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Hydroxypropylcellulose Polymer Molecular Weight: Influence on Erodible Modified Release Matrix Systems

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Abstract

This study investigates the role of hydroxypropylcellulose (HPC) molecular weight (MW) in controlling drug release, with focus on erosion dependent systems. High and and low MW HPC and three newly developed intermediate MW grades were studied in three systems of diverse drug solubility and erosion dependence.

Introduction

The utility of high MW hydroxypropylcellulose with fine particle size (HPC HXF) is well known for swellable controlled release matrices (1-3). Among the useful attributes of HPC HXF are demonstrated robustness under different processing conditions such as wet granulation, roller compaction and direct compression. At levels of 20 to 30%, HPC HXF can form strong gel matrices that are minimally affected by variation in hydrodynamic agitation levels. Drug release from such systems is mediated by swelling and diffusion control. Studies have also highlighted the utility of low MW hydroxypropylcellulose with fine particle size (HPC EXF) as a tough, efficient thermoplastic tablet binder. However, the use of low and intermediate MW HPC in modified release matrix systems has not been well studied.

High and low MW HPC HXF and EXF and three newly developed intermediate MW grades, as shown below, were studied in three diverse model systems where erosion may be of importance.

Klucel™ Pharm HPC	Nominal MW (kDa)	Apparent Viscosity (mPa·s)
EXF	80	300-600 at 10%
JXF	140	150-400 at 5%
GXF	370	150-400 at 2%
MXF	850	4000-6500 at 2%
HXF	1150	1500-3000 at 1%

The matrix formulations included (a) a high dose BCS class I soluble drug (theophylline), (b) a low dose system with strong pH dependent drug solubility (papaverine HCl, high solubility in acidic media, but insoluble in neutral and alkaline conditions) and (c) an intermediate dose BCS class II insoluble drug (nifedipine).

Note: This work was presented at the Annual Meeting of the Controlled Release Society, June 18-22, 2005, Miami Beach, Florida.

Experimental Methods

Wet granulated theophylline tablets, comprising 70% drug and 29.5% HPC, were compressed on an instrumented rotary press. Additional theophylline formulations, comprising 20 and 40% drug, 30% HPC, and q.s microcrystalline cellulose (MCC), were also prepared. Papaverine tablets, comprising 5% drug, 30% HPC, and 64.5% MCC, were wet granulated before compression. Nifedipine tablets, comprising 20% drug, 30% HPC, and 49.5% silicified MCC, were directly compressed. All formulations were lubricated with 0.5% magnesium stearate.

Theophylline tablet dissolution was tested in USP apparatus I (100 rpm) with pH 6.8 phosphate buffer. Using the same apparatus, papaverine tablets were tested for 2 hours in 0.1 N HCl (pH 1.5) followed by 22 hours in pH 6.8 phosphate buffer. For nifedipine, a modified USP apparatus II method was used with pH 4.6 buffer enriched with 1% SLS. Tablet erosion and dissolution medium uptake were determined gravimetrically under the dissolution testing conditions. Dimensional changes due to swelling and erosion were measured from digital images during the dissolution test. The fractional dissolution data (M_t/M_∞) were fit to a tablet surface erosion model with time (t), based on initial tablet radius (a0) and height (b0), drug concentration (c0) and radial (ka) and axial (kb) erosion rates (4):

$$M^t/M_\infty = 1 - (1-k_a t/c_0 a_0)^2 \, (1-2k_b t/c_0 b_0)$$

The model assumes that surface erosion is the rate determining mechanism with negligible diffusional contributions to drug release. Further assumed is a time-independent uniform drug concentration, c0. In this study, the most appropriate version of the model included a single erosion rate contant, ko, (assumes ka=kb) and an estimate of the lag time or initial burst effect, L. Positive L values indicate a lag time, negative L values indicate a burst effect. Therefore,

$$M_t/M_\infty = 1 - [1-k_o(t-L)/c_0 a_0]^2 \, [1-2k_o(t-L)/c_0 b_0]$$

Using the dissolution data to estimate the erosion rate constant, ko, the tablet radius, a, and the tablet height, b, at any time, t, can be derived:

$$a = a_0 - k_o(t-L)/c_0 \qquad b = b_0 - 2k_o(t-L)/c_0$$

The fractional matrix mass remaining, mt/m0 can then be calculated as follows (5):

$$m_t/m_0 = a^2 b/a_0^2 b_0$$

Therefore we used the drug release profiles to model erosion, and the predicted erosion profiles were then compared to actual erosion measurements.

Results and Discussion

High Dose, Soluble Theophylline: Figure 1 indicates that HPC MW is the dominant release rate determining factor. However, the polymer MW effect increases with higher drug load. For 20% drug, t60% varies from 5 to 13 hrs for HPC EXF and HPC HXF, respectively. At 70% drug, t60% varies from 1.5 to ~25 hrs for EXF and HXF, respectively, with an increase in release profile linearity for all MW grades. For low MW HPC grades (EXF and JXF) increased theophylline levels result in faster release. In contrast, higher drug load leads to slower release with high MW HPC grades (MXF and HXF). This indicates a change in release mechanism from purely erosion dependent release to increasingly diffusion mediated release as MW increases. For intermediate MW (GXF), the impact of theophylline level is minimized.

At 70% drug, the erosion and drug release profiles are nearly superimposable for low and intermediate MW grades (EXF, JXF and GXF), indicating that erosion is the rate limiting process for drug release. The dissolution data correlates well with the surface erosion model for formulations with EXF, JXF and GXF grades (Table 1 and Figure 2). For higher MW MXF and HXF, the drug release profiles and predicted erosion profiles are faster than the actual erosion profiles, suggesting that drug diffusion through the highly swollen gel layers significantly contributes to drug release. Figure 3 shows the range of erosion and swelling with this MW series of HPC polymer matrices.

Figure 1
Effect of drug load (20-70%) and HPC MW on drug release from soluble theophylline tablets with 30% polymer level.

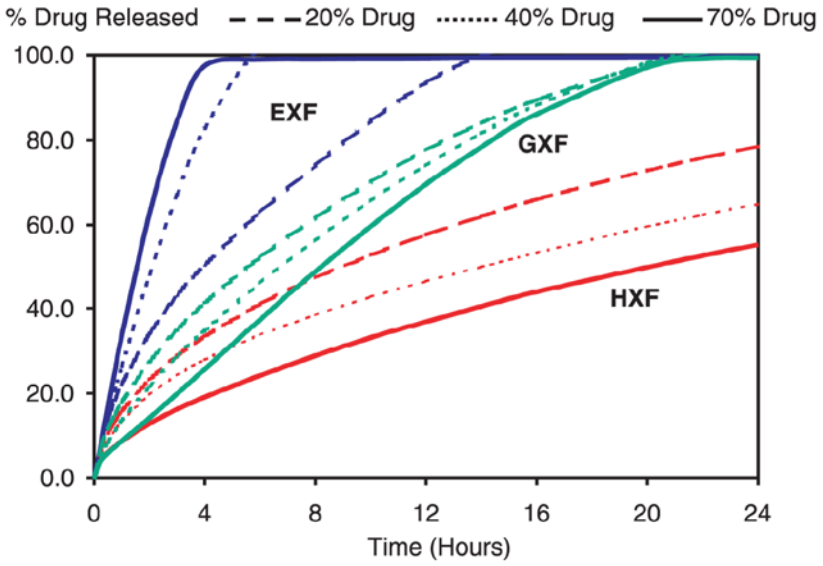


Figure 2
Effect of HPC MW on fractional drug release, predicted erosion and actual erosion of 70% theophylline tablets.

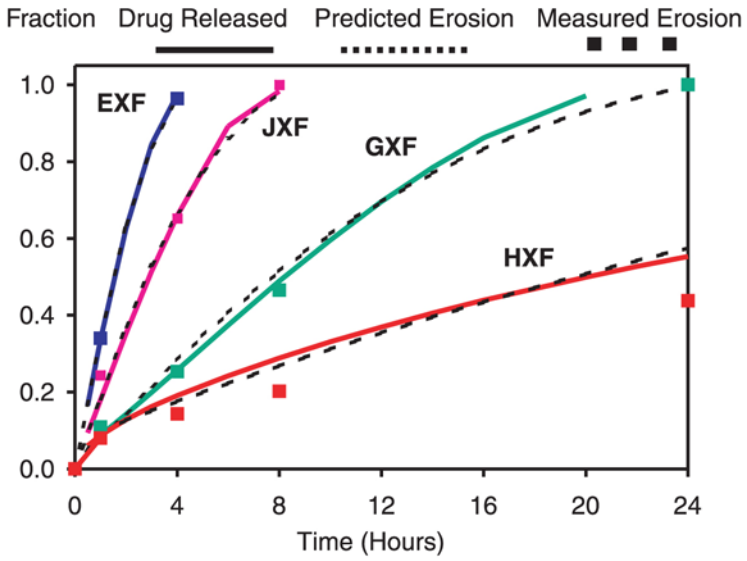
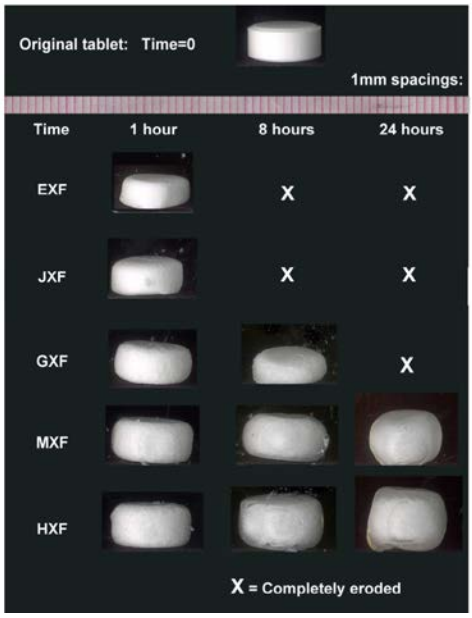


Table 1
Erosion Model Parameters for 70% Theophylline Tablets

Formula	EXF	JXF	GXF	MXF	HXF
k_o (mg/mm^2 hrs)	0.466	0.240	0.083	0.033	0.028
L (hrs)	0.134	0.158	0.084	-1.886	-2.877
R^2 adj	0.99	0.99	0.99	0.98	0.99
Degrees of freedom	4	6	11	13	13

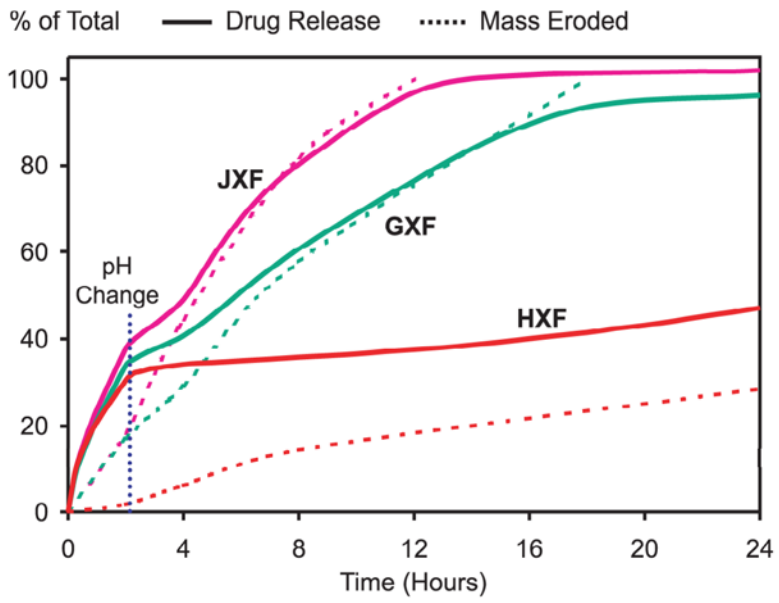
Figure 3
Effect of HPC MW on Erosion and Swelling of 70% Theophylline Tablets



Low Dose, pH Dependent Drug (Papaverine HCl): Regardless of MW, drug release was controlled by diffusion and swelling in acidic conditions, attributed to the high solubility of the drug in acid media. When pH is changed to 6.8 during dissolution testing, the drug loses its solubility, resulting in negligible further release from high MW, low eroding matrix systems. For a low MW HPC polymer matrix, continued drug release occurs due to erosion.

Figure 4 shows erosion rates are considerably slower than the drug release rates for all papaverine formulations in acidic pH (first 2 hours). However for JXF and GXF grades, release and erosion profiles are nearly superimposable after changing to pH 6.8 phosphate buffer, demonstrating erosion control. These grades can reduce pH dependence in matrix systems containing weak bases without the need for additional buffering agents.

Figure 4
Effect of HPC MW on Drug Release and Erosion of Low Dose Papaverine Tablets



Low Soluble Nifedipine: The drug release rate was regulated by varying the MW of HPC, with t40% values of 5 to 20 hours, for HPC EXF and HPC HXF, respectively. Due to delayed wetting, caused by low drug solubility, all formulations show a significant initial lag time. Figure 5 shows that in addition to drug release rates, erosion rates are also MW dependent. However, during the early time period, drug release rates lag significantly behind erosion rates for low and intermediate MW HPC grades (EXF, JXF and GXF). The rates tend toward synchronization with time. This indicates that drug molecule dissolution is the rate limiting step, rather than matrix erosion. Considerable drug dissolution occurs from the eroded drug matrix particles dispersed in the bulk dissolution medium.

Although the surface erosion model provides a good fit to the dissolution data (Table 2), this model is therefore not appropriate in drug dissolution rate limited situations, as predicted and actual erosion rates deviate significantly. For the high MW HPC grades (MXF and HXF), drug release rates exceed erosion rates throughout due to the additional contribution of drug diffusion through the swollen gel layers. Drug diffusion and matrix tablet erosion rates are too slow for high MW types, resulting in limited drug release over 24 hours. However, with lower MW grades, complete drug release in physiological time periods is achieved.

Figure 5
Effect of HPC MW on drug release and erosion of low soluble nifedipine.
Drug release is not well correlated with tablet erosion for this insoluble drug formulation.

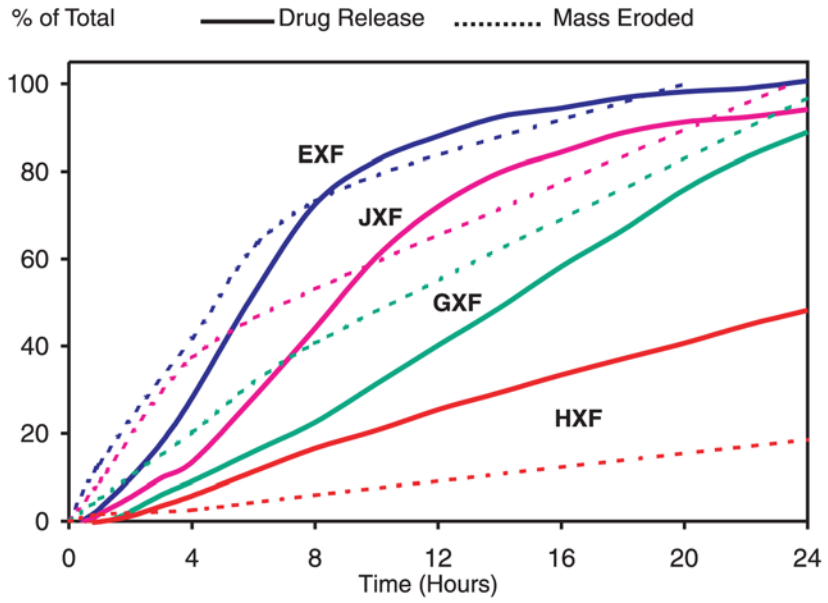


Table 2
Surface Erosion Model Parameters for Low Soluble Nifedipine Formulations

Formula	EXF	JXF	GXF	MXF	HXF
k_o (mg/mm^2 hrs)	0.043	0.030	0.020	0.015	0.008
L (hrs)	1.657	2.668	4.306	3.606	1.232
R^2 adj	0.98	0.98	0.98	0.99	0.99
Degrees of freedom	5	6	8	8	8

Conclusion

Variation in HPC MW is an effective means to control formulation release rates and mechanisms. Three diverse drug formulations with widely differing drug solubility and drug load characteristics consistently show that at a 30% HPC level, higher MW HPC provides significant matrix swelling and diffusion controlled release. Lower MW grades provide surface erosion, and can be used to great advantage to control release of low soluble drugs, pH dependent drugs and high dose formulations as shown in these studies. In contrast, the higher MW grades, with higher swelling and gel forming propensity, are more suitable for high soluble drugs.

References

1. Railkar et al, Drug Dev Ind Pharm 27, 337, 2001.
2. US Patent 4,704,285, granted 11/3/87, expires 11/18/05 (contact Dow Chemical for further info).
3. US Patent 6,103,263, granted 8/15/00, expires 11/17/14.
4. Katzhendler et al, J. Pharm. Sci, 86, 110, 1997.
5. Du_rig et al, J Pharm Pharmacol 51: 1085, 1999.

Materials

1. Klucel™ Pharm hydroxyproplycellulose, grades HXF, MXF, GXF, JXF and EXF, marketed by Ashland Specialty Ingredients, Ashland Inc., Wilmington, DE.
2. Theophylline anhydrous, USP, marketed by BASF Corporation, Mount Olive, NJ.
3. Nifedipine, USP, marketed by Spectrum Corporation, Gardena, CA.
4. Papaverine, USP, marketed by Spectrum Corporation, Gardena, CA.
5. Avicel* PH-101 microcrystalline cellulose, NF, marketed by FMC Corporation, Philadelphia, PA.
6. Prosolv HD* 90 silicified microcrystalline cellulose, NF, marketed by J. Rettenmaier & Söhne GMbh & Co. KG, Rosenberg, Germany.
7. HyQual* magnesium stearate, NF, marketed by Mallinckrodt Inc., a Division of Tyco International, St. Louis, MO.