controlled release drug delivery systems, formulation and processing parameters must be investigated and optimized in order to achieve desirable release profiles and stabilize the amount of drug released throughout the shelf-life of the product. This research study provided useful information for formulation scientists on preformulation, formulation optimization, and characterization during development of controlled drug delivery systems containing cellulose ether polymers.

Appendix A

Symbol Digit Matching Test (SDMT)

Subject Initials & Number _____

Date & Time _____



Appendix B

Patient Recruitment Flyer

ATTENTION!!!

Are you healthy, non-pregnant individual between the ages of 18 and 65?

Would you be willing to take part in a scientific study testing the effects of two different tablets of the same medicine?

For $800 ($200 / visit X 4 visits) would you be willing to be hospitalized for 24 hours a week for four weeks?

You would be requires to undergo scheduled blood sampling and complete tests which study mental alertness.

If you answered “YES” please contact Dr. Robert Talbert in the department of clinical pharmacy at (210) 567-8318.

Appendix C

Consent Form

VA Department of Veterans Affairs VA RESEARCH CONSENT FORM

Subject Name: _____ **Date:** _____

Title of Study: SUBJECT CONSENT TO TAKE PART IN A STUDY OF BIOEQUIVALENCE OF ALPRAZOLAM IN CONTROLLED RELEASE MATRIX TABLETS CONTAINING HYDROXYPROPYL METHYLCELLULOSE WITH DIFFERENT MOLECULAR WEIGHT DISTRIBUTIONS

Principal Investigator: Dr. Robert L. Talbert **VAMC:** San Antonio, TX
Dr. Jay Peters

DESCRIPTION OF RESEARCH BY INVESTIGATOR:

We are asking you to take part in a research study comparing the effects of two different preparations of the same drug (hydroxypropl methylcellulose polymers). The study compares two pills which contain the same amount of the drug alprazolam. The pills are made with different inactive ingredients. The two different pills will be tested on an empty stomach and after eating. Subjects will take four pills. We want to learn if blood levels and effects on thinking of the different pills are similar. We are asking you to take part in this study because you are a healthy person 18 to 65 years of age.

If you decide to take part in the study, you will be given a different pill containing alprazolam on four different occasions. The amount of alprazolam in your bloodstream will be tested with blood draws. You will also be asked to complete a form which evaluates how the medication makes you feel. You will be required to stay in the hospital for a 24 hour period, once a week for four weeks. Blood samples (10 ml each or approximately two teaspoonfuls) will be collected before taking a pill and at 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours while you are in the hospital. You will also be required to return to the hospital on the second and third day, each week (48 and 72 hours), for outpatient blood draws. The total amount of blood removed during the study will be approximately equal to slightly more than one pint (560 ml or about 19 ounces). Common risks associated with blood draws are pain and bruising at the site of blood removal. Rare risks include irritation and/or infection of the blood vessel from which blood is being removed.

During the study, you will be required to take the medications both after eating and on an empty stomach. For the fasting part of the study, you will be required to not eat for 8 hours before you take the study medication and will not be able to eat until 2 hours after you have taken the medication. When you take the medication on a full stomach, you will be required to eat all of a special meal which will be prepared for you at the study site. This meal will be prepared so all people participating in the study have the same amount of food in their stomach when they take the study medication.

Alprazolam is a medication which is used to treat sleeping disorders and anxiety. Consequently, the most common (up to 50% depending on dose) and expected side effect of the medication is drowsiness. Side effects which occur in about one in 10 persons include fatigue, dizziness, headache, nausea, vomiting and memory loss. It is unlikely that any of these side effects will continue once you have stopped taking the medication.

Subject's identification (I.D. plate or name-last, first, middle)

INSTITUTIONAL REVIEW BOARD 11-3-00 Date Approved by IRB UTHSCSA

Signature of Subject

VA Form 10-1086 Jan 1990

Page 1 of 3

VA Department of Veterans Affairs VA RESEARCH CONSENT FORM

Subject Name:_____ **Date:**_____

Title of Study: SUBJECT CONSENT TO TAKE PART IN A STUDY OF BIOEQUIVALENCE OF ALPRAZOLAM IN CONTROLLED RELEASE MATRIX TABLETS CONTAINING HYDROXYPROPYL METHYLCELLULOSE WITH DIFFERENT MOLECULAR WEIGHT DISTRIBUTIONS

Principal Investigator: Dr. Robert L. Talbert **VAMC:** San Antonio, TX
Dr. Jay Peters

Prior to receiving the study medication, you will be examined by a physician and be asked to give blood for routine laboratory tests. These tests will include red and white blood cell counts, platelet counts, liver function tests and a pregnancy test for women. Abnormal or unusual findings in any of these tests may exclude you from participating in the study. If you are taking any medications, you will need to stop taking them 24 hours before beginning each phase of the study to minimize any potential drug interactions.

If you are pregnant or nursing, you cannot take part in this study. We will perform a pregnancy test before you begin the study to make sure that you are not pregnant. You should use birth control while you are taking part in the study because we do not know the effect alprazolam has on an unborn child. If you think you might be pregnant at any time during the study, you should tell us.

You will be compensated financially for taking part in the study in a total amount of $800. To receive the entire amount of money, you must complete all parts of the study. A pro-rated fee of $200 will be paid to you upon completion of each three-day segment of the study. It is important that you be on time for all scheduled appointments and blood draws. Subjects who miss appointments may be removed from the study.

All study related drugs, laboratory tests and clinic visits will be free for the time you are enrolled in the study.

If you are injured as a result of the research procedures, your injury will be treated. You will be responsible for any charges. We have no plans to give you money if you are injured. You have not waived any of your legal rights by signing this form.

Everything we learn about you in the study will be confidential. If we publish the results of the study in a scientific magazine or book, we will not identify you in any way. The results of the study will be given to Dow Chemical, the company that makes hydroxypropl methylcellulose. The University of Texas Health Science Center committee that reviews research on human subjects (Institutional Review Board), The Food and Drug Administration of the U.S. Government and Dow Chemical may also want to see records which identify you as a subject in this study.

Your decision to take part in the study is voluntary. You are free to choose not to take part in the study or to stop taking part at any time. If you choose not to take part or to stop at any time, it will not affect your future medical care at the University of Texas Health Science Center or any of the facilities of the South Texas Veterans Administration Health System. We will tell you about any significant new findings which we learn about during the course of this research which may relate to your willingness to continue taking part.

If you have questions now, feel free to ask us. If you have additional questions later or wish to report a medical problem which may be related to this study, Robert Talbert, Pharm.D. can be reached at (210) 567-8355 during the day or by digital pager (210) 271-6011. To use the pager, you need to have a touch tone (push button) telephone. Dial the pager number as you would any phone number. When you hear 3 short high-pitched beeps, dial in the number where you want the doctor to call you back. Push the # button, hang up and wait for the doctor to return your call. If Dr. Talbert is unavailable, you may page Jay Peters, MD at (210) 235-0693.

INSTITUTIONAL REVIEW BOARD 11-3-00 Date Approved by IRB UTHSCSA

VA Form 10-1086 Jan 1990

_____
Signature of Subject

VA Department of Veterans Affairs VA RESEARCH CONSENT FORM

Subject Name:_____ **Date:**_____

Title of Study: SUBJECT CONSENT TO TAKE PART IN A STUDY OF BIOEQUIVALENCE OF ALPRAZOLAM IN CONTROLLED RELEASE MATRIX TABLETS CONTAINING HYDROXYPROPYL METHYLCELLULOSE WITH DIFFERENT MOLECULAR WEIGHT DISTRIBUTIONS

Principal Investigator: Dr. Robert L. Talbert **VAMC:** San Antonio, TX
Dr. Jay Peters

The University of Texas Health Science Center committee that reviews research on human subjects (Institutional Review Board) will answer any questions about your rights as a research subject (210) 567-2351.

We will give you a signed copy of this form to keep.

YOUR SIGNATURE INDICATES THAT YOU HAVE DECIDED TO TAKE PART IN THIS RESEARCH STUDY AND THAT YOU HAVE READ AND YOU UNDERSTAND THE INFORMATION GIVEN ABOVE AND EXPLAINED TO YOU.

Signature of subject

Signature of witness

Date Time

Signature of Person Obtaining Consent

Printed Name of Person Obtaining Consent
Title:_____

VA Form 10-1086 Jan 1990

INSTITUTIONAL REVIEW BOARD 11-3-00 Date Approved by IRB UTHSCSA

Signature of Subject

Glossary

ALP	Alprazolam
AMG	Acetylated monoglycerides
CPM	Chlorpheniramine maleate
CSD	Calcium sulfate dihydrate
DBS	Dibutyl sebacate
DCA	Dicalcium phosphate anhydrous
DCP	Dicalcium phosphate dihydrate
DEX	Dextrose
DSC	Differential scanning calorimetry
EC	Ethylcellulose
HPLC	High-performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
LAC	Lactose monohydrate
MCC	Microcrystalline cellulose
PEG	Polyethylene glycol
RH	Relative humidity
SEM	Scanning electron microscopy
SUC	Sucrose
TEC	Triethyl citrate
T_g	Glass transition temperature
UV	Ultraviolet spectroscopy

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