Probing the Mechanisms of Drug Release from Hydroxypropylmethyl Cellulose Matrices

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The transient dynamic swelling and dissolution behavior during drug release from hydroxypropylmethyl cellulose (HPMC) matrices was investigated using fluorescein as a model drug. A new flow-through cell capable of providing a well-defined hydrodynamic condition and a non-destructive mode of operation was designed for this purpose to assess the associated moving front kinetics. The results obtained show a continuous increase in transient gel layer thickness irrespective of the polymer viscosity grade or drug loading. This is attributed to the faster rate of swelling solvent penetration than that of polymer dissolution under the present experimental condition. On the other hand, the observed shrinkage of sample diameter over a longer time period demonstrates that polymer dissolution does indeed occur in HPMC matrices. Further, both the rates of polymer swelling and dissolution as well as the corresponding rate of drug release increase with either higher levels of drug loading or lower viscosity grades of HPMC. For water-soluble drugs, the present results suggest that the effect of HPMC dissolution on drug release is insignificant and the release kinetics are mostly regulated by a swelling-controlled diffusional process, particularly for higher viscosity grades of HPMC.

KEY WORDS: hydroxypropylmethyl cellulose (HPMC); swelling; dissolution; moving front kinetics; release mechanism; fluorescein; flow-through cell.

INTRODUCTION

Hydroxypropylmethyl cellulose (HPMC) is a semi-synthetic ether derivative of cellulose, which has been employed extensively since the early 1960's as hydrophilic matrices in oral controlled-release dosage forms (1,2). Its popularity can be attributed to the polymer's non-toxic nature, small influence of processing variables on drug release, ease of compression, and its capability to accommodate high levels of drug loading.

The rapid formation of a viscous gel layer upon hydration has been regarded as an essential first step in achieving controlled drug release from HPMC matrices (2). Mechanistically, two distinctive processes, namely swelling and true dissolution, generally occur during the overall dissolution of glassy polymers (3). A synchronization of movement of both the swelling and dissolution fronts, characterized by a constant gel layer thickness, has been predicted to take place in surface erodible polymer matrices (4). This front synchronization, which occurs sooner with increasing rate of polymer dissolution, has been shown to be responsible for the zero-order drug release from surface erodible systems in the flat sheet geometry (4,5). Experimental results confirming such front synchronization behavior have been reported for several hydrophilic glassy polymer systems including polyvinyl alcohol (PVA) and sodium carboxymethyl cellulose (NaCMC) (6,7) as well as hydrophobic glassy polymers such as polymethyl methacrylate (PMMA) and poly(methyl methacrylate-co-maleic anhydride) (PMMA/MAH) (3,8). One may also expect such front synchronization behavior to occur during the dissolution of other glassy polymers including HPMC (glass transition temperature ~180°C (9)). However, recent reports of a possible deviation from such behavior suggest that the exact mechanism governing drug release from HPMC matrices has yet to be conclusively resolved (7,10).

Although formulation studies on compressed matrices of HPMC or other hydrophilic polymers have been reported extensively in the literature, the associated kinetic analysis often involves only fitting the cumulative release data to a power function of time, thus providing a limited qualitative description of the release behavior (11,12). To further elucidate the mechanisms involved, a detailed examination of various processes taking place in the matrix during the time course of drug release becomes necessary. In this regard, the moving front kinetics, which is most amenable to direct and continuous observation, should yield the desired information. Because of the opaque nature of compressed HPMC matrices, the correlation of moving front position and gel layer thickness with drug release has only been carried out to a limited extent by previous investigators using mostly destructive methods (6,7). These methods, capable of yielding only one single data point from any given sample, are generally cumbersome and less reliable for studying the progression of moving fronts. In addition, a systematic comparison between different grades of HPMC regarding their dissolution and drug release kinetics has not been reported previously.

The present study was undertaken to delineate the mechanisms of drug release from HPMC matrices and to determine the associated kinetics of polymer swelling and dissolution via a non-destructive method. Here, results on the relative contribution of polymer swelling and dissolution to the overall kinetics of drug release from HPMC matrices are presented. A new flow-through cell designed to follow the moving front kinetics under a well-defined hydrodynamic condition is also described.

EXPERIMENTAL

Materials

METHOCEL, a commercially available HPMC, with viscosity grades K4M (Lot No. MM891122402K), K15M (Lot No. MM91013012K), and K100M (Lot No.

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MM99107010102K) were kindly donated by the Dow Chemical Company. According to the manufacturer's specification, the nominal viscosities of a 2% aqueous solution of these polymers are 4,000, 15,000, and 100,000 cps, respectively, and these HPMC grades typically contain 19–24% methyl and 7–12% hydroxypropyl substitutions. Fluorescein sodium salt (MW 376.3), used as a model drug in the release studies, was obtained from Sigma Chemical Company (Lot No. 121H3431).

Methods

Sample preparation. HPMC powder was first dispersed and dissolved in hot distilled water. Upon cooling, a desired amount of the model drug, fluorescein, was then dissolved in the polymer solution. Afterwards, acetone was added to make a 1–1.5% (w/v) polymer solution in a 2:3 mixture of water and acetone. Before film casting, the HPMC solution was quickly degassed under vacuum to minimize the entrapment of air bubbles in the resulting film. Translucent HPMC films of desired thickness were prepared by either single or multiple casting of the polymer solution in a plastic tray followed by slow drying at room temperature. HPMC discs of approximately 16 mm in diameter and 0.3–0.5 mm in thickness were die cut from these HPMC films and used in all swelling and dissolution measurements.

Design of flow-through cell. Schematic drawings of the flow-through cell (constructed out of Delrin and Plexiglas) are shown in Figures 1a and 1b. The two halves of the cell, when bolted together, provide a flow channel having a circular midsection (35 mm diameter) for sample placement with the width of the channel tapering toward the inlet and outlet. Leakage is prevented by the use of O-rings. Both parts have a clear window at the center to allow direct monitoring of polymer swelling and dissolution without disturbing the sample. A continuous flow of solvent around the sample is maintained through the inlet and outlet built into the lower half of the cell. The top window is attached to a threaded cylindrical holder which permits fine adjustment of the distance between the two parallel windows to accommodate sample discs of various thicknesses.

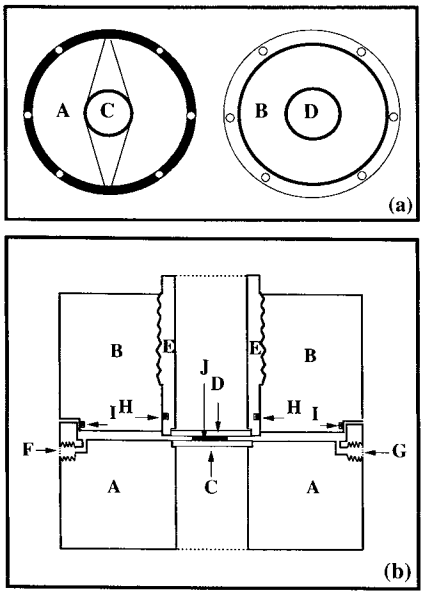

Fig. 1. Schematic diagram of the flow-through cell. (a) top view; (b) cross-sectional view. Key: A, bottom half; B, top half; C, bottom window; D, top window; E, threaded window holder; F and G, water inlet/outlet; H and I, O-rings; J, disc sample.

Swelling, dissolution and release studies. Prior to starting the solvent flow, a disc sample was centered and sandwiched between the two circular windows in the flow-through cell. Hand tightening of the threaded top window holder provided a sufficiently good seal between the sample surface and the window, thus restricting the swelling and dissolution processes to occur only radially. Consequently, water entering the cell only flowed around the circumference of the polymer disc. Hydrodynamically, this configuration is similar to the problem of flow around a cylinder, however, in this case, the cylinder is also confined in a thin channel. As a result, in addition to having curved streamlines, the flow profiles are further complicated by the fact that the velocity components are generally position- as well as angular-dependent. A complete analysis of this problem in terms of flow profiles will be quite cumbersome which is well beyond the scope of this paper. For the purpose of providing reproducible and well-defined flow conditions for the present experiments, all swelling and dissolution data of this study were measured at the two equatorial apexes on the the sample disc (perpendicular to the flow direction) because the velocity components of the flow actually reduce to a single linear tangential velocity at this location.

A constant volume flow rate of 35.7 ± 1 ml/min was maintained during all experiments using a pressurized water reservoir. Depending on the sample thickness and sample diameter, the Reynolds number in the flow channel at the equatorial position was in the range of 30 to 70, well within that for laminar flow. During any given experiment, the sample thickness was fixed and the sample diameter increased initially followed by a gradual decline. However, changes in the sample diameter were never more than 25% (see Figure 6). As a result, the corresponding variations in the Reynolds number were not excessive (also within 25%). Since the mass flux generally varies with the square root of the Reynolds number according to the known mass transfer correlation (13), the corresponding changes in the mass flux during any given experiment would be much smaller (within ~12%). Thus, the hydrodynamic condition of the present flow-through cell was in the well-defined laminar flow region and, within experimental error, a relatively steady mass transfer rate was maintained in all runs.

Swelling and dissolution studies were conducted in deionized water at room temperature. Typically, upon exposure to a swelling solvent, the HPMC sample swells to form a gel layer confined between the moving swelling and dissolution fronts as depicted in the schematic diagram of Figure 2. The time-dependent position of these moving fronts was followed under polarized light using a stereomicroscope (Wild M-420) equipped with camera attachments and digital optical measuring accessories. To monitor the corresponding fluorescein release, aliquots of solvent leaving the flow-through cell were collected at selected time intervals and assayed for fluorescein on a Shimadzu RS 5000U spectrofluorometer using excitation wavelengths of 440, 450 and 460 nm and emission wavelength of 512 nm. The rate of fluores-

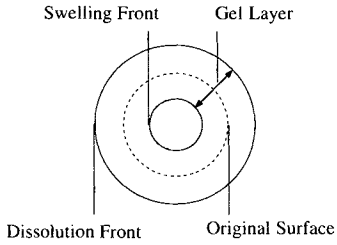

Fig. 2. Schematic diagram of moving fronts during swelling and dissolution of HPMC.

cein release at any given time was calculated from the product of the aliquot fluorescein concentration and the solvent flow rate. The corresponding cumulative fluorescein release was evaluated by integrating the release rate versus time plot.

RESULTS AND DISCUSSION

The photographs of Figure 3 illustrate the swelling and dissolution behavior of a typical HPMC sample in the present flow-through cell. After the initiation of water flow, the glassy HPMC matrix begins to swell and a clear gel layer with increasing thickness is formed. Here, the use of polarized light enhances the contrast such that both the swelling and dissolution fronts are distinctly visible. These photographs also show that the swelling of the HPMC sample is restricted only to the radial direction and no seepage of water between the sample and the window has occurred.

The transient development of gel layer thickness at different levels of fluorescein loading (0, 9, and 20%) is shown in Figures 4a–4c as a function of HPMC viscosity grade. It is clear that the transient gel layer thickness is relatively independent of the viscosity grades at any given fluorescein loading. However, the transient gel layer thickness increases considerably with fluorescein loading. Since the gel layer development is a result of competition between two processes, namely swelling and dissolution, it is possible for their relative rates to remain similar for all viscosity grades (and therefore a similar gel thickness) while their individual rates actually differ. In this case, the presence of a highly water soluble compound, fluorescein, in the HPMC matrix generates an additional osmotic gradient (in addition to that of the polymer swelling), thereby resulting in a faster rate of polymer swelling and a larger increase in gel thickness. Similar dependence of polymer swelling on drug loading has been observed previously in crosslinked hydrogel beads (14,15). Also evident in Figures 4a–4c is the apparent lack of front synchronization under the present experimental condition as represented by the continuous increase in HPMC gel layer thickness.

Mechanistically, solvent penetration is the first step leading to polymer dissolution. The presence of solvent enhances the mobility of polymer chain and gradually transforms a glassy matrix into a rubbery swollen gel. At the gel surface, the polymer concentration has to reach a threshold disentanglement value before dissolution actually takes place (3). In general, the overall kinetics of dissolution is

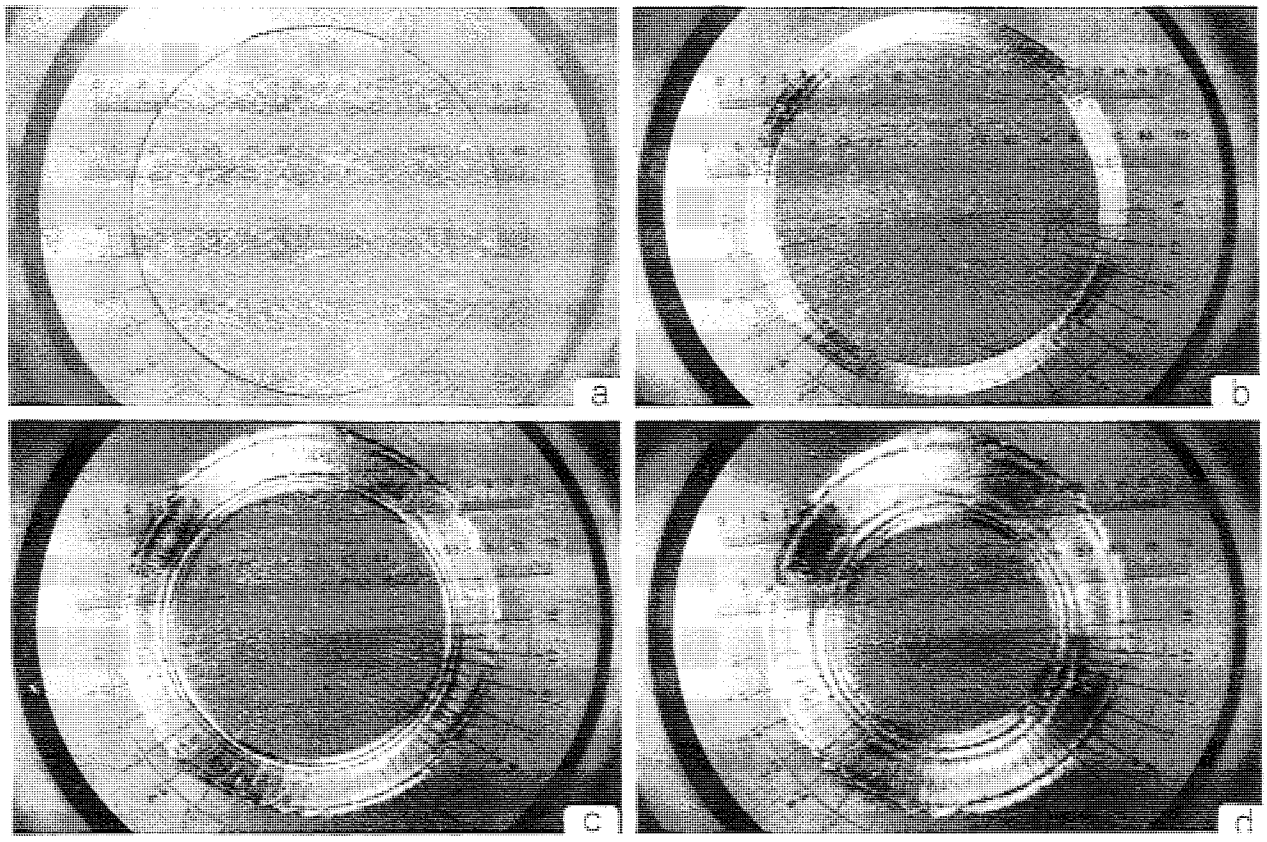

Fig. 3. Photographs showing the progression of swelling and dissolution fronts in a typical HPMC sample: (a) 0 h; (b) 2.5 h; (c) 10.5 h; (d) 18.5 h.

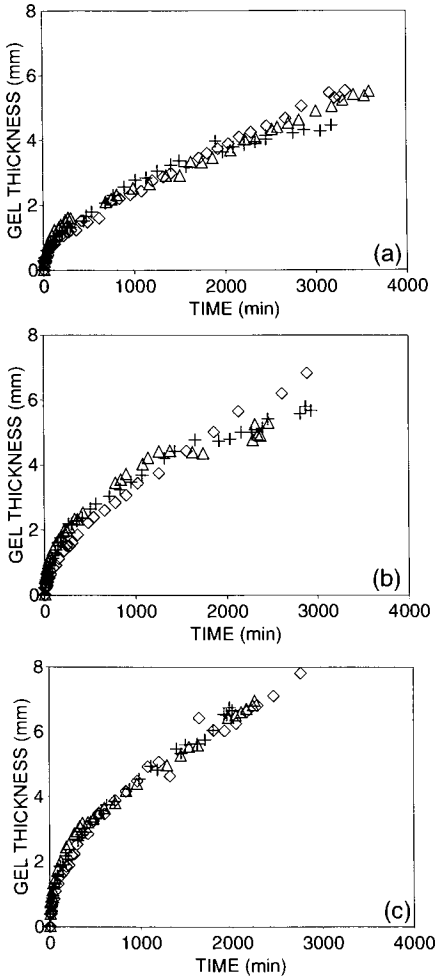

Fig. 4. Effect of fluorescein loading on the transient development of gel layer thickness in HPMC. (a) 0%; (b) 9%; (c) 20% fluorescein. Symbol: Δ, K4M; +, K15M; ◇, K100M Methocel.

governed by the relative contribution of solvent penetration, chain disentanglement, and external mass transfer. If the external mass transfer is rapid due to efficient stirring or fluid flow, the extent of gel formation during dissolution will be controlled only by the relative rate of solvent penetration and chain disentanglement. In this case, a buildup in thickness in the swollen gel layer will result when the solvent penetration is more rapid than chain disentanglement. Typically, this occurs during the initial swelling period of a dissolution experiment. On the other hand, as the rate of solvent penetration is slowed down sufficiently by the increasing diffusional distance while chain disentanglement progresses steadily, little or no change in gel layer thickness may result when both rates become similar. In this case, the development of a constant gel layer thickness manifests the synchronization of movement of both the swelling and dissolution fronts. Once the moving swelling fronts have met at the center, further dissolution due to continuous disentanglement of polymer chains results in the depletion of the remaining gel layer.

It should be recognized that the duration of each of these three characteristic regions, namely regions of swelling, front synchronization and depletion, may vary depending on the hydrodynamic condition as well as the nature of the polymer and the solvent involved. Therefore, the continuous buildup of gel layer thickness as reported in Figures 4a–4c suggests the possibility that these HPMC samples were still in the swelling region under the given experimental conditions. To resolve whether such lack of front synchronization is due to an insufficient rate of external mass transfer or a slower rate of chain disentanglement, an attempt was made to vary the flow rate to affect the rate of dissolution at the gel surface. If the external mass transfer is slow and rate-limiting, increasing the flow rate should facilitate the approach to front synchronization. However, preliminary results obtained so far involving up to 13-fold variations in the flow rate have failed to produce any appreciable changes in the gel layer thickness as well as its increasing trend. This strongly suggests that the external mass transfer rate in the present experimental setup is sufficiently rapid, and, as a consequence, the process of chain disentanglement in HPMC may be slow and rate-limiting.

As the solvent penetration begins, the swelling front moves inward toward the center of the disc sample. On the other hand, the dissolution front moves outward initially before a significant amount of chain disentanglement occurs. To visualize the effect of polymer swelling and dissolution, transient changes in sample diameter normalized to its original value are presented in Figures 5a–5c. An initial increase in sample diameter due to continuous polymer swelling is clearly seen. Here, the sample diameter increases with fluorescein loading and the rate of change in sample diameter is larger for lower viscosity grades of HPMC. Since polymer viscosity is directly related to its molecular weight, the observation of a faster swelling rate with lower viscosity grades of HPMC is certainly consistent with the known molecular weight dependence of the rate of solvent penetration in glassy polymers (16). Once the surface polymer concentration reaches a threshold disentanglement value, polymer dissolution begins to take place. Thereafter, as shown in Figures 5a–5c, the initial outward movement of dissolution front slows down and eventually moves inward, giving rise to a broad maximum followed by a nearly linear decline in the normalized sample diameter at large times. These results provide direct evidence that polymer dissolution does indeed occur in HPMC matrices.

Kinetically, the rate of overall sample dissolution is determined by the relative contribution of the polymer swelling and dissolution processes. The measured dimensional changes can be expressed as:

$$R_{sh} = R_d - R_{sw} \quad (1)$$

where R_{sh} is the overall rate of shrinkage of the sample diameter, R_d is the rate of change in sample diameter due to polymer dissolution and R_{sw} is the rate of change in sample diameter due to polymer swelling. As discussed above, R_{sw} for HPMC exhibits the following trend:

$$R_{sw,K4M} > R_{sw,K15M} > R_{sw,K100M} \quad (2)$$

Similarly, at large times, a faster rate of overall diameter shrinkage is observed with lower viscosity grades:

$$R_{sh,K4M} > R_{sh,K15M} > R_{sh,K100M} \quad (3)$$

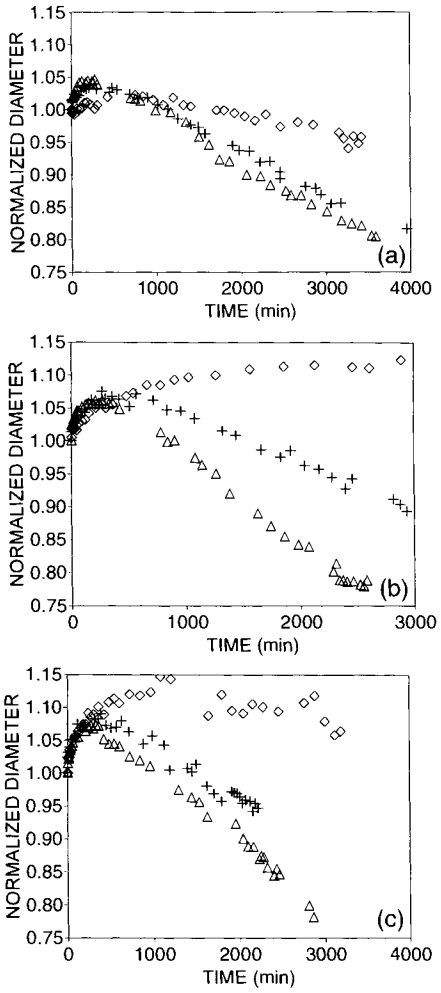

Fig. 5. Effect of fluorescein loading on the transient changes in HPMC sample diameter. (a) 0%; (b) 9%; (c) 20% fluorescein. Symbol: Δ, K4M; +, K15M; ◇, K100M Methocel.

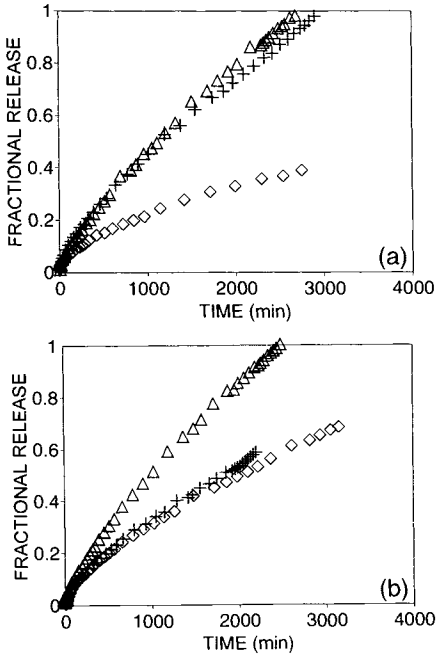

Fig. 6. Effect of loading on the release of fluorescein from HPMC matrices. (a) 9%; (b) 20% fluorescein. Symbol: Δ, K4M; +, K15M; ◇, K100M Methocel.

To satisfy Equations 1–3, the rate of polymer dissolution can only exist in the following order:

$$R_{d,K4M} > R_{d,K15M} > R_{d,K100M} \quad (4)$$

In other words, the dissolution rate of HPMC also increases with decreasing viscosity grades. The slower rate of polymer dissolution with higher viscosity grades can be attributed to the greater effect of chain entanglement associated with their higher molecular weights. It is important to point out that Equations (1)–(4) hold true irrespective of the level of fluorescein loading.

The corresponding fluorescein release profiles for all three viscosity grades are presented in Figures 6a and 6b for fluorescein loadings of 9 and 20%, respectively. A faster rate of fluorescein release is clearly associated with HPMC matrices of either lower viscosity grades or higher fluorescein loading levels. This is consistent with our earlier observations that the rates of HPMC swelling and dissolution also increase with either lower viscosity grades or higher fluorescein loadings. In both cases, the fluorescein release profiles appear to be non-Fickian in nature with the release rate decreasing only slightly with time. A continuous decline in release rate, either due to diffusion or polymer erosion, is generally expected in radially symmetric geometries such as the circular discs studied here. However, in the present case, the decrease in release rate is much slower than expected from the geometry effect alone. Most likely, this can be attributed to a time-dependent increase in diffusion coefficient due to continuous polymer swelling (17). Although a significant increase in surface area may also compensate the release rate decline in highly swellable systems (18), results obtained here do not seem to support such a mechanism. Specifically, despite the continuous increase in gel layer thickness, the magnitude of change in the overall sample dimension (and, hence, sample surface area) due to overall polymer dissolution is actually not significant (max. 25%), particularly for HPMC of higher viscosity grades, during a period where a major fraction (up to 100%) of the drug has been released (compare Figures 5 and 6). This suggests that the release of water soluble compounds such as fluorescein from higher viscosity grades of HPMC follows primarily a swelling-controlled diffusion process. For relatively water-insoluble drugs and/or other more soluble grades of HPMC, however, polymer dissolution may play a more important role in regulating the drug release.

CONCLUSIONS

A new flow-through cell has been designed and tested for the quantitative determination of swelling, dissolution and drug release kinetics in HPMC matrices. This system provides a well-defined hydrodynamic condition and a non-destructive mode of measurement of the associated moving front kinetics. The dynamic swelling and dissolution data so obtained permits the elucidation of mechanisms governing drug release from HPMC matrices. Therefore, the observed

buildup in gel layer thickness with time has been attributed to the rate of penetration of swelling solvent being faster than that of polymer chain disentanglement under the present experimental condition. In this case, the transient gel layer thickness is relatively independent of the viscosity grade of HPMC, but increasing considerably with fluorescein loading as a result of the additional osmotic contribution. Whether such absence of front synchronization behavior is due to a slower rate of either the external mass transfer or the chain disentanglement needs to be further resolved. However, preliminary results obtained so far seem to support the latter possibility. Additional insight has been gained by examining the corresponding transient changes in sample diameter during fluorescein release. Here, after the initial increase in sample diameter due to continuous polymer swelling, subsequent linear decline in sample diameter demonstrates unequivocally that polymer dissolution does indeed occur in HPMC matrices. In addition to increasing with fluorescein loading, both the rates of polymer swelling and dissolution as well as the corresponding rate of fluorescein release actually decrease with higher viscosity grades of HPMC, apparently due to the greater effect of chain entanglement associated with their higher molecular weights. In all cases, the fluorescein release appears to be non-Fickian in nature, most likely caused by a time-dependent increase in diffusion coefficient resulted from continuous polymer swelling. For water-soluble compounds, the present results suggest that the release kinetics is mostly regulated by a swelling-controlled diffusion process, particularly for higher viscosity grades of HPMC, since most of the drug is released while a large portion of the polymer matrix still remains intact.

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