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Swelling and erosion properties of hydroxypropylmethylcellulose (Hypromellose) matrices—influence of agitation rate and dissolution medium composition

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Abstract

The effect of dissolution medium variables, such as medium composition, ionic strength and agitation rate, on the swelling and erosion of Hypromellose (hydroxypropylmethylcellulose, HPMC) matrices of different molecular weights was examined. Swelling and erosion of HPMC polymers was determined by measuring the wet and subsequent dry weights of matrices. It was possible to describe the rate of dissolution medium uptake in terms of a square root relationship and the erosion of the polymer in terms of the cube root law. The extent of swelling increased with increasing molecular weight, and decreased with increasing agitation rate. The erosion rate was seen to increase with decrease in polymer molecular weight, with a decrease in ionic strength and with increasing agitation rate. The sensitivity of polymer erosion to the degree of agitation may influence the ability of these polymers to give reproducible, agitation-independent release, compared to more rigid non-eroding matrix materials, in the complex hydrodynamic environment of the gastrointestinal tract.

Keywords: Hypromellose (hydroxypropylmethylcellulose); Swelling; Erosion; Ionic strength; Polymer size; Agitation intensity

1. Introduction

Hypromellose, also known as hydroxypropylmethylcellulose (HPMC), is a polymer which is widely used in manufacture of matrices for sustained release of drugs. On exposure to water or biological fluid, the dry polymer becomes hydrated, swells and forms a gel barrier layer, which retards the diffusion of drug out of the matrix. Wan et al. (1995) showed that the normalized increase in matrix thickness after 30 min of swelling for HPMC matrix tablets was higher for higher molecular weight HPMC grades. They attributed this to the larger hydrodynamic volume occupied by higher molecular weight chains when hydrated. As the polymer chains become more hydrated and the gel becomes more dilute, the ‘disentanglement concentration’ may be reached, that is, the critical polymer concentration below which the polymer chains disentangle and detach from a gelled matrix. The polymer will then undergo simultaneous swelling, dissolution and diffuse into the bulk medium resulting in erosion of the polymer (Ju et al., 1995a). Soluble drugs are considered to be released by diffusion through the matrix and poorly soluble drugs released by erosion of the matrix (Skoug et al., 1993; Tahara et al., 1995). Moreover, it is consid-

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ered that factors affecting swelling and erosion of these polymers may account for differences between in vitro dissolution results and subsequent in vivo performance, when hydrophilic matrix tablets are compared (Abrahamsson et al., 1999).

Previous studies by Reynolds et al. (1998) examined the erosion of HPMC matrices. They reported, on the basis of drug release data at different stirring rates (0–100 rpm), that release rates were independent of external stirring conditions for the polymer grades used (100–4000 cps). Some progress, in modelling the swelling and erosion processes and in predicting water-soluble drug release, has been made by Siepmann et al. (1999, 2000) and Siepmann and Peppas (2001) using a phenomenological approach and by Narasimhan and Peppas (1997) for drug poly(vinyl alcohol)-based systems. However, more experimental data are necessary particularly to evaluate the effect of hydrodynamics on the polymer erosion process.

In the current work, swelling and erosion of HPMC polymers of differing molecular weights were examined by measuring the wet and subsequent dry weights of matrices. The polymers used were K100M, K15M, K4M, K100LV and a low viscosity polymer, E50LV, which is slightly more hydrophobic due to increased methoxyl substitution. These polymers show a wide range of viscosities, reflecting molecular weight (Keary, 2001) which causes differences in their swelling and erosion behaviours (Sakar and Walker, 1995). Susceptibility of a matrix system to changes in pH and ionic strength is an important consideration in the formulation of sustained release products. The pH of the human gastrointestinal tract ranges from 1.5 to ∼7.0 (Kararli, 1995). Values of ionic strength (μ) between 0.01 to 0.2 occur in the gastrointestinal tract and could lead to changes in bioavailability of formulations based on hydrophilic cellulose matrices (Johnson et al., 1993). The swelling and erosion properties of several polymers were examined in de-ionized water, saline (0.9% w/v NaCl, μ 0.14), saline (μ 0.25), hydrochloric acid medium (pH 1.5) (μ 0.15) and phosphate buffer (pH 7.4) (μ 0.25). These media were chosen to encompass the range of conditions likely to be encountered in vivo.

In the gastrointestinal tract, matrix dosage forms are subjected to agitation in the form of gut motility and pressure in the stomach, duodenum and jejunum. Values for the duodenal pressure of 45 mmHg (Friedman et al., 1965) and pressures in the upper jejunum of approximately 60 mmHg (Beck et al., 1965) have been recorded. Therefore, the susceptibility of these hydrophilic polymer matrices to changes in agitation was considered as an indication of the robustness of the delivery system. The effect of agitation rate on K100LV and K15M was examined in phosphate buffer (pH 7.4). These polymers were chosen since K100LV was seen in previous studies to show both swelling and a large degree of erosion, whereas K15M swelled but did not erode to a significant extent (Gubbins et al., 2003).

2. Materials and methods

2.1. Materials

Hypromelloses; Methocel$^{\text{TM}}$ E50LV, K100LV, K4M, K15M and K100M manufactured by Dow Chemical Company, with nominal number average molecular weights (M_n) of 22,000, 26,000, 86,000, 129,000 and 247,000, respectively, determined by Dow based on viscosity data (Keary, 2001), were used as supplied by Colorcon. Dissolution media were prepared using the following materials; di-sodium hydrogen phosphate dodecahydrate ($Na_2HPO_4{\cdot}12H_2O$) (Merck), sodium di-hydrogen phosphate di-hydrate ($NaH_2PO_4{\cdot}2H_2O$) (Merck), sodium chloride (Merck) and hydrochloric acid 37% (Merck).

2.2. Preparation of discs

200 mg of powder was placed in the cylindrical bore of a 1.3 cm Perkin Elmer stainless steel evacuable pellet die set, between two stainless steel pellets. The cylinder body was then placed on the base of the set. A plunger was introduced into the cylinder body on top of the top pellet. The powder was subject to a pressure (5274 kg cm^{-2}) for 10 min using a Perkin Elmer hydraulic press, after which time the disc formed was ejected from the punch and die set and accurately weighed.

2.3. Wet and dry weight studies

The method used was based on that of Tahara et al. (1995). A USP Apparatus 2 (paddle) dissolution bath

(Sotax AT6) was used set to 37 °C. The rotational speeds employed were 50, 100, 150 or 200 rpm. The dissolution media, phosphate buffer (pH 7.4) (Anon., 1980), saline and the HCl (pH 1.5) medium were made isotonic with NaCl. Ionic strengths were calculated from the concentration and valency of the ions present as outlined in Martin (1993). For static studies the discs were supported on pins at the bottom of the dissolution vessel. 1000 ml of dissolution medium was measured into each of the six vessels of the bath and allowed to equilibrate before starting the experiment. Discs of 13 mm diameter were employed. The experiment consisted of allowing the discs to dissolve in the medium at the chosen agitation rate for certain time periods before they were removed into a pre-weighed weighing boat. The excess dissolution medium was drained and blotted from around the disc without touching the disc. The disc and boat were then weighed to establish the wet weight of the disc. The discs were then dried to a constant weight in an oven at 37 °C. Each determination at each time point was performed in triplicate and the error bars included on the graphs represent one standard deviation.

Several indicators of the extent of swelling and erosion occurring were considered. The relative swelling, calculated as the ratio of the wet weight to the initial weight was determined, as an indication of the extent of matrix swelling using a similar index to Panomsuk et al. (1996).

$$\text{Relative swelling} = \frac{W_\text{w}}{W_\text{i}} \quad (1)$$

where W_w is the wet weight of the disc at a time t and W_i the initial weight of the disc.

The maximum measured dissolution medium uptake occurring over the duration of the experiment was estimated by subtracting the dry weight of the disc from its wet weight at each time point (Tahara et al., 1995):

$$\text{Dissolution medium uptake} = W_\text{w} - W_\text{d} \quad (2)$$

where W_w is the wet weight of the disc at a time t and W_d is the dry weight of the disc at the same time. The dissolution medium uptake per weight of matrix remaining was calculated at each time point for a particular matrix, to correct for the effect of erosion and dissolution in the measurement of degree of dissolution medium uptake. This rate of hydration was obtained by subtracting the dry weight from the wet weight at each time point and dividing this value by the dry weight at that time point.

$$\text{Dissolution medium uptake per unit polymer remaining} = \frac{W_\text{w} - W_\text{d}}{W_\text{d}} \quad (3)$$

The values for dissolution medium uptake per unit matrix remaining were then fitted to a square root equation for the initial points, where a linear relationship existed between uptake and square root of time, and the rate of dissolution medium uptake was estimated from this. The equation for dissolution medium uptake was:

$$\frac{W_\text{w} - W_\text{d}}{W_\text{d}} = a(t^{0.5}) \quad (4)$$

where a is the dissolution medium uptake rate constant and t is the time.

The polymer concentrations at the wet weight peak, called the ‘experimental disentanglement concentrations’, were determined as an approximation of the disentanglement concentration (Ju et al., 1995a). This was estimated from the peak average wet weight for each polymer, since at this point a drop in the water holding capacity of the polymer occurred, despite the constant rate of erosion of polymer from the start. The ratio of dry weight to wet weight for each of the three discs at this time point was calculated. The average of these three values gave the weight fraction of polymer present at that time. The density of the swollen polymer was assumed to be equal to that of water at 0.99325 g/cm^3 (Lide, 1995) and the concentration of polymer at that time could therefore be calculated.

The values of the dry weight data were fitted to the cube root relationship (Hixson and Crowell, 1931) as outlined by Tahara et al. (1995) to determine the apparent polymer erosion rate constant k_2 (Eq. (5)).

$$\left(\frac{W_\text{d}}{W_\text{i}}\right)^{1/3} = 1 - k_2 t \quad (5)$$

where W_d is the dry weight of the matrix at time t and W_i is the initial weight of matrix.

Models were fitted to data using the non-linear curve fitting program Micromath® Scientist™ for Windows™ Version 1.0 (Micromath Inc). The coefficient of determination (CD) and model selection criterion (MSC) were used as measures of goodness of fit for evaluating the suitability of a model (Heelan and Corrigan, 1997).

3. Results and discussion

3.1. Effect of molecular weight on swelling and erosion

The change in wet weight, reflecting swelling, with time for compacts of the five polymer types is plotted in Fig. 1A. The higher molecular weight polymers show the highest maximum average relative swelling, which occurred around 12 h with little erosion. In contrast, the lower molecular weight polymers exhibited maximum swelling in 1–2 h, erosion predominating at later times. The highest molecular weight polymers also show the highest maximum dissolution medium uptake, and a linear relationship (i.e. $\log(W_w - W_d)_{\max} = 0.48 \log M_n + 0.55$) was seen between the log of the maximum average dissolution medium uptake and the log of the number average molecular weight (M_n) (Fig. 2).

The rate of water uptake per unit weight of polymer was non-linear, the rate declining with time. The uptake data were proportional to the square root of time (Fig. 3) and the profiles were therefore fitted to Eq. (4), consistent with the findings of Tahara et al. (1995). The rate profile tended to increase slightly with increased molecular weight. A linear relationship was observed between the dissolution medium uptake rate constant (a) and HPMC molecular weight M_n:

$$a = 3.42 \times 10^{-6} \times M_n + 2.24 \tag{6}$$

as shown in Fig. 4. These results are qualitatively consistent with the findings of Wan et al. (1993) who found that HPMC matrices, prepared from HPMC's having solution viscosities (2%) increasing from 4380 to 44,400 cps, swelled to a greater capacity and at a faster rate with increasing viscosity.

All polymers investigated eroded over time, and no lag prior to the onset of erosion was observed. The lower the molecular weight of the polymer the more rapid the rate of erosion. The erosion rate constant (k_2) of each polymer was determined by fitting the dry weight versus time data with Eq. (5) (Fig. 1B). The estimates of k_2 decreased as polymer molecular weight increased. The relationship between the polymer erosion rate constant (k_2) and the number average molecular weight (M_n) of the polymers is shown in Fig. 5 and was fitted by a power law equation of the form:

$$k_2 = 537\, M_{\mathrm{n}}^{-0.89} \tag{7}$$

An inverse relationship between erosion rate constant and molecular weight was reported by Reynolds et al. (1998). Tahara et al. (1995) reported that the lower viscosity (50 cps) polymer eroded faster than the 4000 cps polymer, consistent with the current work. Thus, the higher molecular weight HPMC polymers

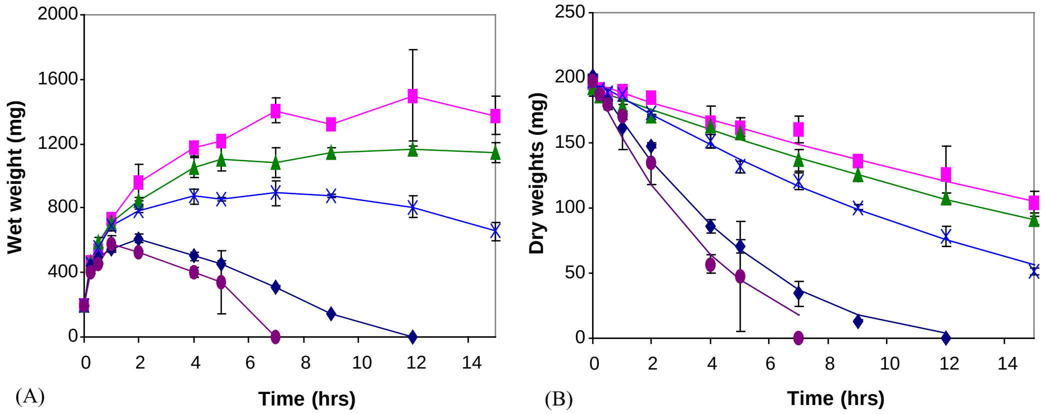

Fig. 1. (A) Wet weights of different molecular weight polymers at 100 rpm in water. (■) K100M, (▲) K15M, (×) K4M, (◆) K100LV, (●) E50LV. (B) Dry weights of different molecular weight polymers at 100 rpm in water showing lines of best fit to cube root equation. (■) K100M, (▲) K15M, (×) K4M, (◆) K100LV, (●) E50LV.

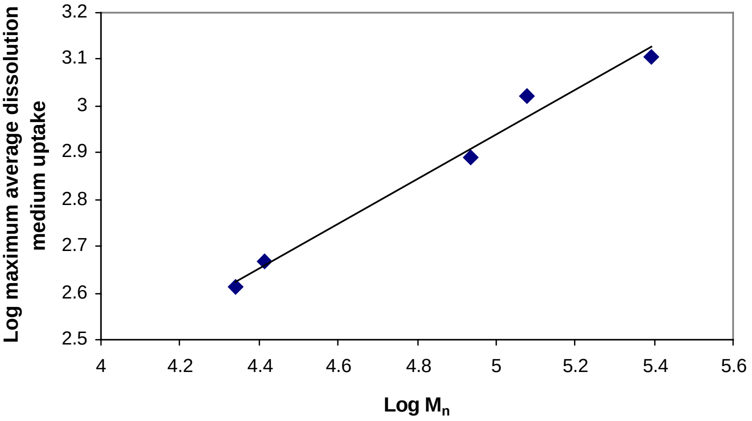

Fig. 2. Relationship between the log of the number average molecular weight of polymer and the log of the maximum average dissolution medium uptake for polymers of different molecular weight at 100 rpm in water.

have a higher intrinsic water holding capacity and the matrices formed from such polymers are less prone to erosion.

3.2. Swelling/erosion model

It was shown above that it is possible to describe the rate of dissolution medium uptake, per polymer unit remaining, in terms of a square root relationship (Eq. (4)) and the erosion of the polymer can be described in terms of a cube root equation (Eq. (5)). Also the values for a and k_2 can be calculated from the molecular weight of the polymer using Eqs. (6) and (7). These calculated parameters may be used to simulate the swelling and erosion profiles of a particular molecular weight polymer. The initial weight, W_i, was estimated at 200 mg. The simulated curves obtained using the calculated parameters (see Table 1) along with the fitted curves for K15M and E50LV are shown in Fig. 6A and B, as these represent the best and worst fits obtained, respectively. Thus, it can be seen that when the calculated parameters are used to simulate data, the model can give a good approximation to the actual values.

Several authors have considered polymer erosion in terms of a disentanglement concentration and a dif-

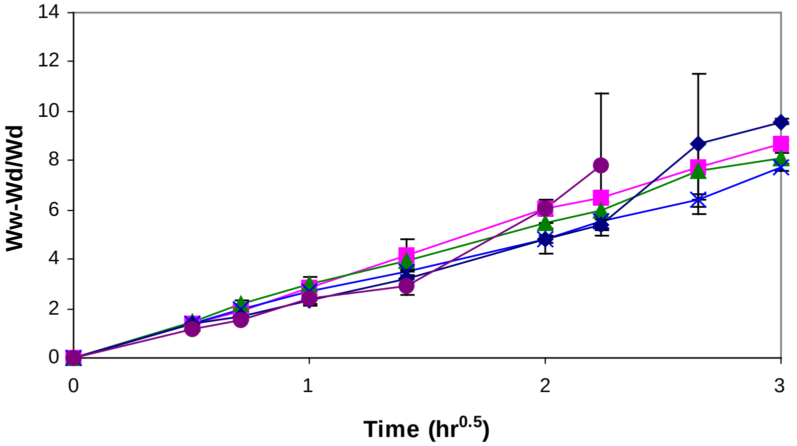

Fig. 3. Dissolution medium uptake per unit polymer remaining for different molecular weight polymers, plotted versus $t^{0.5}$ in water at 100 rpm. (■) K100M, (▲) K15M, (×) K4M, (◆) K100LV, (●) E50LV.

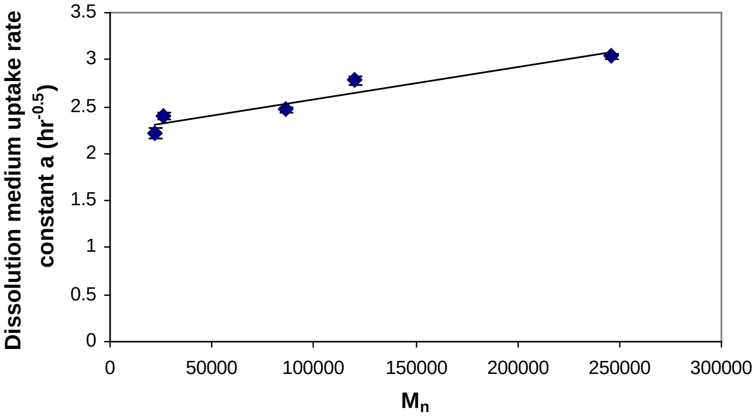

Fig. 4. Relationship between the dissolution medium uptake rate constant and the number average molecular weight of the polymer (M_n).

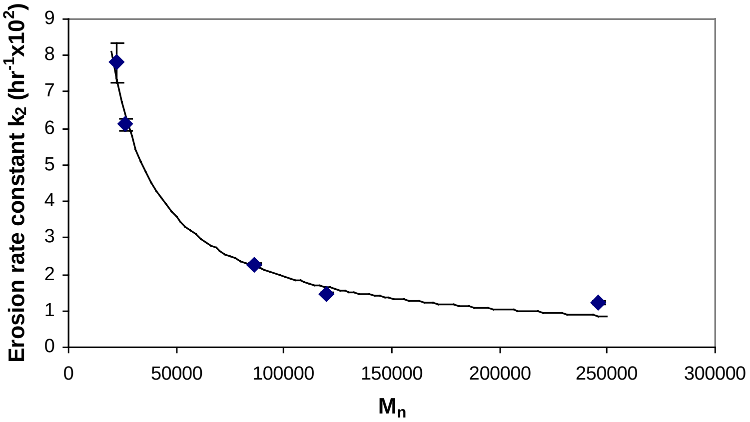

Fig. 5. Relationship between the erosion rate constant k_2 and number average molecular weight (M_n) of the polymers.

fusion coefficient, both of which relate to molecular weight. Ju et al. (1995b) considered the disentanglement concentration of a polymer, and proposed an equation (Eq. (8)) to relate the disentanglement concentration to the molecular weight of the polymer:

$$C_{\mathrm{pdis}} = a_5(M)^{b_5} \tag{8}$$

where C_{pdis} is the calculated disentanglement concentration of the polymer expressed in g/ml, M is the molecular weight of the polymer, a_5 and b_5 are con-

Table 1

Parameters estimates for the ‘swelling/erosion’ model for different molecular weight polymers in de-ionized water at 100 rpm

Polymer	Number average molecular weight M_n[a]	a (h$^{-0.5}$) (±S.D.)	k_2 (h^{-1} × 10^2) (±S.D.)	MSC	CD
E50LV	22,000	2.64 ± 0.16	8.35 ± 0.42	2.17	0.896
K100LV	26,000	2.45 ± 0.04	6.07 ± 0.09	4.39	0.988
K4M	86,000	2.47 ± 0.04	2.14 ± 0.04	4.65	0.991
K15M	120,000	2.71 ± 0.04	1.37 ± 0.04	5.01	0.994
K100M	247,000	2.92 ± 0.08	1.16 ± 0.07	4.03	0.983

[a] Correspondence with Dow Corning Chemical Company.

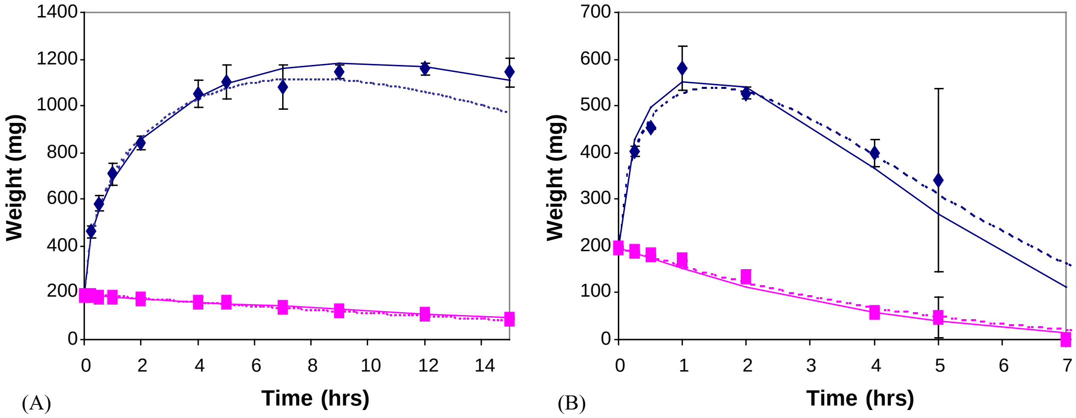

Fig. 6. (A) Swelling and erosion profiles of K15M at 100 rpm in water showing (◆) wet weights, (■) dry weights, (—) line of best fit to swelling/erosion model and (- - -) average parameter simulated line. (B) Swelling and erosion profiles of E50LV at 100 rpm in water showing (◆) wet weights, (■) dry weights, (—) line of best fit to swelling/erosion model and (- - -) average parameter simulated line.

stants. An estimate of the disentanglement concentration was obtained in the current work, from the peak in the average wet weight profile. The relationship between the values of C_{pdis} thus estimated and molecular weight was consistent with Eq. (8) as shown in Fig. 7, giving estimates of a_5 and b_5 of 79×10^{-3} and -0.97, respectively. The disentanglement concentrations determined in the current work are proportional to but higher than those reported by Ju et al. (1995b). The differences may arise from the different methods (Kato et al., 1986) used to determine C_{pdis} and the polymer sources. Furthermore, their assumptions of homogenous swelling and no polymer release before C_{pdis} was reached may not strictly hold (Ju et al., 1995b).

3.3. Dissolution medium composition

The effect of dissolution medium composition on the swelling and erosion of HPMC polymers was then examined. The wet weight versus time profiles of K100LV are shown in Fig. 8 and large differences are evident between the media. The time to attainment of maximum wet weight tended to increase (from ∼2 to ∼6 h) with increasing ionic strength of the medium and the erosion rate also decreased. The effect was

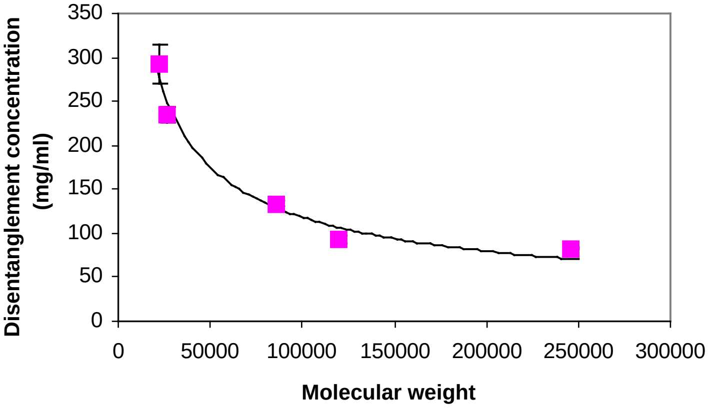

Fig. 7. Relationship between disentanglement concentration and molecular weight, showing line of best fit to Eq. (8). (■) Experimental.

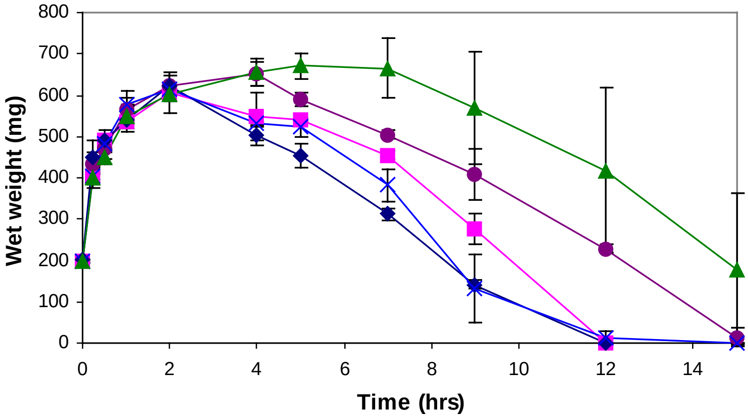

Fig. 8. Wet weight of K100LV discs at 100 rpm in different dissolution media. (▲) Buffer (μ 0.25), (●) saline (μ 0.25), (■) saline 0.9% w/v (μ 0.14), (×) acid (μ 0.15), (◆) water (de-ionized).

much less with the higher molecular weight polymer K15M and no erosion was evident over the 15-h experimental period (not shown). It would appear that none of the observed effects are pH mediated as none of the trends that were observed correlated with the pH of the medium. This is to be expected, as the polymer itself is non-ionic. The rate of dissolution medium uptake decreased linearly with increasing ionic strength for all polymers as did the erosion rate constant (k_2). The relationship between erosion rate and ionic strength for different polymers is shown in Fig. 9. A relatively linear decrease in erosion rate constant (k_2) with increasing ionic strength was observed for the three polymers: K100LV, K4M and K15M. The decrease in erosion rate as the ionic strength increased can be attributed to the 'salting out' of the polymer by the inorganic ions present in the dissolution media. As the ionic strength of the medium increases, the polymer molecular chains loose water of hydration due to the ions competing for the available water of hydration (Alderman, 1984). The polymer still appears able to form a protective gel layer and consequently does not disintegrate, as was seen by Mitchell et al. (1990) for HPMC matrices using ionic strengths which were above those used here. According to Sloop et al. (1994), a polymer which is cross-linked generally shows a lower degree of swelling. This may be attributed to the smaller

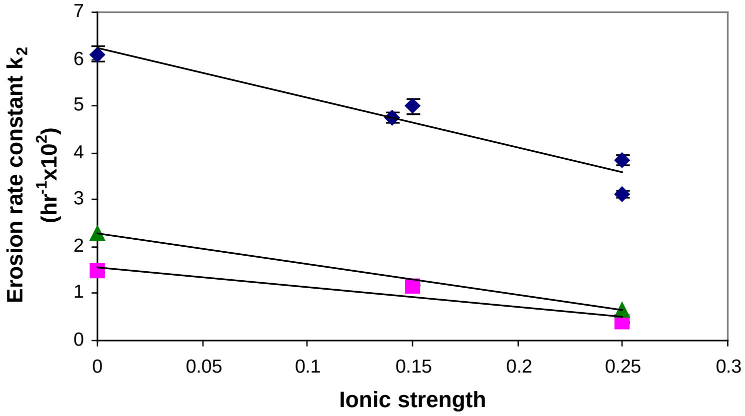

Fig. 9. Relationship between erosion rate constant k_2 and ionic strength for different polymers at 100 rpm. (◆) K100LV, (▲) K4M, (■) K15M.

size of the void spaces present (Ju et al., 1995a). The increase in maximum average dissolution medium uptake and the increase in maximum average relative swelling occurring with increasing ionic strength (Fig. 8) reflects the greater sensitivity of erosion to ionic strength. The decrease in erosion rate with increase in ionic strength is more apparent for K100LV, as it is more susceptible to erosion. The slightly lower erosion rate of K100LV in phosphate buffer over that in saline at the same ionic strength, may be due to the presence of the phosphate ions as well as sodium ions. These cause the polymer to dehydrate to a greater extent than the sodium ions alone (Schott, 1995). This type of behaviour was also seen by Vazquez et al. (1992) who also attributed differences in release from HPMC matrices to high concentrations of phosphate ions being present, rather than the high ionic strength of the medium. Thus, although HPMC is a non-ionic polymer, its swelling and erosion behaviour can be influenced by the ionic composition of the medium, which has implications for the use of these polymers in the design of constant release ER products.

3.4. Agitation rate

The effect of agitation rate on the swelling and erosion of HPMC polymers, K100LV and K15M, was then examined. The peak in the wet weight versus time profile, in the case of K100LV, decreased with increased agitation rate (Fig. 10), reflecting the more rapid erosion at the higher rpm. A similar trend was also observed for K15M (data not shown). The maximum average relative swelling and the maximum average dissolution medium uptake values for K100LV decreased rapidly as the agitation rate increased from 0 to 50 rpm and then decreased at a more gradual rate. Both polymers showed a higher erosion rate constant as the agitation rate increased. From the slope of the plot of log erosion rate constant versus the log agitation rate, K15M seemed more susceptible than K100LV to increases in agitation (Fig. 11), despite its higher molecular weight and this may be linked to the greater swelling of this polymer. The slopes of the log–log plots were 0.73 for K100LV and 1.56 for K15M.

The above results can be attributed to the increased rate of detachment of polymer chains away from the matrix surface, as the stirring rate increased, since these polymers are prone to erosion. Agitation decreases the diffusion layer thickness also resulting in increased mass transport from the matrix surface (Reynolds et al., 1998).

The disentanglement concentration increased as stirring rate increased from 0 to 50 rpm for K100LV and then remained constant, whereas K15M showed a constant increase in disentanglement concentration with increase in agitation. This difference can be attributed to the large differences in the degree of swelling of K15M relative to K100LV with increasing agitation rate, as the polymer system must be more concentrated to withstand the shear effect at increased agitation.

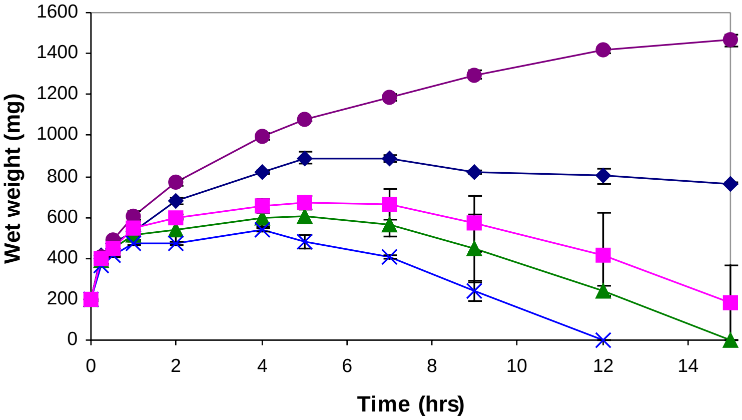

Fig. 10. Wet weights of K100LV at different agitation rates in buffer (pH 7.4). (●) 0 rpm, (◆) 50 rpm, (■) 100 rpm, (▲) 150 rpm, (×) 200 rpm.

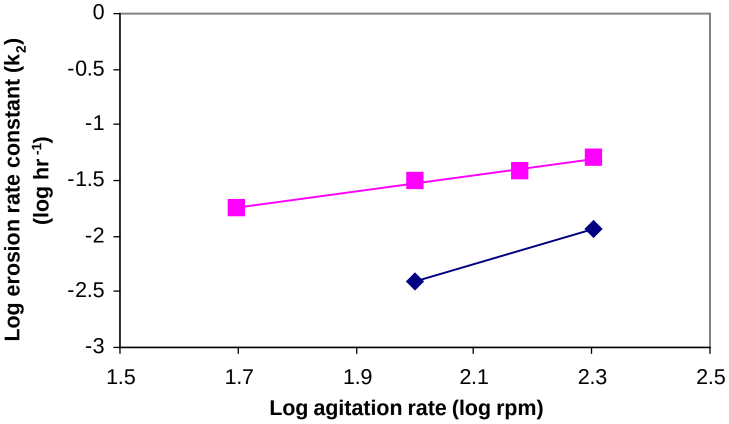

Fig. 11. Relationship between log of erosion rate constant k_2 and log of agitation rate for K100LV(■) and K15M(◆) in buffer (pH 7.4).

The slight decrease in dissolution medium uptake rate constant with increasing agitation rate may be due to the inability of the polymer chains to hydrate fully before they are eroded off the matrix. The dependence of the dissolution medium uptake rate constant on agitation rate for K15M, despite no apparent relationship being evident for K100LV, may be attributed to the lower overall rate of swelling of K100LV, with the result that the values obtained for *a* for K100LV are not significantly different. The results concur with those of Konrad et al. (1998) who showed that the velocity of the swelling front of K4M matrices was not significantly different between matrices at varying agitation rates, whereas the rate of advance of the erosion front outwards decreased with increasing agitation rate. This led to a lower gel layer thickness forming for systems at higher agitation rates, relative to systems at lower agitation rates over the duration of the experiment. Katzhendler et al. (1997) noted an increase in the erosion rate constant of tablets containing 20% K100LV with amoxacillin trihydrate, as the agitation rate increased from 50 to 200 rpm. When a plot of log of erosion rate constant versus log of agitation rate was drawn, the slope was found to be 0.76 which is close to the value of 0.73 for pure K100LV discs obtained in the present work (Fig. 11).

The strong sensitivity of polymer erosion to the degree of agitation may limit the ability of these polymers to give reproducible, agitation-independent release, compared to more rigid non-eroding matrix materials, in the complex hydrodynamic environment of the gastrointestinal tract. These findings would not be considered advantageous in the design of extended release products where agitation-independent dissolution of the drug is desirable. Likewise, these findings would militate against the likelihood of obtaining good in vivo–in vitro correlations (IVIVCs) when using HPMC to form matrices for sustained release of drugs, because of the sensitivity of polymer swelling and erosion to hydrodynamics and dissolution media composition. In this context, Aoki et al. (1992) reported that phenylpropanolamine HCl release from HPMC-based formulations was faster in vivo than in vitro, when using the paddle method at 100 rpm and a similar trend is evident in the IVIVC obtained by Rohrs et al. (1997) for the release of a soluble low dose drug from a hydrophilic polymer matrix. Butler (1997) reported that the release of a soluble drug from Methocel matrix tablet formulations at 100 rpm (Apparatus 2) was underdiscriminatory, with small changes in dissolution in vitro resulting in much larger changes in vivo.

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