A Framework to Investigate Drug Release Variability Arising From Hypromellose Viscosity Specifications in Controlled Release Matrix Tablets

SHAWN A. MITCHELL, KAREN M. BALWINSKI

Water Soluble Polymers, The Dow Chemical Company, Midland, Michigan 48674

ABSTRACT: Substitution level, particle size, and molecular weight are key properties of hypromellose (HPMC) known to be important to its performance in pharmaceutical-controlled release applications. The hypromellose monographs indirectly specify acceptable ranges for the molecular weight of HPMC products, expressed as the apparent viscosity of a 2% aqueous solution. The purpose of this study was to provide a framework to systematically investigate the amount of drug release variability that might be expected for typical controlled release formulations over the monograph viscosity ranges for hypromellose. An approach to estimate the expected drug release variability was developed based on scaling laws in the literature. New experimental data were generated with pentoxifylline, theophylline, and hydrochlorothiazide as model drugs to explore the applicability of this approach to a range of formulations. This methodology predicted that drug release variability over the United States Pharmacopeia (USP) viscosity ranges would be greatest for the lower viscosity grades of hypromellose, such as E50 and K100 LV. Drug release variability due to hypromellose viscosity variations is expected to be larger for formulations having substantial contributions from erosional drug release, and smaller for formulations with a predominantly diffusional drug release mechanism. These predictions need to be validated experimentally. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:2277–2285, 2008

Keywords: hypromellose; HPMC; controlled release; matrix system; molecular weight; viscosity

INTRODUCTION

The apparent viscosity of an aqueous solution of hypromellose (HPMC) is related to the average molecular weight of the polymer chains. The molecular weight of HPMC is known to impact drug release performance. Previous studies in the literature have demonstrated that increasing the viscosity grade of HPMC utilized can result in slower drug release for some formulations, while other formulations exhibit little change in drug release despite the increase in HPMC molecular weight.[1,2] A quantitative relationship between average molecular weight of HPMC and drug release performance was elucidated in two articles by Ju et al.[3,4] These articles presented mathematical models and scaling laws based on the concept of polymer disentanglement concentration, allowing one to estimate the impact of a change in HPMC weight fraction[3] or viscosity grade (e.g., K4M versus K15M)[4] on the release rate of a soluble drug. Equations for the erosion rate of the polymer (HPMC) were also presented.

Tahara, Yamamoto, and Nishihata[5] showed that the drug release mechanism for two model

drugs (solubility = 3 mg/mL and 0.5 mg/mL) was dominated by diffusion, while the release mechanism for a less soluble drug (0.08 mg/mL) could be altered by controlling the rate of polymer erosion in the tablet. The viscosity grade of HPMC in the formulation was found to have a large influence on the rate of polymer erosion from the tablet. Subsequent work by Reynolds et al.[6] presented an approach to quantify the erosional and diffusional contributions to the overall drug release rate, and demonstrated that the erosional component of drug release scaled with polymer erosion. Reynolds et al. concluded that even though the polymer erosion rate was significant for a low molecular weight HPMC (USP Type 2208, K100 LV), its contribution to drug release for theophylline and propranolol hydrochloride, reasonably soluble drugs, was modest at best (i.e., drug release was still dominated by diffusion).

These previous studies provide a foundation for assessing the impact of HPMC molecular weight variations on drug release from controlled release hydrophilic matrix tablets, but the application of this work to formulation development may not always be apparent. For example, Khanvilkar, Huang, and Moore[7] studied the drug release difference when spanning most of the United States Pharmacopeia (USP) viscosity range for an HPMC product, K15M. They found no significant difference in the drug release profile of a soluble drug when using HPMC from the low end of the monograph viscosity range versus the high end of the range, as well as for viscosity blends. However, it was not clear whether this conclusion should be expected to be valid for comparable formulations, or was specific to that particular formulation. The purpose of the present study was to provide a framework to systematically explore the drug release variability that might be expected over the monograph viscosity ranges for hypromellose products.

EXPERIMENTAL

Intrinsic Viscosity Measurement

Samples of hypromellose (HPMC, The Dow Chemical Company, Midland, MI) were dissolved in deionized water and analyzed on a Viscotek model 300 TDA detection system. The detectors were equilibrated at 35°C. Deionized water was used as the mobile phase at a flow rate of 1.0 mL/min, delivered by a Waters model 510 HPLC pump. Prior to the pump, the mobile phase passed through a Viscotek model DG-800 solvent degasser. A Waters model WISP 712 autosampler was used to inject 100 μL of sample. The DRI detector for concentration determination and the viscometer were calibrated using a 112 K molar mass pullulan standard. The analysis software was the Viscotek SEC package, using a "Batch IV" viscometry calculation method.

Tablet Preparation

Hypromellose (USP Type 2208, METHOCEL™ K4M, The Dow Chemical Company) was used as supplied. Pentoxifylline (Spectrum, Gardena, CA), theophylline (BASF, Florham Park, NJ), hydrochlorothiazide (HCTZ, Abbott Laboratories, Chicago, IL), and lactose (FFL 316, Foremost Farms, Baraboo, WI) were each sieved through a 20-mesh screen before use. Pentoxifylline, theophylline, or hydrochlorothiazide (50 wt%), HPMC K4M (30 wt%), and lactose (20 wt%) were placed into a jar and blended by rotation for 5 min each. An automated one station Carver press equipped with a 9.5 mm (0.375 inch) round flat face tooling was hand fed with pre-weighed portions of the formulation to produce 400 mg tablets. The compression force for the tablets was 13.3 kN (3000 lbs) with a 6 s dwell time. Tablet thickness was 4–4.5 mm and aspect ratio (2a/L) was 2.1–2.4. Tablet crushing strength (hardness) was 19–25 kp (27–35 Strong-Cobb units, average of 10 tablets, Key International tester, Model HT-500). Since lubricant was not added to the formulations, it was applied onto the die to prevent the tablets from sticking. A magnesium stearate in acetone solution was periodically applied to the top and bottom faces of the tooling to prevent sticking, and the first tablet following lubrication was discarded.

Release Studies

In vitro dissolution testing was performed on a Distek single bath dissolution system (Model 2100A) equipped with a Vankel auto sampler (Model VK8000). Detection of the drug, polymer, and filler was performed chromatographically. The dissolution media consisted of 900 mL of micro-filtrated nanopure water (not degassed) at

$37°C \pm 0.5°C$. Standard vessels were utilized with USP Apparatus II (paddles) at a stir rate of 50 RPM. As described in the literature,[8,9] tablets ($n = 6$) were placed into stationary hanging baskets to minimize variability in the measurement. The baskets were adapted from a USP Apparatus I basket and were suspended in the dissolution media approximately 25 mm from the center of the agitator shaft and 20 mm above the paddle tip. Samples (1.7 mL) were automatically drawn from each vessel through a 45-micron tip filter at specified time intervals and collected in 2 mL vials. Quantification of the amount released for each formulation component was accomplished by chromatographic analysis of the samples with UV and RI detection.

Chromatographic Analysis

Each 1.7 mL sample was filtered through a 0.45-micron (nylon-13 mm) syringe filter and then analyzed on a Waters Alliance System 2690 Separations Module (model SM7) equipped with a Waters 2410 Differential Refractometer (RI detector, model 410) and an Applied Bio Systems UV Detector. A Mac Mod HIFLO 0.5 µL pre-column filter and YMC pack Diol 120-NP column (A-703-5-NP S-5 µm, 12 mm, 250×4.6 mm) were utilized at ambient temperature. The mobile phase was micro filtered water pumped at 0.8 mL/min, with an injection volume of 100 µL. Dissolved drug was quantified by UV detection (290 nm) at ambient temperature, and HPMC and lactose were quantified by RI detection at 45°C. Retention times were 2.2–2.4 min for HPMC, 4.1–4.2 min for lactose, 4.8 min for theophylline, 5.6 min for hydrochlorothiazide, and 6.1–6.6 min for pentoxifylline.

RESULTS

Calculation of Predicted HPMC Molecular Weight (M_w) Ranges

The USP viscosity requirements for hypromellose as a 2% aqueous solution are summarized in Table 1. The intrinsic viscosity of HPMC was correlated to Ubbelohde tube 2% solution viscosity data over the range 3–110000 cps (Tab. 2) using a Viscotek triple detection array instrument, as described in the Experimental section. The following relationship was obtained by linear least squares regression ($R^2 = 0.98$):

$$[\eta]_{\text{HPMC}} = 1.0778 \times \text{Ln}(2\% \text{ viscosity}) - 1.2631$$

The Mark–Houwink–Sakurada relationship from a previous study[10] was used to relate HPMC intrinsic viscosity to average molecular weight:

$$[\eta]_{\text{HPMC}} = 0.0002 M_w^{0.8216}$$

$$M_w = \left(\frac{[\eta]_{\text{HPMC}}}{0.0002}\right)^{\frac{1}{0.8216}}$$

Combining these two relationships provided an equation to estimate HPMC average molecular weight (M_w) from Ubbelohde tube solution viscosity measurements:

$$M_w = \left(\frac{1.0778 \times \text{Ln}(2\% \text{ viscosity}) - 1.2631}{0.0002}\right)^{\frac{1}{0.8216}}$$

Using this equation, the predicted molecular weight (M_w) was calculated for hypromellose products at the lower limit (M_{LL}) and upper limit (M_{UL}) of the viscosity specification ranges in Table 1. The results of these calculations are shown in Table 3.

Table 1. USP Viscosity Requirements (2% Aqueous Solution) for Hypromellose Products

Product	Minimum Ubbelohde Tube Viscosity (cps)	Maximum Ubbelohde Tube Viscosity (cps)
E50, E50 LV	40	60
K100 LV	80	120
K4M, E4M	3000	5600
E10M	7500	14000
K15M	11250	21000
K100M[a]	75000	140000

[a]The manufacturer's current viscosity specification for K100M is 80000–120000 cps.

Table 2. Measured Intrinsic Viscosity [η] and Ubbelohde Tube Viscosity (2% Solution) for HPMC Samples

Intrinsic Viscosity (dl/g)	Ubbelohde Tube Viscosity, 2% Solution (cps)
0.671	3.60
2.42	40.0
7.352	3866
7.474	4318
7.552	3903
7.726	6007
7.882	4058
8.00	5393
8.965	18528
10.748	78657
12.355	110000

Predicted Impact of HPMC Viscosity Changes on Drug Release

For formulations where drug dissolution is much faster than diffusion and the drug does not interfere with matrix hydration, drug release at a fixed polymer weight fraction can be estimated by the equation of Ju et al.[4]:

$$\text{Drug Release} = \frac{m_{\text{d}}(t)}{m_{\text{d}}(\infty)} = b'M^{-0.24}$$

where M is the weight average molecular weight (M_{w}) of the HPMC in the formulation, and $m_{\text{d}}(t)/m_{\text{d}}(\infty)$ is the fraction of drug released at time t. The parameter b' changes with time. For a controlled release formulation containing an HPMC product at the upper limit (UL) of its viscosity specification, b' at $x\%$ of drug release is:

$$b'_{\text{at}x\%} = \frac{[m_{\text{d}}(t)/m_{\text{d}}(\infty)]_{\text{at}x\%}}{M_{\text{UL}}^{-0.24}} = x M_{\text{UL}}^{0.24}$$

At a constant polymer weight fraction, if the HPMC material at the upper limit (UL) of the viscosity specification was replaced with an equivalent HPMC material at the lower limit (LL) of the viscosity specification, the expected change in drug release would be:

$$\Delta(\text{Drug Release})_{\text{at}x\%}^{\text{UL}\rightarrow\text{LL}}$$
$$= b'_{\text{at}x\%}(M_{\text{LL}}^{-0.24} - M_{\text{UL}}^{-0.24})$$
$$= x\left[\left(\frac{M_{\text{UL}}}{M_{\text{LL}}}\right)^{0.24} - 1\right] \tag{1}$$

Figure 1 depicts the application of Eq. (1) to the predicted molecular weight ranges for hypromellose products summarized in Table 3. The y-axis in Figure 1 represents the expected difference in the percent of drug released when using an HPMC product at the minimum viscosity specification limit versus an HPMC product at the maximum viscosity specification limit as a function of the extent of drug release (x-axis). The slope of the lines is related to the molecular weight ratio of the two HPMC products, as indicated in Eq. (1) and Table 3.

Predicted Impact of HPMC Viscosity Changes on Polymer Erosion

The extent of polymer (HPMC) erosion from the tablet can be estimated by the equation presented by Ju et al.[4]:

$$\text{Polymer Erosion} = \frac{m_{\text{p}}(t)}{m_{\text{p}}(\infty)} = b M^{-1.05}$$

where M is the weight average molecular weight (M_{w}) of the HPMC in the formulation, and $m_{\text{p}}(t)/m_{\text{p}}(\infty)$ is the fraction of HPMC that has been eroded (i.e., released) from the tablet at time t. It is noted that, consistent with the relationship stated above, Reynolds et al.[6] also concluded that polymer erosion scaled with the reciprocal of molecular weight. The parameter b changes with time. Using analogous terminology to the drug

Table 3. Predicted Molecular Weight (M_{w}) Values for Current Hypromellose Viscosity Specifications[*]

Product	M_{LL} (kDa)	M_{UL} (kDa)	$M_{\text{UL}}/M_{\text{LL}}$	$(M_{\text{UL}}/M_{\text{LL}})^{0.24} - 1$	$(M_{\text{UL}}/M_{\text{LL}})^{1.05} - 1$
E50, E50 LV	107	128	1.199	0.045	0.210
K100 LV	144	166	1.156	0.035	0.164
K4M, E4M	361	402	1.112	0.026	0.118
E10M	421	463	1.099	0.023	0.104
K15M	448	490	1.094	0.022	0.099
K100M	582	611	1.049	0.012	0.051

[*]UL, viscosity specification upper limit; LL, viscosity specification lower limit.
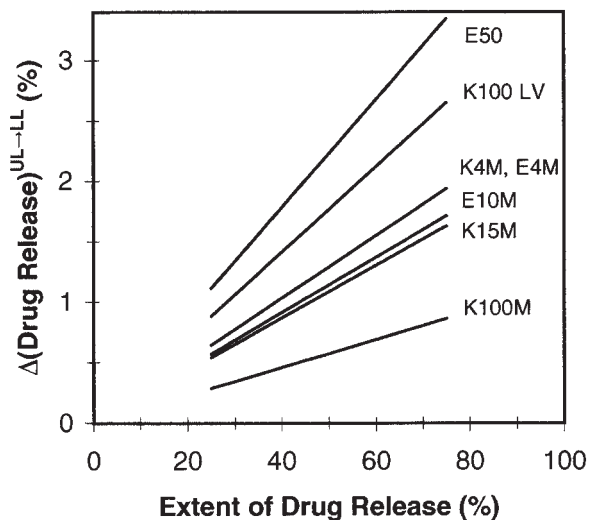
Figure 1. Expected variability in drug release due to current hypromellose viscosity specifications (UL = viscosity specification upper limit, LL = viscosity specification lower limit).
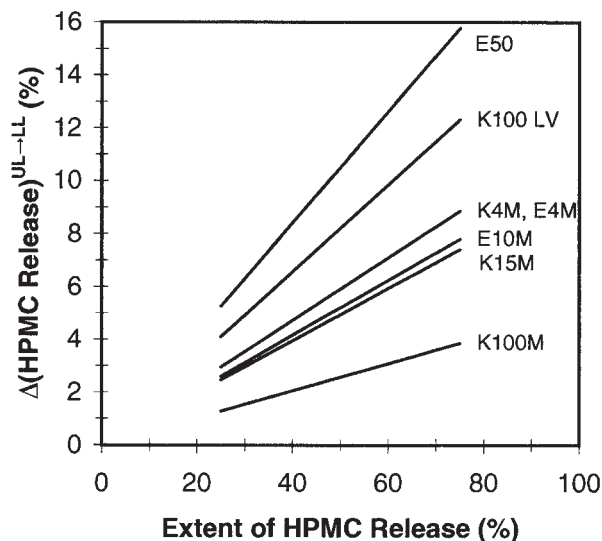
Figure 2. Expected variability in polymer release due to current hypromellose viscosity specifications (UL = viscosity specification upper limit, LL = viscosity specification lower limit).

release treatment presented above, for a controlled release formulation containing HPMC product at the upper limit of its viscosity specification, b at $x\%$ of HPMC release is:

$$b_{\text{at}\,x\%} = \frac{[m_{\text{p}}(t)/m_{\text{p}}(\infty)]_{\text{at}\,x\%}}{M_{\text{UL}}^{-1.05}} = x\,M_{\text{UL}}^{1.05}$$

At a constant polymer weight fraction, if the HPMC material at the upper limit of the viscosity specification was replaced with an equivalent HPMC material at the lower limit of the viscosity specification, the expected change in HPMC release would be:

$$\Delta(\text{HPMC Release})_{\text{at}\,x\%}^{\text{UL}\rightarrow\text{LL}}$$
$$= b_{\text{at}\,x\%}(M_{\text{LL}}^{-1.05} - M_{\text{UL}}^{-1.05})$$
$$= x\left[\left(\frac{M_{\text{UL}}}{M_{\text{LL}}}\right)^{1.05} - 1\right] \tag{2}$$

Figure 2 shows the application of Eq. (2) to the predicted molecular weight ranges for hypromellose products summarized in Table 3. The y-axis in Figure 2 represents the expected difference in the percent of HPMC released from the tablet when using an HPMC product at the minimum viscosity specification limit versus an HPMC product at the maximum viscosity specification limit as a function of the extent of HPMC release (x-axis). The slope of the lines is related to the molecular

weight ratios of the two HPMC products, as indicated in Eq. (2) and Table 3.

Release of Drug, K4M, and Lactose From Controlled Release Tablets

Figure 3a, b, and c shows the release of lactose and drug (pentoxifylline, theophylline, or hydrochlorothiazide, respectively) plotted versus time[0.45]. Following the methodology presented by Reynolds et al.,[6] the initial data points in Figure 3 were fit to a linear regression line indicating the diffusional drug release component. The difference between the symbols and the diffusion line in Figure 3 indicated the erosional contribution to drug release, which was plotted in Figure 4. The HPMC release data was also plotted in Figure 4. The diffusion and erosion rate constants (i.e., the slopes of the lines in Figures 3 and 4) are summarized in Table 4. Figure 5 shows the fraction of total drug release due to the erosional contribution over time, with the remainder of the drug release being attributed to diffusion.

DISCUSSION

According to the methodology applied in this study, drug release variability over the USP viscosity specification ranges for hypromellose

a

b

c
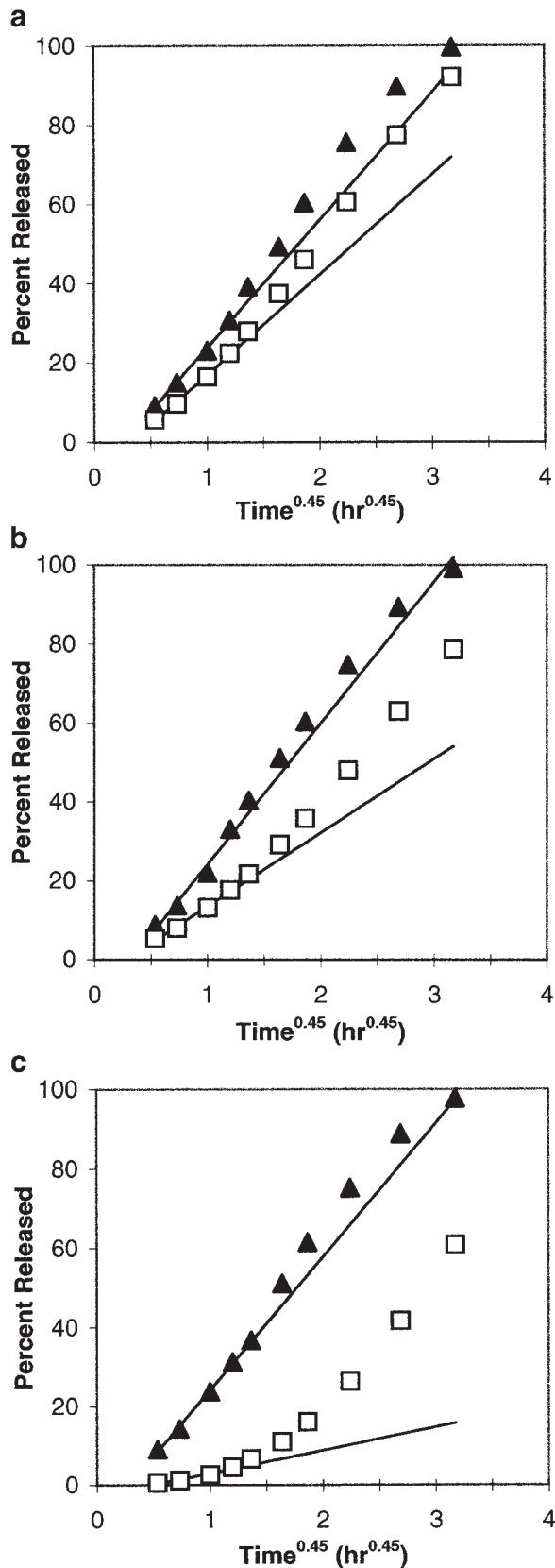
products is expected to be quite small (Fig. 1). While more drug release variability was predicted for the lower viscosity HPMC products, it was still less than 3% in nearly all cases. HPMC release variability due to the viscosity specifications was also predicted to be greater for the lower viscosity products, and is expected to be larger than the drug release variability. As shown in Figure 2, the expected HPMC release variability across the viscosity specification range was generally less than 10%, with the exception of K100 LV and E50.

The accuracy of the predicted molecular weight limits shown in Table 3 is not known at this time. These calculated values were generally consistent with typical M_w values obtained experimentally for these products and reported in the literature.[10] Experimental molecular weight values obtained for typical K4M, E4M, and K15M material fell within the predicted limits shown in Table 3, with the measured M_w for the other products less than 20% outside their predicted range. In general, the accuracy of the predicted M_w value would be expected to be better when the intrinsic viscosity of the HPMC is within the ranges used to generate the correlations (Fig. 1 in reference 10, and Tab. 2). However, even within these ranges, it is reasonable to expect inaccuracies in the predicted molecular weight values shown in Table 3. For simplicity of presentation, the overall values for the Mark–Houwink–Sakurada parameters ($K = 2 \times 10^{-4}$, $a = 0.8216$) were utilized from Figure 1 in the previous study,[10] rather than the chemistry-specific values for K and for E products shown in Table 10 of the reference. This choice and correlation errors of similar magnitude (e.g., due to temperature differences) could introduce up to about 8% error in the predicted molecular weight values in Table 3. A 10% uncertainty or error in one of the other correlation coefficients in the M_w equation could result in roughly 12% error in the predicted molecular weight values.

Nonetheless, systematic imperfections in the absolute values of the predicted molecular weight values in Table 3 should not be a significant concern here because it is the ratio between the maximum and minimum allowed molecular weight that appears in the analysis. Similarly,

Figure 3. Drug (□) and lactose (▲) release profiles versus time[0.45] for drug (50%), K4M (30%), lactose (20%) tablets in water: (a) pentoxifylline; (b) theophylline; (c) hydrochlorothiazide.
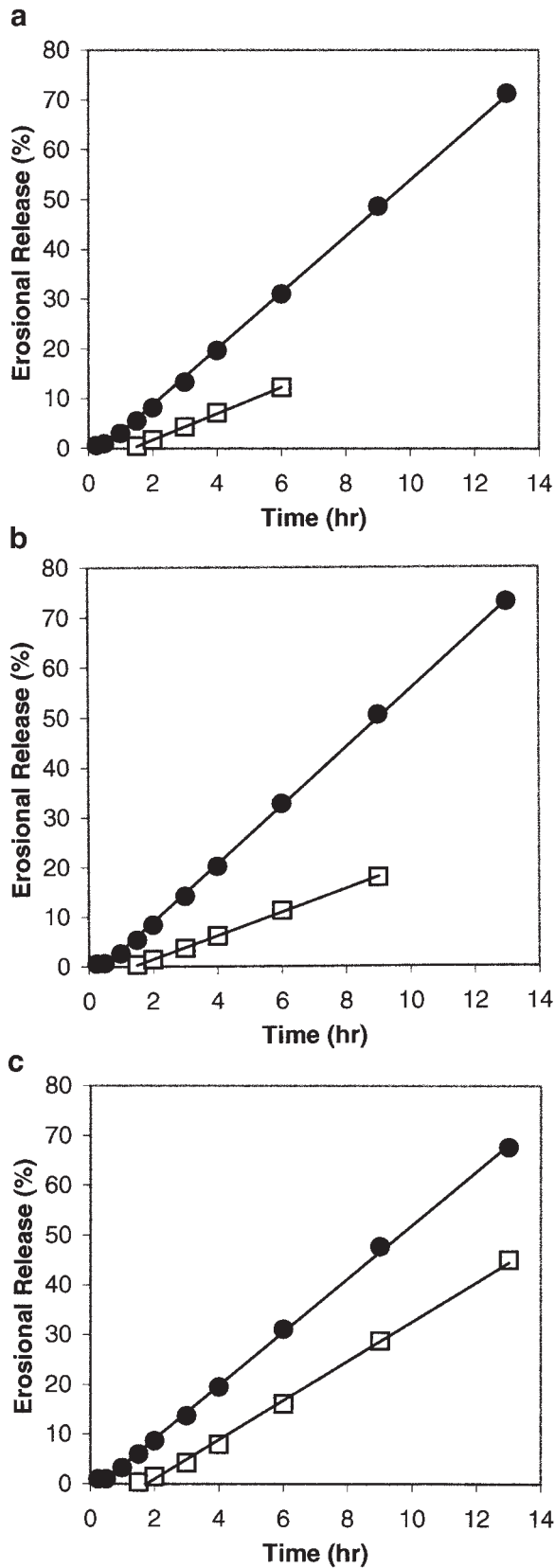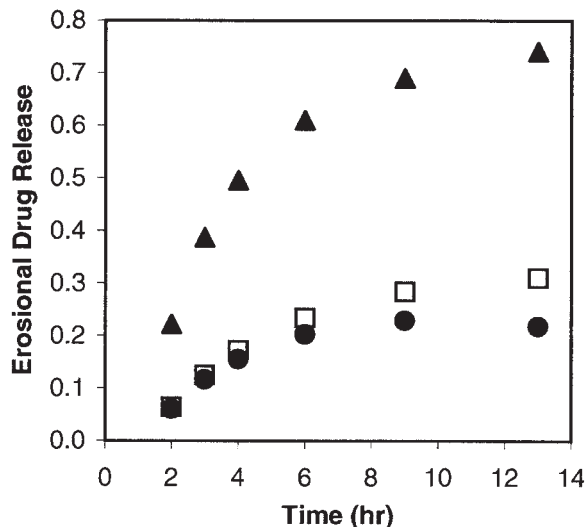
Table 4. Estimated Diffusion and Erosion Release Rates for Drug (50%), HPMC (30%), Lactose (20%) Tablets

	Diffusion Rate (% h$^{-0.45}$)	Erosion Rate (% h^{-1})
Pentoxifylline tablets		
Pentoxifylline	25	2.7
Lactose	32	
HPMC (K4M)		5.6
Theophylline tablets		
Theophylline	19	2.4
Lactose	36	
HPMC (K4M)		5.8
Hydrochlorothiazide tablets		
Hydrochlorothiazide	5.8	4.0
Lactose	34	
HPMC (K4M)		5.4

the use of M_{w}, as opposed to M_{n}, in this analysis would be inconsequential provided molecular weight polydispersity is consistent. However, errors in the predicted molecular weight ratios ($M_{\text{UL}}/M_{\text{LL}}$) in Table 3 would alter the amount of release variability expected. Despite these limitations, this approach was deemed useful as a first attempt to explore this topic. Subsequent studies to experimentally verify the predictions from the present analysis are recommended, and would entail molecular weight determination and *in vitro* drug release studies for otherwise equivalent HPMC materials at the minimum and maximum viscosity specification limits. Comparison of results from the present analysis and a future experimental analysis could potentially help advance understanding in this subject area.

The methodology applied in this study utilized the apparent viscosity of a 2% aqueous solution as a surrogate for the average molecular weight, consistent with monograph specifications. Khanvilkar et al.[7] concluded that for a diffusion-controlled formulation, a blend of a lower and higher viscosity grade of HPMC can be substituted for an intermediate viscosity grade without impacting drug release if the apparent viscosity is comparable. Reynolds et al.[6] showed that under static conditions, the polymer erosion rate for a blend of K100 LV and K4M fell in-line with polymer erosion rates for uncombined products

Figure 4. Erosional release of drug (□) and hypromellose K4M (●): (a) pentoxifylline; (b) theophylline; (c) hydrochlorothiazide.

Figure 5. Estimated fraction of the total amount of drug release contributed by tablet erosion: (▲) hydrochlorothiazide; (□) theophylline; (●) pentoxifylline.

(within 10%). In these previous studies, diffusional drug release and polymer erosion rates did not appear to be determined by molecular weight polydispersity and other characteristics of the molecular weight distribution not described by the apparent solution viscosity. However, the impact of molecular weight polydispersity on drug and polymer release from HPMC hydrophilic matrix tablets warrants further study.

Ju et al.[4] validated their model against experimental data in the previous study, establishing its credibility. Diffusion-dominated drug (adinazolam mesylate) release and polymer release were in agreement with the experimental data, within 15% error. The scaling laws derived from this model were utilized in the present study, so the drug release equation presented in Eq. (1) and depicted in Figure 1 represents diffusional drug release. Reynolds et al.[6] found that the erosional component of drug release and the polymer erosion rate both scaled with the inverse of the average molecular weight of the polymer. Therefore, the erosional component of drug release may be strongly influenced by the polymer erosion Eq. (2), and drug release variability for erosion-dominated formulations may resemble the expected HPMC release variability shown in Figure 2.

However, the model presented by Ju et al.,[4] upon which Eq. (1) and (2) are based, incorporated several assumptions, most notably that dissolution of the drug is much faster than diffusion (only diffusion is considered) and the drug does not interfere with matrix hydration. The authors noted that these assumptions introduce limitations on the applicability of the model, and that it would only be valid for fairly soluble drugs at low drug loading or where no drug–polymer interactions occur. Given these limitations, it was not known whether the polymer erosion equation could be used as a first approximation for drug release in an erosion-dominated formulation.

To address this question, experimentation was conducted on drug/HPMC/lactose formulations containing one of three different model drugs: pentoxifylline (aqueous solubility 77 mg/mL), theophylline (8 mg/mL), or hydrochlorothiazide (1 mg/mL). The model drugs were selected to span a range of aqueous solubility and elicit different contributions from diffusional and erosional drug release. As shown by the slopes of the lines in Figures 3 and 4, the diffusional and erosional drug release rates for these formulations were determined by applying the methodology presented by Reynolds et al.[6] From Figure 5, drug release from the tablets containing pentoxifylline was dominated by diffusion, while drug release for the tablets containing hydrochlorothiazide was dominated by erosion. Drug release from tablets containing theophylline was dominated by diffusion, similar to the pentoxifylline tablets, but with a slightly larger erosional component.

The identity of the drug present in the formulation and the dominant drug release mechanism did not substantially alter the diffusional release rate of lactose or the erosional release rate of HPMC (Tab. 4), suggesting insignificant or similar drug–polymer interactions. It was also noted that in the hydrochlorothiazide formulations, in which the erosional component of drug release played a dominant role (Fig. 5), the erosional drug release rate approached the release rate of the HPMC. Therefore, we conclude that it may be reasonable to apply the polymer release equation as a first approximation of drug release in certain erosion-dominated formulations.

Experimental data showing large drug release variability within the USP viscosity specification range (at constant HPMC substitution level and particle size) relative to the expected variability shown in Figures 1 and 2 might suggest nonconformance to the Ju et al. model, potentially due to violation of a key assumption in the model. For example, if drug release is suspected to be substantially more sensitive to HPMC viscosity fluctuations than indicated in Figure 1 for diffusion-dominated systems or Figure 2 for

erosion-dominated systems, this may indicate that the drug or other formulation component is significantly interfering with matrix hydration, rendering the formulation hyper-sensitive to HPMC molecular weight variations. In this way, comparison of experimental drug release data with Figures 1 and 2 could potentially provide some insight into the conditions present within the tablet during dissolution and assist in the development of robust controlled release formulations. However, as noted above, this could also be indicative of inaccuracy in the predicted HPMC molecular weight ratios (M_{UL}/M_{LL}) shown in Table 3.

CONCLUSIONS

This study provides a framework to systematically investigate the amount of drug release variability that might be expected for typical controlled release formulations over the monograph viscosity ranges for hypromellose. This methodology predicted that drug release variability over the USP viscosity ranges would be greatest for the lower viscosity grades of hypromellose, such as E50 and K100 LV. Drug release variability due to hypromellose viscosity variations is expected to be larger for formulations having substantial contributions from erosional drug release, and smaller for formulations with a predominantly diffusional drug release mechanism. These predictions need to be validated experimentally.

ACKNOWLEDGMENTS

REFERENCES

1. Ford JL, Rubinstein MH, Hogan JE. 1985. Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl-methylcellulose matrices. Int J Pharm 24:327–338.
2. Cheong LWS, Heng PWS, Wong LF. 1992. Relationship between polymer viscosity and drug release from a matrix system. Pharm Res 9:1510–1514.
3. Ju RTC, Nixon PR, Patel MV. 1995. Drug release from hydrophilic matrices. 1. New scaling laws for predicting polymer and drug release based on the polymer disentanglement concentration and the diffusion layer. J Pharm Sci 84:1455–1463.
4. Ju RTC, Nixon PR, Patel MV, Tong DM. 1995. Drug release from hydrophilic matrices. 2. A mathematical model based on the polymer disentanglement concentration and the diffusion layer. J Pharm Sci 84:1464–1477.
5. Tahara K, Yamamoto K, Nishihata T. 1995. Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910. J Control Release 35:59–66.
6. Reynolds TD, Gehrke SH, Hussain AS, Shenouda LS. 1998. Polymer erosion and drug release characterization of hydroxypropyl methylcellulose matrices. J Pharm Sci 87:1115–1123.
7. Khanvilkar KH, Huang Y, Moore AD. 2002. Influence of hydroxypropyl methylcellulose mixture, apparent viscosity, and tablet hardness on drug release using a 2^3 full factorial design. Drug Dev Ind Pharm 28:601–608.
8. Wingstrand K, Abrahamsson B, Edgar B. 1990. Bioavailability from felodipine extended-release tablets with different dissolution properties. Int J Pharm 60:151–156.
9. Abrahamsson B, Alpsten M, Bake B, Larsson A, Sjogren J. 1998. In vitro and in vivo erosion of two different hydrophilic gel matrix tablets. Eur J Pharm Biopharm 46:69–75.
10. Keary CM. 2001. Characterization of METHOCEL™ cellulose ethers by aqueous SEC with multiple detectors. Carbohydrate Polym 45:293–303.