

A Study of Polymer Blending and Polymer Erosion of Different Viscosity Grades of Hypromellose for Hydrophilic Matrix Tablets



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Introduction

Hypromellose[†] polymers are commonly used in hydrophilic matrix tablets as rate-controlling polymers to provide sustained drug release.

An important characteristic of hypromellose in non-disintegrating matrix tablets is to hydrate quickly and to form a protective layer around the matrix.¹

Upon placement in an aqueous medium, several processes occur simultaneously and influence drug release, namely, solvent uptake, swelling of the matrix, dissolution of the drug, and hydration and dissolution of the polymer chain due to chain disentanglement.

Polymer erosion has been previously shown to be dependent on polymer molecular weight; the rate of polymer erosion of hypromellose polymers increases with a decrease in polymer molecular weight.^{2,3}

The use of polymer blends of hypromellose viscosity grades has been previously reported,^{2,4,5} but in most cases these formulations contained additional excipients. It is expected that soluble excipients may affect polymer erosion, since there is competition for water between the additives and polymer. Thus, it may be desirable to examine the effect of polymer blends on drug release for a drug and polymer system without excipients. This would potentially provide control of drug release *via* the appropriate choice of polymers, by utilizing the different erosion contributions of the individual polymers to produce the desired overall drug release.

Electrolytes in solution tend to pull water away from hydrophilic colloids, since the ions have a greater affinity for water.⁶ This effect may impact the hydration process of hypromellose polymers in the matrix tablets, and, therefore, affect the polymer erosion process of the matrix at the tablet surface.

Objective

To evaluate polymer erosion during dissolution of matrices comprised of similarly substituted hypromellose viscosity grades, with and without drug, and to examine the blending of two grades to simulate the performance of different intermediate viscosity grades. Also, to investigate the effect of ions in the dissolution media on polymer erosion.

Experimental

Materials

METHOCEL* K chemistry (hypromellose USP Type 2208) hypromellose products with 2% w/v solution viscosities of 130, 300, 680, 800, 2670, and 4000 mPa•s.

Methods

Tablet Preparation

- The polymers were dried in a vacuum oven prior to use in order to remove residual moisture for the gravimetric technique erosion studies.
- Tablets compressed using a Carver press with 1/2-inch flat-faced punches and die at a compression force of 35.1 MPa (1000 lb) with a 10-second dwell time.

Erosion Studies

- Polymer erosion studies were conducted in 900 mL of deionized, de-aerated water equilibrated at $37.0 \pm 0.5^\circ\text{C}$ in USP dissolution vessels. In the case of examining the effect of ions on polymer erosion, 0.1N HCl and pH 7.0 phosphate buffer of 0.1, 0.15, 0.175, 0.20, 0.35, and 0.65M media were used.
- Polymer erosion of the hypromellose matrices was determined utilizing the gravimetric method and/or the gel permeation chromatography (GPC) technique.
- Due to flotation of the hypromellose disks, tablets were individually placed under #10 mesh screens to keep them submerged. The paddles were placed 2.5 cm above the screen and rotated at 100 rpm.
- For the experiments using the gravimetric technique, three new disks were used for every designated time point. The time points were 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours.
- For the experiments utilizing the GPC method of analysis, 10 mL of solution were withdrawn from each dissolution vessel at 2, 4, 6, 8, and 12 hours. The samples were refrigerated overnight to ensure that the polymer was fully hydrated. Before injecting into the column, the solutions were filtered through a 0.8 micron filter.

GPC Conditions

- Column: Shodex Ohpak SB-802 HQ.
- Eluent: 0.05N NaCl with 50 ppm Brij 35 at a flow rate of 0.6 mL/minute.
- Detector: Waters 410 Differential refractometer.

Results and Discussion

Erosion of Polymer Compacts

Pure Polymer and Polymer Blends

An inverse power law relationship between polymer erosion rate and weight average molecular weight, M_w , was previously established for a broad range of viscosity grades of hypromellose⁷, and is shown in Figure 1. This scaling law is useful in predicting polymer erosion rates for various mixtures of different polymer grades.

To compare the performance of blend samples with intermediate viscosity grades, various blends were prepared by utilizing a weighted-average calculation of the average molecular weight values for the 130 and 4000 mPa•s samples.

The erosion rates in deionized water with polymer blend samples of 130 and 4000 mPa•s were within 10% error of the pure polymer model predictions⁷, as shown in Figure 2.

This power law relationship has potential utility in predicting polymer erosion for matrix tablets containing an active and blends of lower and higher molecular weight polymers.

Effect of Dissolution Media

To investigate the effect of ions in the dissolution media on polymer erosion of the tablets, erosion studies were conducted in 0.1N HCl and pH 7.0 phosphate buffer of varying buffer concentrations.

Initial erosion studies using a gravimetric technique indicated that erosion rates in 0.1N HCl were similar to those in deionized water for the respective polymers. As seen in Figure 3, erosion studies using the GPC technique reveal similar degrees of erosion for the lower molecular weight K130 polymer in water and 0.1N HCl, whereas the erosion of the higher molecular weight K4M was slightly slower over time in 0.1N HCl relative to deionized water. This effect of chloride ions on K4M erosion requires further study.

Also shown in Figure 3, polymer erosion of both K130 and K4M is less at later times in 0.1M pH 7.0 phosphate buffer. The presence of phosphate species in the dissolution media apparently slows erosion as a result of slowing polymer hydration.

It is assumed that chloride ions do not compete for water of hydration to the extent that phosphate ions do in these polymer compacts; thus the overall degree of polymer erosion is less at later times for matrix tablets in phosphate buffer media relative to 0.1N HCl. This is consistent with the rank order of salts in the lyotropic series.⁴ Chloride ions are lower in the lyotropic series, and apparently do not affect polymer hydration as much as phosphate ions.

Figure 4 shows a plot of % polymer eroded vs. time for K130 compacts in increasing phosphate buffer concentration media. It is apparent that as the phosphate concentration is increased from 0.1 to 0.175M phosphate, the degree of polymer erosion decreases. This is possibly due to a decrease in the rate of hydration of the polymer. However, at 0.35M phosphate concentration, the tablets disintegrated in a short period of time. At 0.20M phosphate concentration, some tablets remained intact over the entire 12 hour study with negligible

erosion, while several tablets quickly disintegrated. At phosphate concentrations above 0.20M, the media was not as good a solvent for K130 so the tablets disintegrated. While at phosphate concentrations below 0.20M, the aqueous media is a good solvent and the rate of polymer hydration is adequate to establish a gel layer around the matrix.

Erosion of Drug: Polymer Tablets

The polymer erosion profiles of pure polymer compacts and 3:1 polymer: theophylline matrix tablets in deionized water are shown in Figure 5.

As previously reported by Reynolds⁸, matrix tablets that contain drug tend to erode to a greater extent relative to tablets without drug. The lower polymer concentrations in the matrix tablets containing drug produce gel layers of lower viscosity with fewer polymer-polymer entanglements.

To compare the performance of blend samples with intermediate viscosity grades, various blends were prepared by utilizing a weighted-average calculation successful in the polymer-only compact erosion study. The relative ratios of K130 and K4M were calculated utilizing the weight average molecular weight values for these samples.

When percent theophylline release is plotted *vs.* time, Figure 6, similar drug release profiles exist for most of the intermediate polymer grades with respect to the corresponding blends of K130 and K4M.

A plot of % polymer eroded for matrix tablets containing drug *vs.* time (Figure 7) depicts similar degrees of erosion between straight polymer grades and polymer blends.

Comparing drug release and polymer erosion profiles for the different polymer grades (Figures 6 and 7, respectively), it is apparent that greater differences exist between polymer grades for the polymer erosion profiles. This suggests that in order to impact overall drug release from hypromellose matrix tablets, a significant change in polymer erosion must occur. Ju *et al.*³ similarly found that polymer erosion of a hypromellose matrix tablet shows greater sensitivity to a polymer change than drug release.

Conclusions

An inverse power law relating polymer erosion rate and weight average molecular weight has utility in predicting polymer erosion from hypromellose matrix tablets comprised of either the intermediate viscosity grade or polymer blends.

Erosion of hypromellose matrix tablets in deionized water and 0.1N HCl were comparable for low molecular weight K130 polymer, while erosion in 0.1M pH 7.0 phosphate buffer was lower at later times for both K130 and K4M polymers. This is apparently a result of slowing the hydration process of the polymer chains.

Appropriate blends of lower and higher molecular weights were determined by a weighted-average calculation using weight average molecular weight that resulted in similar drug release profiles relative to matrix tablets containing intermediate viscosity grades.

Note: Although the official monograph name of “hydroxypropyl methylcellulose” (“HPMC”) has been changed to “hypromellose,” reference listings here continue to use the prior nomenclature to facilitate reference to existing publications in libraries and information retrieval systems.

References

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Figure 1

Erosion Rate *vs.* $MW_w^{-0.68}$ for all polymers studied. The listed values represent the 2% w/v solution viscosities of the polymers examined.

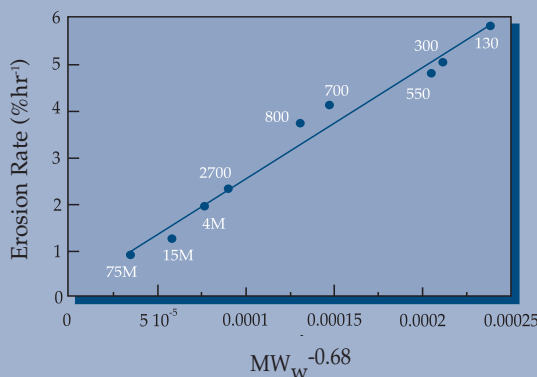


Figure 2

Erosion rate versus $MW_w^{-0.68}$ for pure polymers and for polymer blends of K130:K4M in the designated ratios. (a) 32:68 (b) 64:36 (c) 75:25 (d) 95:5.

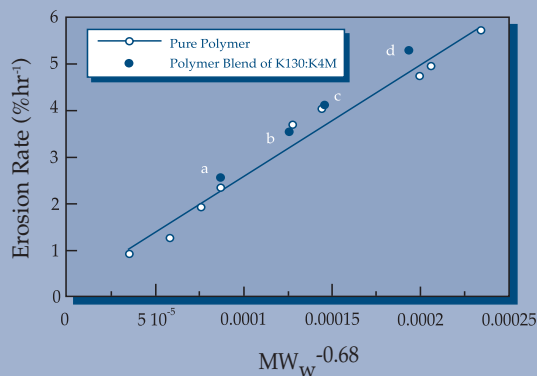


Figure 3

% Polymer eroded *vs.* time for K130 and K4M in deionized water, 0.1N HCl, and 0.1M phosphate buffer (pH 7.0).

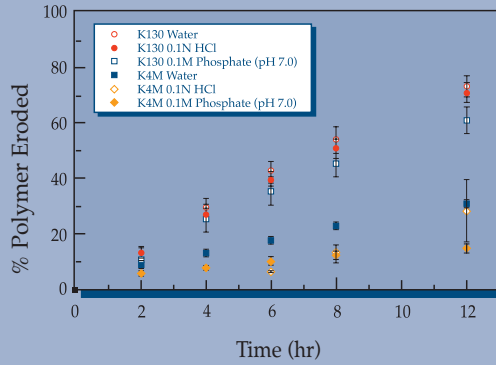


Figure 4

% Polymer eroded *vs.* time for compacts of K130 in pH 7.0 phosphate buffers of varying concentrations.

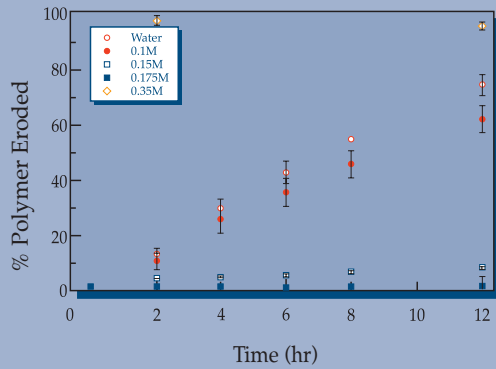


Figure 5

% Polymer eroded *vs.* time for tablets containing pure polymer compared with polymer and theophylline (3:1).

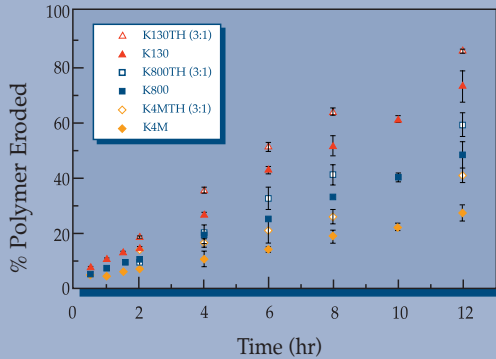


Figure 6

% Theophylline release vs. time for polymer:theophylline (3:1) matrix tablets comparing straight polymer performance to polymer blends.

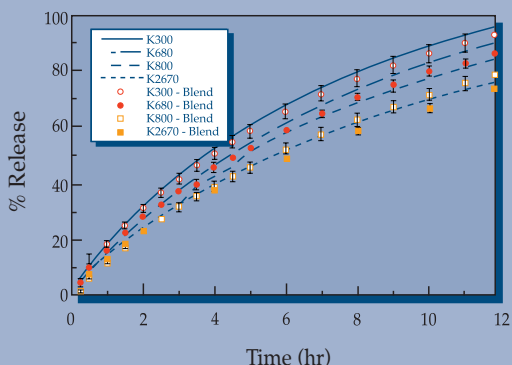
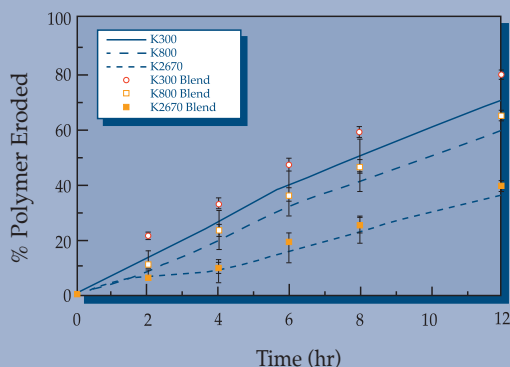


Figure 7

% Polymer eroded vs. time for theophylline: polymer (1:3) comparing straight polymer performance and polymer blends.



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