Swelling of Hydroxypropyl Methylcellulose Matrix Tablets. 2. Mechanistic Study of the Influence of Formulation Variables on Matrix Performance and Drug Release

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Abstract □ We characterized the effect of hydroxypropyl methylcellulose (HPMC)/lactose ratio and HPMC viscosity grade (molecular weight) on solute release and swelling of matrix tablets. We used a semiquantitative optical imaging method to monitor the swelling of matrices with HPMC content from 20% to 80% (w/w) and four viscosity grades. Several aspects of the swelling process common to all formulations were revealed: (i) swelling is anisotropic with a preferential expansion in the axial direction, (ii) swelling is isotropic with respect to the gel layer thickness and composition in both axial and radial directions, (iii) the gel layer develops in three stages, and (iv) water penetration is Fickian in nature and essentially constant for all formulations. We monitored simultaneously drug, lactose, and HPMC release. Lactose and drug release rates were superimposed, indicating a similar diffusional release mechanism and no interaction with HPMC. The strong dependence of HPMC release on viscosity grade is explained on the basis of the concept of polymer disentanglement concentration. We analyzed drug release rates using a model for a reservoir-type release system that incorporates swelling kinetics. HPMC/lactose ratio modulates drug release rate by altering drug diffusivity, a function of gel composition. In contrast, HPMC viscosity grade impacts matrix dissolution and gel layer thickness development below a critical molecular weight. For slowly dissolving matrices containing high viscosity grade (>4000 cps) HPMC, similar drug release rates are observed mainly due to the same drug diffusivity as a result of the identical gel composition and thickness. For fast dissolving matrices (≤100 cps) swelling inhomogeneity is proposed as being responsible for a higher apparent drug diffusivity and release rate.

Introduction

Our previous investigations of hydroxypropyl methylcellulose (HPMC)-based extended-release dosage forms containing adinazolam mesylate and alprazolam indicate that diffusion is the predominant mechanism of drug release.[1-4] This conclusion is supported by our recent study of the concentration dependence of drug diffusivity in the presence of the major components (drug, lactose, and water) in HPMC gel solution.[3] Using the Higuchi equation for soluble drugs, we demonstrated that the dependence of drug diffusivity upon the concentrations of HPMC, lactose, and drug can be correlated to the change in drug release rate as a function of formulation composition.[4] However, a limitation of this modeling work is the lack of consideration of swelling kinetics of the matrix (the Higuchi model assumes a nonswelling, nondissolving matrix[5]).

As described in a companion report.[6] we developed an optical imaging method based on an understanding of the light scattering mechanism for polymer gels. This approach does not restrict the physical geometry of the matrix tablets and is generally applicable for studying the swelling kinetics of matrix tablets *in situ*. This method not only allows direct measurement of tablet dimensional changes and gel layer evolution during swelling but also provides a semiquantitative determination of the HPMC concentration profile across the gel layer.

Here we describe a comprehensive characterization of the release mechanism of HPMC matrices that vary systematically in HPMC/lactose ratio and HPMC molecular weight, based on the *in situ* measurement of both swelling and solute release kinetics. Adinazolam mesylate, a water soluble drug, is used as a model since its diffusional behavior and release kinetics have been well characterized.[1-3] A detailed analysis of the swelling kinetic data (total tablet dimension, gel layer thickness, and water penetration rate) is given including a critical discussion of the limitations of the optical imaging technique. The swelling and drug release kinetics as a function of formulation composition are analyzed using a mathematical model that allows the deconvolution of the confounding effects of the diffusion and swelling mechanisms.

Experimental Section

Materials—Methocel Premium (HPMC) K100LV (molecular mass ≈ 25 kDa), K4M (molecular mass ≈ 95 kDa), K15M (molecular mass ≈ 120 kDa), and K100M (molecular mass ≈ 250 kDa) were received from Dow Chemical Company. The median diameter particle sizes of these materials, determined by light diffraction, are 59, 66, 50, and 62 μm for K100LV, K4M, K15M, and K100M, respectively; geometric standard deviations ranged between 2.5 and 2.7. Adinazolam mesylate, was supplied by Pharmacia & Upjohn, Inc. Magnesium stearate (Witco Chemical Company, Inc.) was used as lubricant, and lactose (NF hydrous spray process STD from Foremost Foods Co.) was used as filler.

Tablet Formulas and Preparation—Cylindrical tablets with different HPMC/lactose ratios and HPMC viscosity grades were made for this study. In the experiment with varying HPMC/lactose ratios, K4M was used as the model polymer. Tablets with HPMC/lactose ratios (w/w) of 80/17, 65/32, 50/47, 35/62, and 20/77 were studied and are referred to as the concentration series. Tablets that varied in HPMC viscosity grade contained a constant HPMC/lactose ratio of 35/62 and are referred to as the molecular weight (MW) series. All tablets contained 6.25 mg of adinazolam mesylate and 1.25 mg of magnesium stearate and weighed 250 mg, thus fixing the surface area and volume of the tablets. Direct compression with a manual hydraulic press (Fred Carver Inc., Model Carver Laboratory Press C) and a pressure of 4000 pounds (17.8 kN) was applied in the axial direction to prepare tablets having a diameter of 8.0 mm. The thickness of the tablets varied with the formulation, with a range of 3.8–4.3 mm.

Swelling and Solute Release—All swelling and solute release experiments were conducted at room temperature (22 ± 1 °C) in 700 mL of deionized water with agitation provided by a stir bar rotating at 200 rpm. Swelling was monitored using an optical imaging method (see ref 6), and samples were collected simultaneously at discrete times using a fraction collector (Dissoette, Hanson Research) for subsequent quantitation of drug, lactose, and HPMC. These samples

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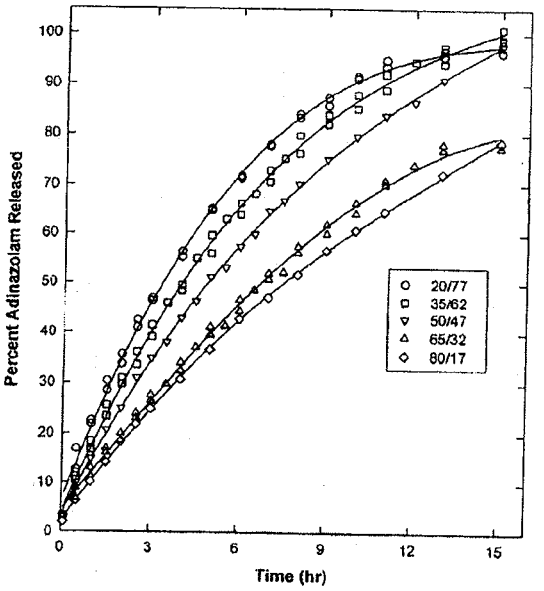

Figure 1—Drug release profiles of the concentration series of adinazolam mesylate matrix tablets with various HPMC/lactose ratios as indicated. Each profile represents the average of at least two experiments (axial and radial). All formulations contained HPMC-K4M, and the total tablet mass was fixed at 250 mg.

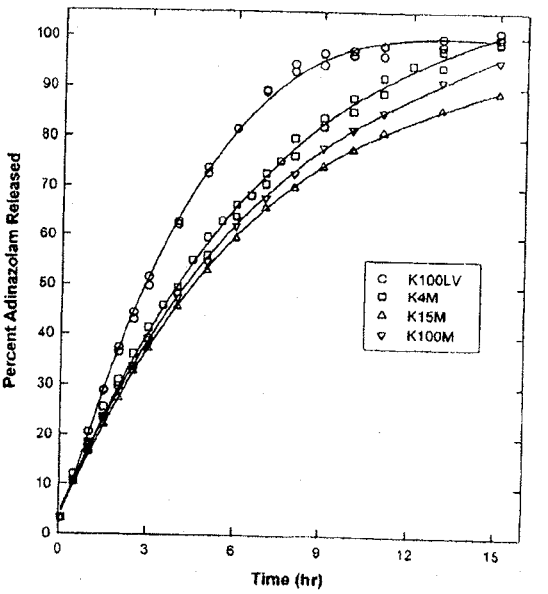

Figure 2—Drug release profiles of the MW series of adinazolam mesylate matrix tablets with various viscosity grades of HPMC as indicated. Each profile represents the average of at least two experiments (axial and radial). The HPMC/lactose ratio was 35/62, and the total tablet mass was fixed at 250 mg.

were recapped and stored in the refrigerator before analysis. The amounts of adinazolam mesylate and HPMC in the samples were then quantitated using the simultaneous HPLC assay method described in ref 1 with one minor modification: a shorter column (7.5 mm × 15 cm TSK GFC 200, particle size = 5 μm) with a mobile phase of 13/87 acetonitrile/buffer was used because it resulted in a shorter retention time for drug (7.5 vs 15 min) and therefore a faster run time.

Lactose release was determined using a separate chromatographic system. A Zorbax NH_2 column was used at 35 °C with refractive index detection and 80% acetonitrile/water as the mobile phase. With this system, the peak height response for lactose was linear over the 0.05–1.0 mg/mL range. Quantitation was performed using external standards prepared at concentrations corresponding to 50% and 100% of the label amount in the respective formulation.

Results and Discussion

Drug Release—Figure 1 shows adinazolam mesylate release profiles for the concentration series. As reported previously,[7–10] drug release rates decrease with increasing HPMC content. Figure 2 shows that drug release rate decreases to a limiting value with increasing HPMC molecular weight. The formulation containing K100LV, the lowest molecular weight HPMC, exhibits a significantly faster drug release rate compared to the other formulations, whereas differences in release rates among tablets containing K4M, K15M, or K100M are evident only at times greater than 4 h. The decrease in release rate to a limiting value with increase in HPMC molecular weight has been observed previously[7] and is consistent with theoretical predictions.[12] Note that the release rates for K15M and K100M do not follow the expected trend with molecular weight, although the differences are relatively small.

HPMC Release—HPMC release rates were monitored to compare the matrix dissolution kinetics. Figure 3 shows fractional HPMC release profiles for the MW series. Since a fixed percentage of HPMC is used in these formulations, a plot of the absolute mass of HPMC released is identical to Figure 3. The rank order in HPMC release rate (K100LV ≫ K4M > K15M > K100M) indicates a distinct dependence upon the HPMC molecular weight, in agreement with theoretical predictions based upon the polymer disentanglement concentration.[11–13] The data are also consistent with the observations by Lee in studies of HPMC films prepared with K4M, K15M, and K100M viscosity grades.[14]

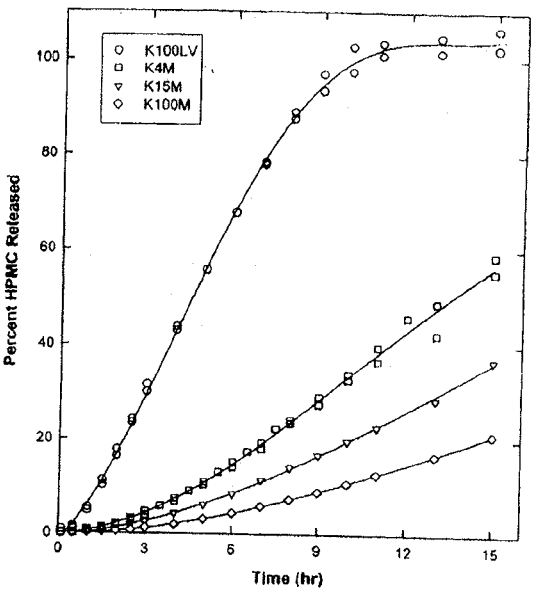

Figure 3—Fractional HPMC release profiles for the MW series.

For the concentration series, Figure 4 shows that the matrix dissolution rate is inversely proportional to the HPMC/lactose ratio when plotted as fractional release. However, when plotted in terms of absolute mass of HPMC dissolved (not shown), the release profiles are superimposed. The constant

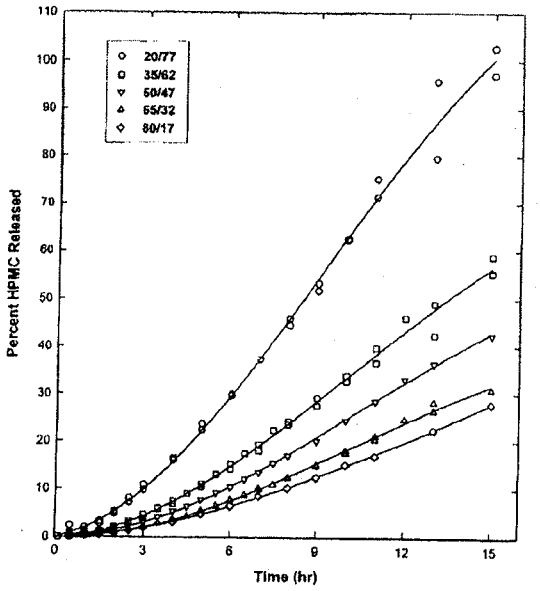

Figure 4—Fractional HPMC release profiles for the concentration series.

mass of polymer released from these matrices containing variable amounts of HPMC can also be explained on the basis of the concepts of the polymer disentanglement concentration and the equivalent molecular weight of a matrix.[12,13] Although the same amount of HPMC was released for all the formulations in the concentration series, their relative matrix dissolution rates are dramatically different due to the difference in formulation composition.

Lactose Release—Lactose release rates were studied because lactose is present in relatively large amounts in the matrices and is presumably directly related to the swelling kinetics and compositional changes of matrix tablets. The lactose release profiles for representative formulations from the concentration series and the MW series are illustrated in Figures 5–6. The lactose release profiles are accompanied by the release profiles of drug and polymer. There are several noteworthy differences to be addressed regarding the release kinetics of drug, lactose, and HPMC.

First, the lactose release profiles are superimposable (within assay error) to the corresponding drug release profiles for both the concentration and MW series. This suggests that the mechanism of lactose release is essentially the same as that of the drug (diffusion through the gel) and there are no lactose–drug or lactose–HPMC interactions. This is consistent with the similar diffusion kinetics exhibited by adinazolam and lactose in water or polymer gels.[15] Second, significant differences in the shapes of the release profiles of drug/lactose and HPMC are manifested. In general, the former exhibit an exponential function whereas the latter show a sigmoidal shape. Third, the drug and lactose release rates are typically much faster than the HPMC release rates except for the K100LV matrix (Figure 6). For this case, the release rates of drug and lactose still lead the polymer release rate by at least 10% until 100% of drug/lactose is released. These results suggest that during the swelling process matrix tablets are gradually transformed into gels which mainly consist of HPMC.

Anisotropic Matrix Swelling—As discussed in a companion report,[6] the time-dependent tablet dimension in either radial or axial directions is measured with high accuracy and precision. Figure 7 shows the overall tablet swelling (normalized to the dimension of the dry tablet) in both the radial and axial directions for the MW series. The swelling behaviors of the formulations containing K4M, K15M, and K100M exhibit a dominant, 3-fold increase in the axial direction that continues throughout the observation time. In contrast, the normalized tablet dimensions in the radial direction increase rapidly to about 1.4-fold the initial dimension and then plateau in about 5 h. The low molecular weight HPMC-K100LV formulation shows dramatically different swelling behavior, a consequence of its much faster matrix dissolution discussed previously (Figure 3). Note that the axial tablet dimension exhibits a continuous increase, though to a much smaller extent than the higher molecular weight grades, whereas a rapid decrease is observed in the radial direction at $t > 1$ h.

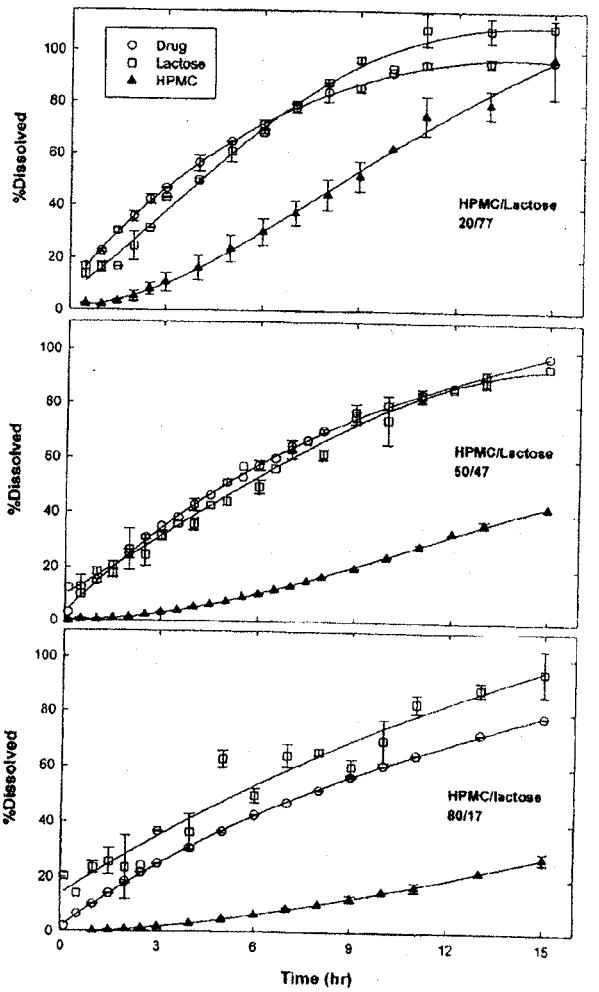

Figure 5—Representative drug, HPMC, and lactose release profiles from the concentration series. Error bars correspond to 1 standard deviation about the mean of 2–3 determinations.

Overall tablet swelling for the concentration series (data not shown) is similar to that for the MW series (Figure 7). In the axial direction, an exponential increase in tablet size is observed in rank order with the HPMC/lactose ratio. For example, at 10 h the 20/17 and 80/17 matrices exhibit about 2.5- and 3.3-fold expansion, respectively. In contrast, swelling in the radial direction exhibits a rapid 1.3-fold expansion.

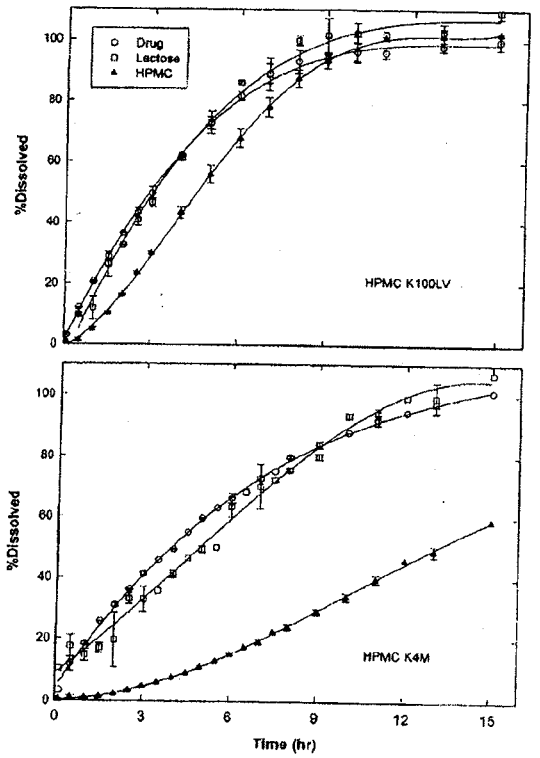

Figure 6—Representative drug, HPMC, and lactose release profiles from the MW series. Error bars correspond to 1 standard deviation about the mean of 2–3 determinations.

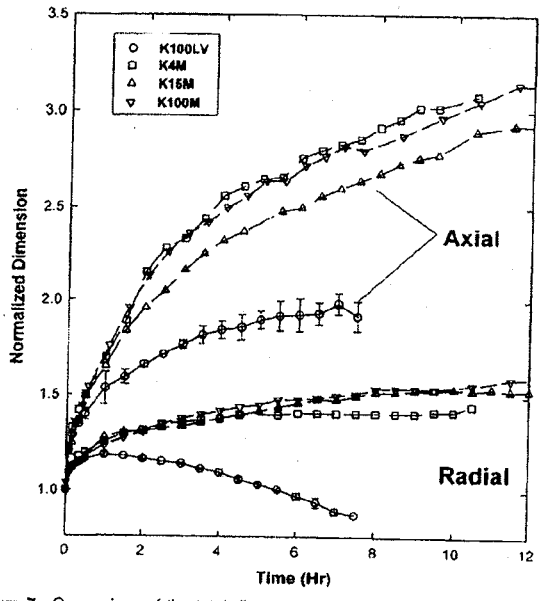

Figure 7—Comparison of the total dimensions of the swollen tablet (normalized to the initial dimensions of the dry tablet) in the radial and axial directions, respectively, for the MW series. Error bars for the K100LV tablet correspond to 1 standard deviation about the mean of 2 determinations.

which then plateaus in about 3 h. This plateau is essentially *independent* of the HPMC/lactose ratio.

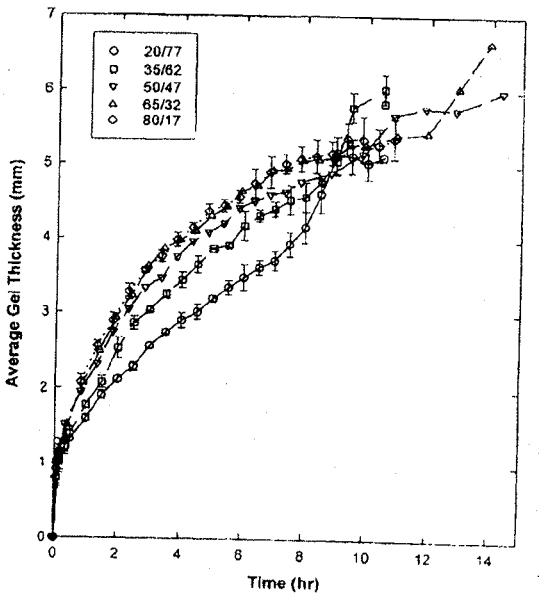

Figure 8—Average of the radial and axial gel layer thickness measurements vs time for the concentration series. Error bars for 80/17, 35/62 and 20/77 formulations correspond to 1 standard deviation about the mean of 4 determinations.

In general, an anisotropic feature of the swelling process of HPMC matrix tablets is clearly indicated by the preferential expansion in the axial dimension relative to the radial dimension for both sets of formulations. Our results are consistent with similar studies reported in the literature.[16–17]

Isotropic Matrix Swelling—The isotropic features of the swelling process (equal gel layer thicknesses and identical compositions in the radial and axial directions) have been discussed in ref 6. In this work, we discovered that isotropic swelling was exhibited by all formulations studied. Accordingly, in the remainder of this report we use the average of the radial and axial gel thicknesses for better precision when discussing this parameter.

Gel Evolution—The dynamic gel thicknesses observed for both the concentration and MW series are plotted in Figures 8 and 9, respectively. Several important features regarding the development of the gel layer are worth noting. First, a continuous increase in the gel layer thickness is observed, irrespective of the polymer viscosity grade or HPMC/lactose ratio. As noted above, the swelling rate is faster than the matrix dissolution rate for these formulations. Second, the gel layer thickness and its growth rate depend on the polymer viscosity grade or the HPMC/lactose ratio. For example, in the MW series, the formulation containing the low viscosity grade (K100LV) exhibits the thinnest gel thickness and slowest growth rate due to its fastest matrix dissolution rate. In contrast, the three formulations containing higher HPMC viscosity grades exhibit similar gel thicknesses and growth rates. Differences in gel layer thicknesses among the concentration series are observed in rank order with the HPMC/lactose ratio. Though intuitively reasonable, the differences in the gel thicknesses in the concentration series are likely superficial due to the presence of undissolved lactose at the gel–core interface (vide infra). Third, there are three distinct gel growth phases that can be readily identified. An initial, rapid growth in gel thickness occurs at short times ($t < 2$ h), followed by a relatively slow increase at intermediate times ($2\text{ h} < t < 6\text{–}10$ h). In the final stage, there is an acceleration of gel growth that results from the merging of the water

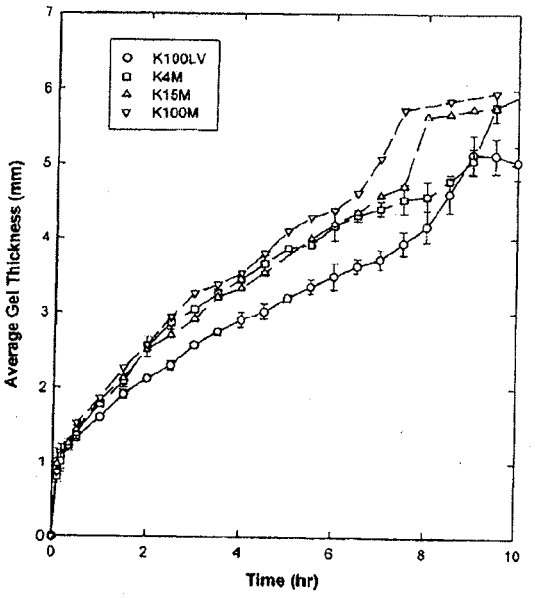

Figure 9—Average of the radial and axial gel layer thickness measurements vs time for the MW series. Error bars for the K100LV and K4M formulations correspond to 1 standard deviation about the mean of 4 determinations.

penetration fronts in the center of the tablets. The time at which this final stage occurs is dependent on the formulation.

Our experimental observation of the three-phase gel layer growth agrees with the theoretical work for solvent front penetration (Fickian diffusion) in polymer matrices of radially symmetric geometries by Lee et al.[18] and also by Ju et al.[12] Qualitatively, a sharp decrease in the rate of front movement was observed at the very early swelling stage due to an increase of the diffusional resistance (fast polymer swelling increases the diffusion path length). During the second stage, the penetration front moves at a relatively constant rate due to the attainment of a pseudo steady state of gel formation. In the final swelling stage, the gel layer thickness sharply increases due to a fast increase of water diffusivity as both fronts meet.

Apparent Water Penetration—It is difficult to detect the true water penetration front.[6] Thus, an apparent water penetration rate is measured on the basis of the detection of the apparent gel front (see Figure 1 of ref 6), which is synchronized to the true water penetration front. We discuss water penetration in terms of either the diminishment in the size of the glassy core or the distance of water movement toward the center of the tablet.

Diminishment of Apparent Glassy Core—The length of the apparent glassy core in the axial (L_c) or radial (d_c) directions was obtained by subtraction of the gel thickness, h, from the total tablet dimension as shown in eqs 1 and 2,

$$L_c = L - 2h \quad (1)$$

$$d_c = d - 2h \quad (2)$$

where L and d represent the transient tablet dimension in the axial and radial directions, respectively. Figure 10 presents the time-dependent apparent glassy core dimensions computed by the above equations for the MW series. In the radial direction (Figure 10A), there is a sharp decrease in d_c at very early times (t < 30 min) followed by a near-linear decrease. The overlap of these curves suggests a *constant*

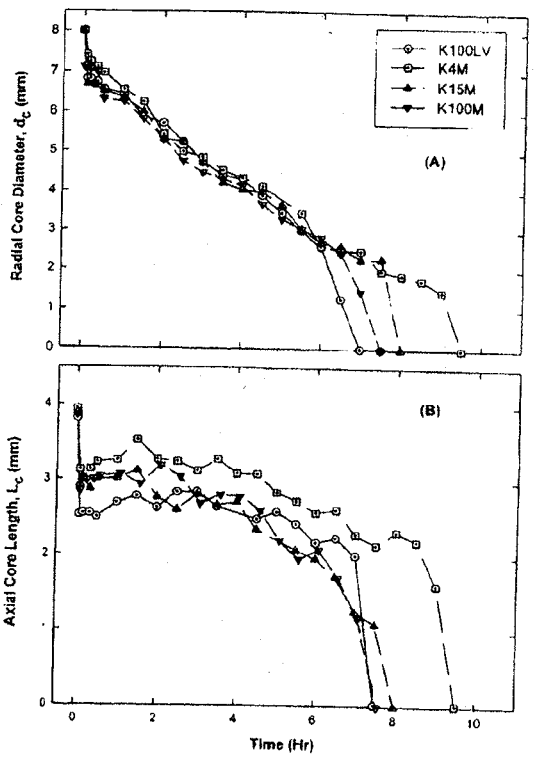

Figure 10—Time dependence of the diminishment of the apparent glassy cores in the (A) radial and (B) axial directions for the MW series.

water penetration rate for all formulations. This is consistent with our previous finding that water diffusivity is dependent only on the total concentration of viscosity-inducing agents irrespective of their chemical nature or polymerization degree.[3] This result is nonetheless intriguing given the drastic difference in matrix dissolution (Figure 3) and overall radial swelling (Figure 7) between the K100LV formulation and the three formulations of higher viscosity grades. In contrast, the decrease in the apparent glassy core in the axial direction is nearly constant between 1 and 4 h (Figure 10B), presumably due to its expansion as a result of decompression in this direction.[16,17]

The dimension of the apparent glassy core in the radial direction for the concentration series is plotted in Figure 11. The similar rates of disappearance of the apparent glassy core for the 80/17, 65/32, and 50/47 formulations are indicative of the constant water penetration rate, confirming the conclusion from the MW series. However, the data for the 35/62 and 20/77 formulations are inconsistent in that the water penetration appears *slower* compared to the other formulations. As explained below, this discrepancy most likely results from a systematic error in the gel thickness measurement due to the presence of undissolved lactose in the gel.

Consider the 20/77 formulation at the apparent gel front (see Figure 1, ref 6), where the water content is about 50% (w/w) (the detection limit of the optical imaging technique).[6] On the basis of the reported room temperature solubility of lactose in water (~0.3 g/mL or 23% w/w),[24] only about 50% of the lactose present at this front in the gel will dissolve. Light blockage from undissolved lactose particles is expected to lead to a bias in the gel thickness measurement due to the incorrect location of the apparent gel front. On the basis of this argument, the bias in the gel thickness measurement is

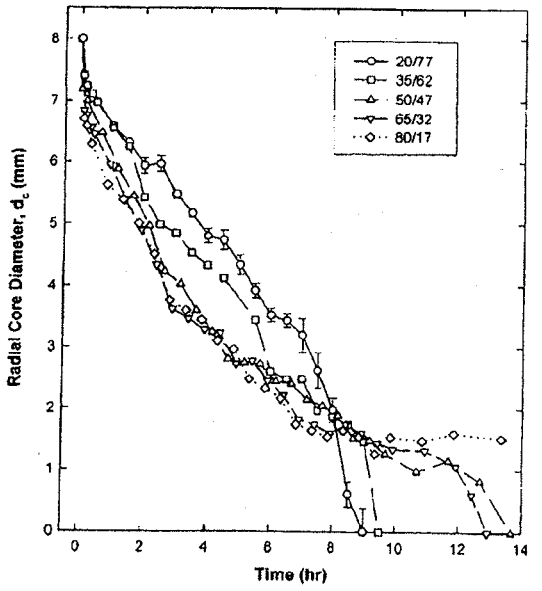

Figure 11—Time dependence of the diminishment of the apparent glassy core in the radial direction for the concentration series. Error bars for the 20/77 matrix correspond to 1 standard deviation about the mean of 2 determinations.

expected only in formulations with lactose content greater than 50%. In contrast, the bias of the gel thickness measurement is constant for all formulations in the MW series due to the constant HPMC/lactose ratio (35/62). Therefore, we infer that the conclusion of constant water penetration rate made for the MW series is also applicable to the concentration series. We base this on the facts that (i) water diffusivity depends only on the total concentration of viscosity-inducing agents in the system irrespective of their chemical nature or polymerization degree[3] and (ii) the water penetration experiences the strongest resistance at the true water penetration front where no composition changes occur except for hydration.

Water Penetration Distance—We consider water penetration distance only in the radial direction because of the isotropic swelling and little expansion in this direction. The apparent water penetration distance, x, at a given time is derived from the difference between the initial tablet diameter, d_0; and the diameter of the apparent glassy core, d_c, as shown in eq 3.

$$x = (d_0 - d_c)/2 \tag{3}$$

Plots of x as a function of time (not shown) up to 7–8 h were fitted to the equation $x = kt^n$, where k is a proportionality constant, t is time, and n is the diffusional exponent. The values of k and n thus obtained are summarized in Table 1. The value of n ranges between 0.44 and 0.58, in reasonable agreement with theory, which predicts $n = 0.45$ for Fickian diffusion in a cylinder.[19] Although there is a distinct trend in the value of n for the concentration series, this result suggests that water penetration into HPMC matrices is a Fickian diffusion process, as opposed to case II (polymer relaxation controlled) diffusion, irrespective of the polymer content or molecular weight. Further, the water diffusivity at the swollen glassy–gel layer interface can be estimated using the Einstein diffusion equation, $x^2 = 6Dt$.[20] Plots of x^2 versus time were approximately linear with slopes corresponding to the apparent water diffusivity. The average value of 4×10^{-7} cm^2/s thus obtained is in general agreement with the water diffusivity observed in organic solids or polymer matrices.[19,21–23]

Table 1. Results of Fitting the Water Penetration Distance to $x = kt^n$ [a]

Formulation	$k \pm$ SD	$n \pm$ SD	N
HPMC Concentration Series			
20/77	0.74 ± 0.04	0.56 ± 0.04	14
35/65	0.83 ± 0.03	0.58 ± 0.03	12
50/47	1.10 ± 0.05	0.50 ± 0.02	17
62/35	1.24 ± 0.03	0.46 ± 0.02	20
80/17	1.29 ± 0.04	0.44 ± 0.02	22
HPMC-MW Series			
35/65 K100LV	0.97 ± 0.06	0.48 ± 0.04	13
K4M	0.83 ± 0.03	0.58 ± 0.03	12
K15M	0.98 ± 0.06	0.51 ± 0.04	13
K100M	1.00 ± 0.04	0.51 ± 0.03	13

[a] Data were fitted through 7–8 h.

Finally, the time differences for complete water penetration (denoted by the sharp decrease of the apparent glassy core at later times) into the center of the tablets deserve comment. The differences in the time required for front convergence among the MW series do not follow the rank order with respect to HPMC viscosity grade or particle size. We cannot offer an interpretation. However, as shown in Figure 11, these times show a correlation with the rank order of the HPMC/lactose ratio. This can be interpreted on the basis of the change of water diffusivity in the gels. Once water reaches the center of the tablet, lactose depletion via diffusion creates gel compositional differences among the formulations. This results in significantly faster water diffusivity for formulations with higher lactose content; these formulations will need less time to transform the apparent dry core to the gel with a hydration level of 50% and thus to be detectable.

Drug Release Mechanism—A principal goal of this work is to characterize the mechanism by which drug release rate from HPMC matrices is modulated as a function of common formulation variables (HPMC concentration, viscosity grade). Our previous work[3,4] and the work of others[8–10] suggest that drug diffusivity in the matrix is altered as HPMC concentration is varied. However, the role of the swelling of polymer matrices in modulating drug release is not completely understood.[25,26]

Mathematical models that incorporate both swelling and diffusivity are not readily available.[27,28] We adapted a mathematical model for the diffusional release of drug from reservoir (membrane) systems,[29] in order to deconvolute the contributions of drug diffusivity and matrix swelling to the observed drug release rate. The rationale for this approach is that, at any point in time prior to complete hydration (i.e., disappearance of the glassy core), swellable HPMC matrices can be considered reservoir (membrane) controlled-release systems with dynamic dimensions due to swelling. Accordingly, eq 4 gives the instantaneous release rate, dM_t/dt, of drug from a reservoir system of cylindrical geometry, which is modified to include drug release contributions from both the radial and end surfaces:

$$\frac{dM_t}{dt} = \left[\frac{2\pi L}{\ln(r/r_c)} + \frac{2\pi r^2}{h}\right] k D_d \Delta C \tag{4}$$

where r_c and r are the radius of the apparent glassy core and total tablet, respectively; D_d is the apparent drug diffusivity across the gel; L is the axial length of the cylinder; h is the thickness of the membrane (the gel layer thickness); k is a proportionality constant; and ΔC is the drug concentration difference across the gel layer. The two terms included in the brackets on the right side of eq 4 are the surface areas of the cylindrical tablet in the radial and axial directions with $\ln(r/r_c)$ and h to account for the diffusion resistance, respectively.

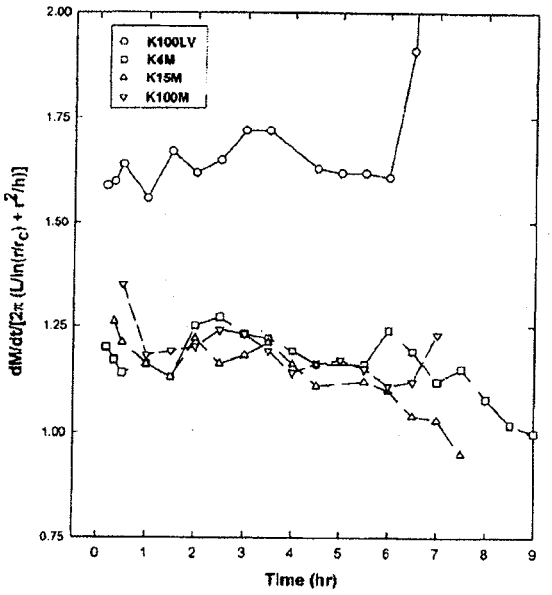

Figure 12—Plot of A vs t for the MW series. The value at each time is proportional to the apparent drug diffusivity in the gel layer.

Application of eq 4 is made possible by the simultaneous measurement of both drug release and swelling kinetics. Rearranging yields eq 5.

$$A = \frac{dM_t/dt}{\left[\frac{2\pi L}{\ln(r/r_c)} + \frac{2\pi r^2}{h}\right]} = kD_d\Delta C \qquad (5)$$

where the values of the term A are derived from the drug release profile (dM_t/dt) and swelling data ($r_c = d_c/2$, $r = d/2$, h, and L) for each formulation. We assume that the partition coefficient, k, is constant during swelling among all formulations. The drug concentration difference across the gel, ΔC, is also a constant (until water penetrates to the tablet center) since the drug load is the same for all formulations examined in this work and sink conditions for dissolution of drug exist. Thus, plotting of A vs time yields a constant ($kD_d\Delta C$) that is proportional to the apparent drug diffusion coefficient in the gel. This analysis effectively deconvolutes the contribution of the swelling kinetics to drug release and indicates whether a correlation exists between the drug release kinetics and drug diffusivity.

Figure 12 shows the plots of A vs t for the MW series. The drug release and swelling data for this analysis are restricted up to approximately 70% drug release. The plots for the formulations containing K4M, K15M, and K100M, respectively, are superimposed within the applicable time region (0.5–7 h). The results suggest that the apparent drug diffusivity is essentially the same for formulations containing the three higher HPMC viscosity grades (K4M, K15M, and K100M). These results are in good agreement with our previous findings that drug diffusivity in HPMC gels is determined by the gel composition (the concentrations of HPMC and lactose)[3] and is not a function of HPMC viscosity grade.[3,9] Therefore, the same drug diffusivity is expected due to the identical HPMC/lactose ratio of the formulations in the MW series. In contrast, the plot for the K100LV formulation (Figure 12) deviates from the other plots, suggesting a substantially higher apparent drug diffusivity. Because this

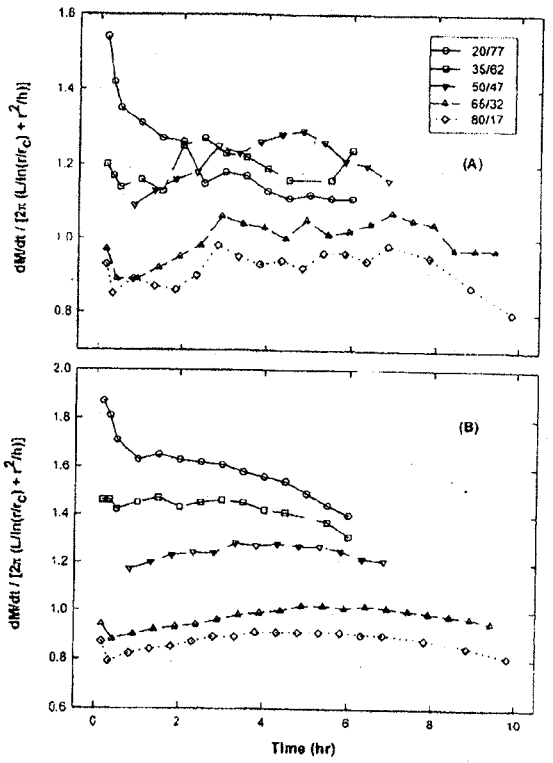

Figure 13—Plot of A vs t for the concentration series using (A) the raw data and (B) the adjusted values of r_c and gel layer thicknesses.

analysis has accounted for differences in swelling among these formulations, it is difficult to interpret this result. One hypothesis is that the model does not account for inhomogeneous swelling of the gel layer, which has been observed by Melia.[30] The rapid matrix dissolution and thin gel layer of this formulation may accentuate the impact of inhomogeneous swelling, which would not be observed for matrices containing K4M, K15M, or K100M due to their much thicker gel layers. We emphasize that further investigation is necessary.

Figure 13A plots A vs t for the five formulations in the concentration series based on the experimentally determined swelling parameters (Figures 8 and 11). A stepwise increase in apparent drug diffusivity is observed with a decrease in HPMC/lactose ratio for the 80/17, 65/32, and 50/47 formulations. Qualitatively, this trend suggests that changes in formulation composition impact drug release rate by their impact on drug diffusivity in the gel layer. However, it is obvious that the formulations containing high lactose contents (20/77 and 35/62) do not fit this trend, presumably due to the systematic error in gel thickness measurement caused by undissolved lactose. To account for this systematic error, we assumed a constant water penetration rate (vide supra) for all formulations in the concentration series and recalculated the gel thicknesses in the following manner. The pooled core diameter–time profiles (d_c vs t) for the 50/47, 65/32, and 80/17 formulations shown in Figure 11 were fitted to a cubic equation. The fitted equation was used to generate "simulated" core diameters (d_c) at each observation time. The *adjusted* gel layer thicknesses were then calculated by substituting the simulated values of d_c into eq 2; note that the experimental values of the total radial dimension, d, which were determined accurately in all cases, were used. As shown in Figure 14, the adjusted gel layer thickness profiles of all

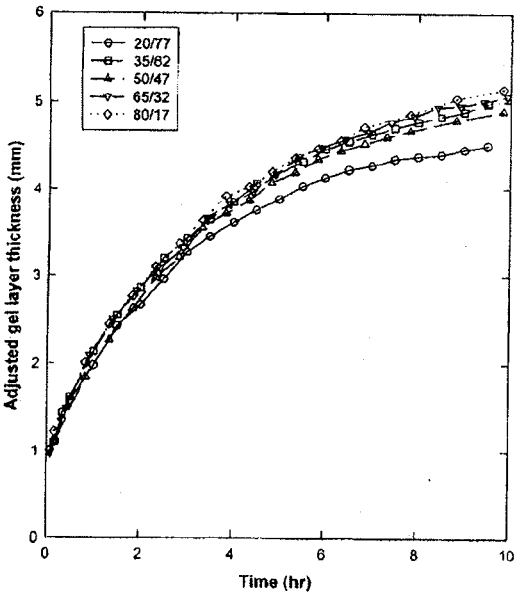

Figure 14—Adjusted gel layer thicknesses for the concentration series computed by assuming identical water penetration rates (i.e., the same d_c vs t profiles) for all formulations. See text for details.

Table 2. Comparisons between the Normalized Ratios of the Drug Diffusivities That are Observed (D_{obsd}) and Predicted (D_{calcd}), Respectively, for the Concentration Series with an Assumption of 70% Hydration of the Gel

Formulation (HPMC/Lactose)	D_{obsd} (t = 1 h)[a]	D_{obsd} (t = 4 h)[a]	D_{calcd}[b]
80/17	1.00	1.00	1.00
65/32	1.12	1.06	1.22
50/47	1.44	1.37	1.48
35/62	1.76	1.55	1.81
20/77	1.98	1.72	2.20

[a] Normalized ratios of the drug diffusivity obtained from the data in Figure 13B with respect to the 80/17 formulation at two specified times (1 and 4 h). [b] Normalized ratios of the drug diffusivity that is calculated using the equation $D = D^{\circ} \exp[-k_H C_H - k_L C_L]$, where $k_H = 7.85$ and $k_L = 3.48$ for HPMC and lactose, respectively, and C_H and C_L are the concentrations of HPMC and lactose. See ref 3 for details.

five formulations in the concentration series are close to each other, although a small difference is still observed for the 20/77 formulation at $t > 3$ h. Using the *adjusted* values of r_c and h, term A is then recalculated and plotted in Figure 13B. The two formulations containing high lactose content (20/77 and 35/62) follow the rank order with the other three formulations in that the apparent diffusivities are inversely proportional to the HPMC/lactose ratio. Further, we compared experimental drug diffusivities (normalized to the 80/17 formulation) calculated from Figure 13B to predicted diffusivities using the empirical formula given in ref 3. Table 2 provides these ratios at 1 and 4 h, respectively, for each formulation. A hydration level of 70% is chosen as an average across the gel layer, thus yielding an average drug diffusivity. The agreement between the experimental and predicted normalized drug diffusivities supports the assumption of constant water penetration and use of adjusted gel layer thicknesses in the above analysis.

We conclude for the concentration series that differences in drug release rates are primarily attributed to differences in drug diffusivity in the gel layer, a function of formulation composition. This conclusion is consistent with our studies of drug diffusivity in HPMC gels.[3,4] We caution, however, that our conclusions are strictly valid for soluble drugs at moderate to low matrix loadings. For insoluble drugs or soluble drugs at very high loadings,[31] matrix dissolution determines drug release rate.

Conclusions

This study further confirms that diffusion is the dominant release mechanism for water soluble drugs from polymer matrix tablets. Formulation composition may modify drug release by modulating (i) the gel layer thickness and/or (ii) drug diffusivity in the gel. A mathematical model that incorporates swelling kinetics (e.g., dynamic tablet dimension, gel thickness) was used to determine the mechanism by which key formulation variables impact drug release. The analysis indicates that variation in HPMC/lactose ratio alters the drug release rate mainly by altering the drug diffusivity in the gel layer. In other words, the impact of swelling on drug release in the concentration series is insignificant over a wide range of HPMC/lactose ratios. Conversely, for the MW series, HPMC viscosity grade has a critical impact upon both the matrix dissolution rate and the gel layer thickness development. For matrices containing HPMC above a limiting viscosity grade (i.e., K4M), the similar drug release rates observed are attributed to similar drug diffusivities, which result from identical gel compositions and thicknesses. For matrices containing low viscosity grade HPMC (K100LV), drug release (and apparent drug diffusivity) is greater than expected due the impact of inhomogeneous swelling, likely a manifestation of the rapid matrix dissolution.

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