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Effect of formulation variables on drug and polymer release from HPMC-based matrix tablets

K.C. Sung[a,b,*], Phillip R. Nixon[a], John W. Skoug[c], T. Robert Ju[a], Ping Gao[c], E.M. Topp[b], M.V. Patel[a]

[a]*Drug Delivery Research and Development, Pharmacia and Upjohn, Kalamazoo, MI, USA*
[b]*Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, KS, USA*
[c]*Analytical Research and Specifications Development, Pharmacia and Upjohn, Kalamazoo, MI, USA*

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Abstract

The objective of this work was to assess the effect of two formulation variables, hydroxypropylmethylcellulose (HPMC)/lactose ratio and HPMC viscosity grade, on the release of a model drug and HPMC, as well as the mechanism of drug release from HPMC-based matrix tablets. A water-soluble compound, adinazolam mesylate, was used as the model drug. Both drug and HPMC release were found to be a function of the formulation variables, with higher drug and HPMC release rates for formulations with lower HPMC/lactose ratios and lower HPMC viscosity grades. However, the K15M and K100M formulations had identical drug release profiles. All the drug release data fit well to the Higuchi expression. By comparing the drug and HPMC release data, it was concluded that diffusion of drug through the hydrated gel layer was the predominant drug release mechanism for most of the formulations studied.

Keywords: Hydroxypropylmethylcellulose; Matrix tablets; Adinazolam mesylate; Dissolution; Diffusion; Matrix dissolution

1. Introduction

Swellable and erodible systems prepared by incorporating drugs in hydrophilic polymeric matrices have received considerable attention for sustained release formulations. Different types of hydrophilic polymers have been reported and used in these systems (Ranga Rao and Pad-

* Corresponding author. Current address: Department of Pharmacy, Chia-nan Junior College of Pharmacy, Tainan, Taiwan.

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malatha Devi, 1988). Among the hydrophilic polymers, hydroxypropylmethylcellulose (HPMC) is frequently used due to its non-toxic nature and ease of manufacturing. Several important formulation variables such as HPMC concentration, HPMC viscosity grade, dosage size and manufacturing process have been used to modulate drug release from the HPMC-based matrices (Alderman, 1984; Ford et al., 1985; Doelker, 1987; Ranga Rao and Padmalatha Devi, 1988; Hogan, 1989). Among these variables, HPMC concentration and HPMC viscosity grade are most often used in regulating drug release (Ford et al., 1985; Doelker, 1987; Hogan, 1989). In general, these two formulation variables may affect drug release profiles both kinetically and mechanistically. Therefore, in order to understand the effect of these two formulation variables on drug release, it is desirable to examine them in a systematic way.

Drug release mechanisms from swellable and erodible hydrophilic matrices have been described by several authors (Peppas et al., 1980; Lee and Peppas, 1987; Conte et al., 1988; Harland et al., 1988; Skoug et al., 1993; Pham and Lee, 1994; Gao et al., 1995). As a matrix contacts the dissolution medium, the polymer undergoes a relaxation process and two fronts are established around the matrix: the penetration front and the dissolution front. The penetration front is defined as the interface between the non-relaxed polymer and the gel; the dissolution front is defined as the interface between the gel and the dissolution medium. At the penetration front, the hydration, swelling and coalescence of polymer particles occur, whereas at the dissolution front, polymer chain disentanglement and dissolution of the hydrated matrix occur. The gel layer thickness, which determines the diffusional path length of the drug, corresponds to the distance between the penetration and dissolution fronts (Lee and Peppas, 1987; Harland et al., 1988; Skoug et al., 1993; Pham and Lee, 1994; Gao et al., 1995). According to the physical picture described above, drug release from swellable and erodible hydrophilic matrices can be attributed to polymer dissolution (matrix erosion mechanism), drug diffusion through the gel layer (diffusion mechanism), or a combination of both (Alderman, 1984; Doelker, 1987; Mitchell et al., 1993; Skoug et al., 1993; Pham and Lee, 1994; Gao et al., 1995). Previous publications (Alderman, 1984; Doelker, 1987; Skoug et al., 1993) suggest that for drugs with low water solubility, drug release is mainly via erosion; for a soluble drug, the drug can dissolve and diffuse through the hydrated gel layer and diffusion is predominant.

In much of the published literature, drug release data were fitted to the Higuchi model for a porous matrix system to determine the drug release mechanisms. However, the effect of matrix erosion on drug release is not included in this treatment. The degree of matrix erosion can be assessed by measuring the amount of polymer released into the dissolution medium. Therefore, in order to reveal the mechanism affecting drug release from different formulations, it is important to analyze both drug and polymer release data.

The model drug used in this study is adinazolam mesylate. Its pK_a and aqueous solubility at room temperature are 5.7 and > 50 mg/ml, respectively. Lactose was used as diluent. HPMC concentrations in the tablet were varied by changing the relative amounts HPMC and lactose in the tablet. In addition, various HPMC molecular weights were studied; molecular weight variations in HPMC are commonly expressed as viscosity grade. Larger viscosity grades correspond to greater polymer molecular weight.

There are two major goals in the present study. The first goal is to assess the effect of two formulation variables, the HPMC/lactose ratio and HPMC viscosity grade, on drug and HPMC release. The second goal is to utilize the drug and HPMC release data to gain insight into the mechanism of drug release from the HPMC-based matrix tablets studied.

2. Materials and methods

2.1. Materials

HPMC K100LV, K4M, K15M, and K100M were obtained from the Dow Chemical Company. The manufacturer's certificate of analysis reported

their viscosities in 2% aqueous solution to be 92, 4870, 15 096, and 105 300 cps, respectively. The model compound, adinazolam mesylate, was supplied by the Upjohn Company. Magnesium stearate (EA food grade, Witco Chemical Company) was used as a lubricant, and lactose (NF Spray Process #315, Formost Foods) was used as a filler.

2.2. Tablet formulation and preparation

Tablets prepared with different HPMC/lactose ratios and HPMC viscosity grades were used in the study. In the experiments with varying HPMC/lactose ratios, K4M was used as the model polymer since its properties have been well documented (Ford et al., 1985; Mitchell et al., 1993; Skoug et al., 1993; Gao et al., 1995). The HPMC/lactose weight ratios included 80:17, 65:32, 50:47, 35:62 and 20:77. Formulations with 35% HPMC and 62% lactose were used in all of the viscosity grade (K100LV, K4M, K15M and K100M) experiments according to the manufacturer's suggested tablet HPMC percentage (20–40%). The weight of the tablets were 500 mg. By holding the tablet weight constant, the surface area and volume of the dry compacts were essentially fixed. All tablets contained 12.5 mg (2.5% w/w) of adinazolam mesylate and 2.5 mg (0.5% w/w) of magnesium stearate. Direct compression with a manual hydraulic press (Fred Carver, Model Carver Laboratory Press C.) at 4000 psi of pressure was used to prepare 500 mg tablets.

2.3. Dissolution experiments

Fig. 1 shows the dissolution apparatus used in this study. This unconventional dissolution method allowed the release kinetic and swelling kinetic data to be collected simultaneously. For the scope of this paper, only drug and polymer release data were reported and discussed. The dissolution samples were collected automatically by a Dissoette (Hanson Research, CA, Model No. 27-000-206). The tablet was held in place in the release medium (700 ml deionized H_2O) by mounting on a stand sitting inside a beaker. Deionized water was used as the release medium so that the effect of buffers on drug release could be eliminated. The beaker was placed on a magnetic stirring plate and was covered with a glass plate to prevent medium evaporation. The tablet was fixed on the top of the stand by drilling a tiny hole into the tablet and inserting the stand (with some epoxy glue) into that hole. The diameter and height of the beaker were 14.5 cm and 7.2 cm, respectively. The position of the stand was fixed for each run. The stirring rate of the 3.9-cm stir bar was kept at 265 rpm. Before each experiment, sampling times (up to 14 h) were programmed into the Dissoette system. All experiments were performed overnight at ambient temperature (22°C), and the collected dissolution samples were subjected to further HPLC analysis.

2.4. HPLC assays

Adinazolam mesylate release was monitored using high performance liquid chromatography (HPLC). The chromatographic system consisted of a pump (Waters Model 510), an autosampler (Waters 712 WISP), a UV detector (Milton Roy Max N series) and a recorder (Sargent-Welch Model DXKR). An in-house computer system was used for data collection and storage. A C-8 reverse phase silica column (Brownlee RP-8, 10 μm, 4.6 mm × 13 cm) was utilized for separation,

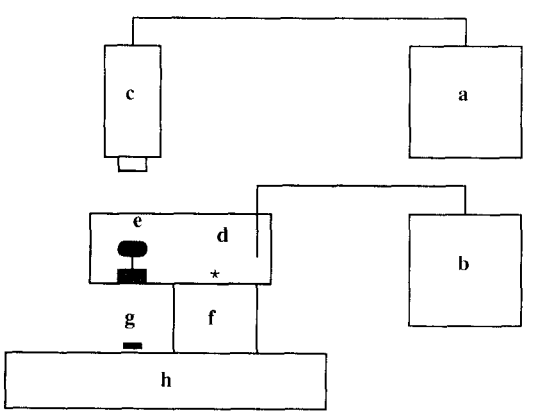

Fig. 1. The diagram of the fully automated system used for swelling and dissolution experiments: (a) image analysis system; (b) Dissoette, (c) camera; (d) beaker; (e) tablet on a stand; (f) stirring plate; (g) light slots; and (h) light box.

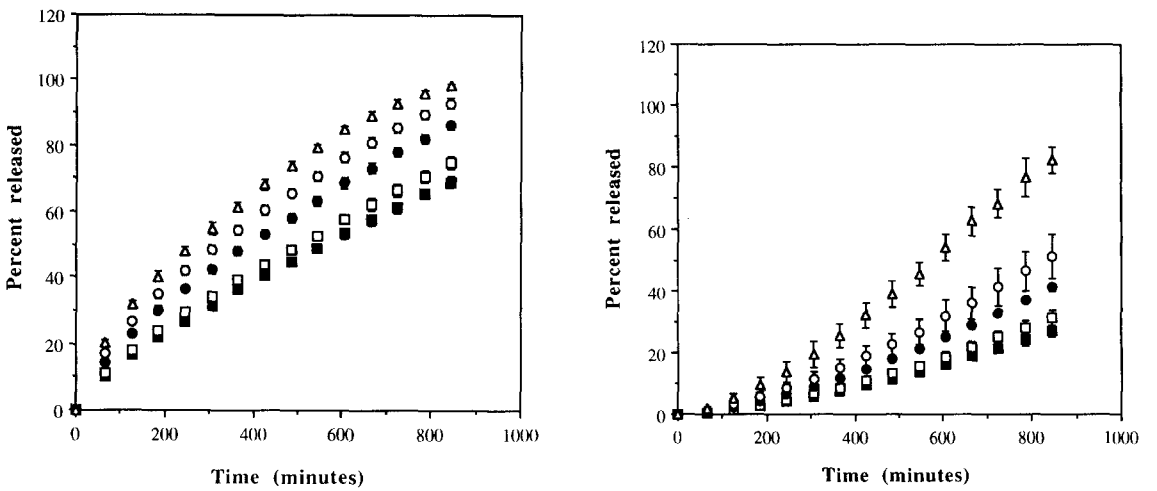

Fig. 2. (a) The percent adinazolam mesylate released vs. time profiles for formulations with various HPMC/lactose ratios: (■) 80:17; (□) 65:32; (●) 50:47; (○) 35:62; and (△) 20:77. Mean ± S.D. are presented ($n = 3$–4). (b) The percent HPMC released vs. time profiles for formulations with various HPMC/lactose ratios: (■) 80:17; (□) 65:32; (●) 50:47; (○) 35:62; and (△) 20:77. Mean ± S.D. are presented ($n = 3$–4).

while a tetrahydrofuran–acetonitrile–phosphate buffer system (100:700:1200) was used as the mobile phase. The flow rate was 1.5 ml/min, and the UV wavelength for detection was 254 nm. The injection volume was 20 μl. Under these conditions, the retention time of adinazolam mesylate was approximately 4.7 minutes. Adinazolam mesylate concentrations were determined by measuring the peak area and comparing with the peak area of known standards. Further details concerning the assay method are available elsewhere (Skoug et al., 1993).

A gel permeation chromatography method with differential viscometric detector was used to measure the HPMC released. This method has been reported previously (Skoug et al., 1993) for the HPMC K4M; the same procedure was applied here to all four viscosity grades. The HPMC response was measured using a differential viscometric detector (Viscotek Model 110, Porter TX), using a TSK G2000 SW column (7.5 mm × 30 cm) for the separation. With the exception of the detector and the column, the chromatographic system also contained a pump (Waters Model 510), an autosampler (Waters WISP 717) and a recorder (Sargent-Welch Model DXKR). The mobile phase composition was 0.01 M sodium sulfate plus 0.02% sodium azide. The flow rate was 1 ml/min, and the injection volume was 75 μl. Because the average molecular weight of the HPMC used exceeded the molecular weight cut-off of the column, the HPMC retention volume was close to the exclusion limit (5.5 min). The HPMC standards for each molecular weight series are prepared by using the viscosity grade of interest. The concentrations of the HPMC standards used for the K4M, K15M and K100M samples were 0.04 mg/ml and 0.1 mg/ml; different standard concentrations (0.4 mg/ml and 0.9 mg/ml) were used for the K100LV formulation in order to fit the concentration ranges of the samples. Again, HPMC concentrations were determined by measuring peak area and comparing with the peak area of known standards.

3. Results and discussion

3.1. Drug and polymer release

Fig. 2(a) and (b) shows the effect of HPMC/lactose ratio on adinazolam mesylate and HPMC release, respectively. A greater drug release rate was observed for tablets with lower HPMC/lac-

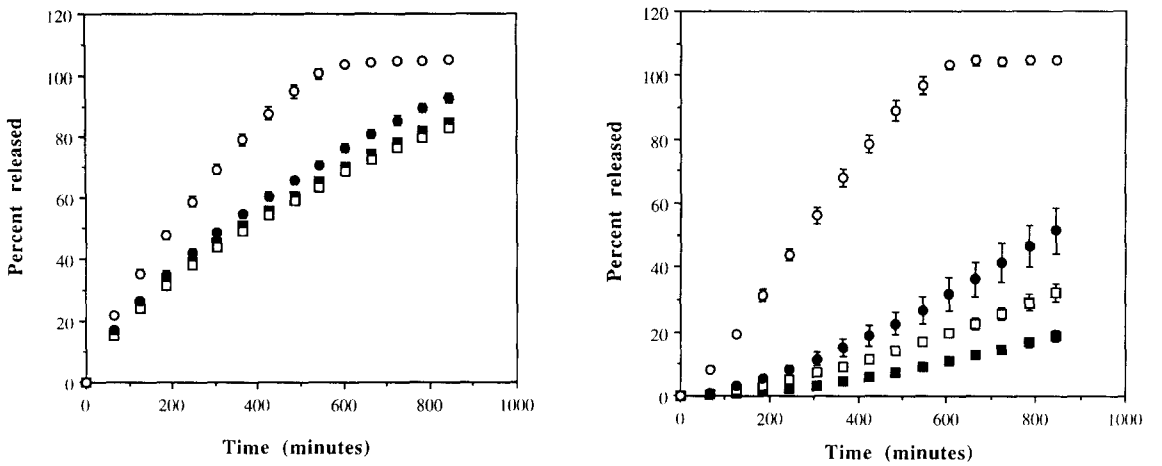

Fig. 3. (a) The percent adinazolam mesylate released vs. time profiles for formulations with various HPMC viscosity grades: (■) K100M; (□) K15M; (●) K4M; and (○) K100LV. Mean ± S.D. are presented ($n = 3$–4). (b) The percent HPMC released vs. time profiles for formulations with various HPMC viscosity grades: (■) K100M; (□) K15M; (●) K4M; and (○) K100LV. Mean ± S.D. are presented ($n = 3$–4).

tose ratios (Fig. 2(a)). Changes in the instantaneous drug release rate with time were reflected in the curvature in the drug release profiles for all formulations. These results are consistent with previous reports (Alderman, 1984; Doelker, 1987; Hogan, 1989) and demonstrate that changes in the HPMC/lactose ratio can be used to produce a wide range of drug release rates. As with the drug release results, faster HPMC release (on a percentage basis) was obtained for tablets with lower HPMC/lactose ratios (Fig. 2(b)). These convex-shaped release profiles indicated that the instantaneous HPMC release rates (and therefore the instantaneous matrix dissolution rate) increased with time. The final pH of the dissolution medium was approximately 5.4, about 0.4 pH units below the initial pH. Given that the performance of HPMC-containing matrices is relatively independent of pH, the observed change in pH during the experiment is insignificant.

The influence of HPMC viscosity grade on adinazolam mesylate release is shown in Fig. 3(a). A constant HPMC/lactose ratio (35:62) was used while the viscosity grade of HPMC was varied. The fastest drug release rate was observed for the K100LV formulation. The K4M formulation exhibited a slightly greater drug release rate than the K15M and K100M formulations. The lack of difference in the drug release profiles for K15M and K100M formulations suggests the existence of a 'limiting HPMC viscosity', i.e., for the system studied, the drug release rate no longer decreased when the viscosity grade was increased above 15 000 cps. As observed in the HPMC/lactose ratio series, the instantaneous drug release rate decreased with time for the viscosity grade series, which is reflected in the curvature of percent drug released profiles. Fig. 3(b) shows the cumulative HPMC released (on a percentage basis) versus time profiles for the formulations containing different HPMC viscosity grades. Formulations containing the higher HPMC viscosity grades have slower HPMC release rates. That is, the K100LV formulation had the fastest, and the K100M formulation the slowest, polymer release rate. A significantly greater HPMC release rate was observed for the K100LV formulation, with complete matrix dissolution at around 600 min. No 'limiting HPMC viscosity' was observed for polymer release from this series of formulations. The instantaneous HPMC release rates (and therefore the instantaneous matrix dissolution rate) also increased with time for the K4M, K15M and K100M formulations.

Table 1
The Higuchi rate constants (%released/min$^{1/2}$) of various formulations. Mean ± S.D. are presented ($n = 4$)

Formulation	Rate constant
80:17	2.72 ± 0.04
65:32	2.85 ± 0.07
50:47	3.17 ± 0.05
35:62	3.47 ± 0.08
20:77	3.70 ± 0.10
K100M	3.17 ± 0.03
K15M	3.13 ± 0.04
K4M	3.47 ± 0.08
K100LV	4.86 ± 0.16

3.2. Drug release mechanism

For a water-soluble drug that has completely dissolved when the tablet is hydrated, the Higuchi expression describing Fickian drug release from a single face of a non-swelling tablet is frequently used to describe the drug release profiles of matrix extended-release dosage forms. Despite the fact that this treatment suffers from a number of approximations, it is a useful tool for analyzing drug release data and for obtaining drug release rates. According to this model, a straight line is expected for the percent drug release versus square root of time plot if drug release is based on a diffusion mechanism.

The slopes of the square root of time plots (up to 60% of total drug released) for formulations with various HPMC/lactose ratios and HPMC viscosity grades are shown in Table 1. Greater square root of time rate constants (Higuchi rate constants) were observed for formulations with lower HPMC/lactose ratio. Table 1 also shows that the K100LV formulation has a much greater Higuchi rate constant; the K100M and K15M formulations have essentially the same rate constant.

Fig. 4(a) and (b) show the percent drug released versus square root of time plots (up to 60% of total drug released). It is notable that the r^2 values of the linear regressions were greater than 0.99 and the residuals were randomly distributed for all the formulations studied, indicating that the data fit the Higuchi model well. This simple analysis of the drug release data, within the limitations of the model, are consistent with a diffusional mechanism of release. However, matrix dissolution (also commonly referred to as matrix erosion), which is an important characteristic of swellable and erodible systems, is not considered

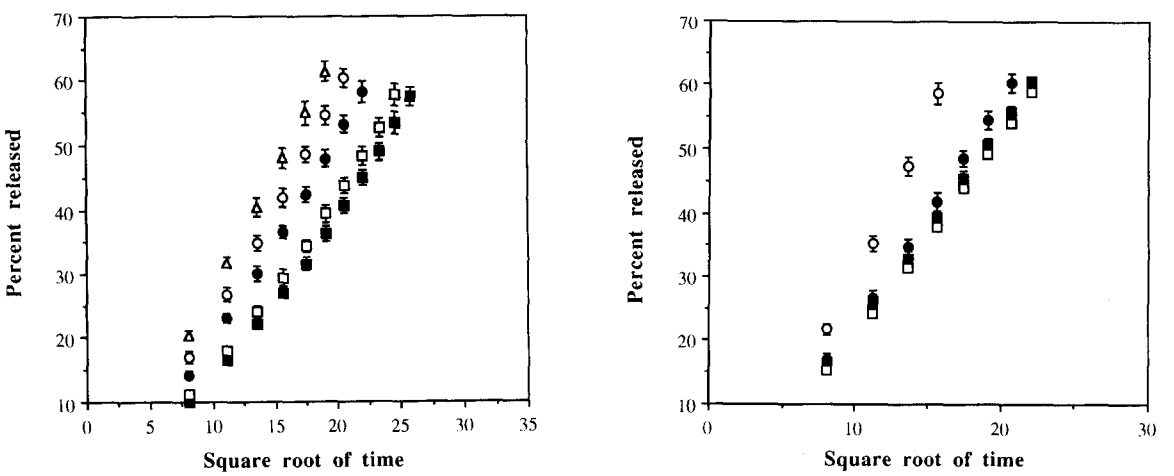

Fig. 4. (a) The percent adinazolam mesylate released vs. square root of time (min$^{1/2}$) plots for formulations with various HPMC/lactose ratios: (■) 80:17; (□) 65:32; (●) 50:47; (○) 35:62; and (△) 20:77. Mean ± S.D. are presented ($n = 4$). (b) The percent adinazolam mesylate released vs. square root of time (min$^{1/2}$) plots for formulations with various HPMC viscosity grades: (■) K100M; (□) K15M; (●) K4M; and (○) K100LV. Mean ± S.D. are presented ($n = 4$).

in the square root of time model. Therefore, the mechanistic information obtained using the Higuchi equation should be viewed with caution. Additional analysis, such as that discussed below and elsewhere (Skoug et al., 1993; Gao et al., 1996), is needed to make more definitive mechanistic conclusions.

The polymer release data generated in this study provide complementary information regarding the mechanism of drug release (Skoug et al., 1993). In general, the drug release rates within the two series of formulations increased with increased matrix dissolution rates. This finding indicates that the swelling kinetics of the matrices, which control the matrix dissolution, were an important determinant of drug release. However, changes in the swelling kinetics of the matrices can lead to changes in drug release through two distinct mechanisms. If the drug does not completely dissolve in the hydrated matrix, faster matrix dissolution would result in increased drug release through what is often referred to as matrix erosion. Alternatively, swelling kinetics changes can lead to changes in the diffusional pathlength and/or diffusional resistance of the gel layer. Specifically, for a drug that completely dissolves at the medium penetration front and is released by a diffusional mechanism, a thicker and/or more tortuous gel layer should result in slower drug release (Gao et al., 1996).

Quantitatively characterizing the mechanism of release using polymer release data is possible when drug and polymer release (on a percentage basis) are superimposable. In this case, one may conclude that drug is released through a 'matrix erosion' mechanism (Skoug et al., 1993). When polymer release is slower than drug release, it can be concluded that diffusion contributes at least partially to drug release. For the 80:17, 65:32, 50:47, 35:62 and 20:77 formulations, about 32, 34, 42, 49, and 55%, respectively, of the total drug were released at 305 min; whereas only 6, 6, 9, 12 and 20%, respectively, of the total HPMC was released at the same sampling time. For the K100M, K15M and K4M formulations, about 45, 44, and 49% of the total drug versus about 3, 7, 12% of the total HPMC were released at 305 min. Therefore, based solely on the polymer and drug release data for these formulations, it is clear that adinazolam mesylate release occurs predominantly through a diffusional mechanism of release. The mechanism of release for the K100LV formulation is more difficult to assess, however, since the drug and polymer release rates were closer than those observed for the other formulations. Nevertheless, for the reasons outlined below, we believe that adinazolam mesylate was released primarily through a diffusional mechanism from the K100LV formulation as well as from the other formulations studied.

Adinazolam mesylate is a relatively soluble drug that is likely to be completely dissolved at the medium penetration front. Therefore, undissolved drug is unlikely to be released by 'matrix erosion'. Also, as noted above, the square root of time analysis is consistent with a diffusional mechanism of release. Furthermore, optical imaging (swelling kinetics) and drug release modeling efforts on similar formulations (including a K100LV-containing formulation) have supported the conclusion that adinazolam mesylate is released primarily by diffusion of the drug through the gel layer (Gao et al., 1996). Lastly, although the K100LV data highlight the large differences in the swelling kinetics of the formulations studied, the mathematical modeling work of Ju et al. (1995) has shown that, for the case of diffusion-controlled release of a soluble drug, the differences between HPMC and drug release decrease with a decrease in the 'equivalent molecular weight' of the matrix. Indeed, the difference in drug and polymer release is predicted to nearly diminish at an equivalent molecular weight of about 10 000. Therefore, since the equivalent molecular weight of the K100LV-containing matrix in this study was calculated to be about 10 000, the similarity of drug and polymer release for that formulation is consistent with the model predictions.

The observed concave drug release and convex HPMC release profiles of the formulations studied may be attributed to the matrix swelling. As the swelling process proceeds, the gel layer gradually becomes thicker (Gao et al., 1996) and therefore the drug concentration gradient along the diffusional pathlength is decreased. The gradually

decreased drug concentration gradient resulted in progressively slower drug release rates and concave drug release profiles. The continuous polymer hydration during the matrix swelling process will decrease the matrix HPMC concentration to a critical value called the 'disentanglement concentration' (Lee and Peppas, 1987; Gao et al., 1996; Ju et al., 1995), which results in gradually increased polymer release rates and convex HPMC release profiles.

In summary, the effects of two formulation variables, HPMC/lactose ratio and HPMC viscosity grade, on adinazolam mesylate and HPMC release were examined. Higher drug and HPMC release rates were observed for formulations with lower HPMC/lactose ratios and lower viscosity grades; however, the K15M and K100M formulations had identical drug release profiles indicating that a 'limiting viscosity grade' exists. The drug release data for all formulations fit well to the Higuchi model. Data analysis using the drug and polymer release profiles indicated that diffusion was the predominant drug release mechanism for the formulations studied.

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