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Hydroxypropylcellulose in Modified Release Matrix Systems: Polymer Molecular Weight Controls Drug Release Rate and Mechanism

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Objective

To study the effect that hydroxypropylcellulose (HPC) polymer molecular weight (MW) exerts on drug release rates and mechanism from matrix tablets.

Introduction

Hydroxypropylcellulose (HPC) is a versatile nonionic cellulose ether, combining dual solubility in water and polar organic solvents with high surface activity and true thermoplasticity. In the formulation of modified release matrix systems, HPC is well known for its efficiency in controlled release⁽¹⁻³⁾ and its outstanding compactibility⁽⁴⁾. Fine particle size HPC grades are of particular importance as reduction in particle size can reduce drug release rates^(1, 2). This effect has been attributed to a more rapid rate of hydration, leading to more rapid formation of the diffusion-controlling gel layer around the dry tablet core. Finer particle size also significantly increases HPC tablet compactibility and binder efficiency⁽⁵⁾.

Fine particle size HPC has traditionally been available as high and low molecular weight (MW) grades designated as Klucel™ Pharm hydroxypropylcellulose, grades HXF and EXF, with typical mean particle size between 80 and 100 µm. This study evaluates the importance of HPC MW in modified release. For this purpose, three new fine particle grades of Klucel Pharm HPC were developed with intermediate MW. These grades are designated as MXF, GXF and JXF. The grades of fine particle size HPC polymer used in these studies are detailed below.

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

Model formulations comprising a BCS Class I soluble drug (theophylline) and a BCS Class II insoluble drug (nifedipine) were used. Additional variables for the theophylline formulations included polymer level (20 and 40%) and an increase in drug load (40%). While a number of reports have been published on MW effects in hypromellose (HPMC) based systems, there is little published data on these aspects with respect to HPC.

Note: This work was presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, November 7-11, 2004, Baltimore, Maryland.

Procedures

Directly compressed nifedipine and theophylline tablets comprising 20% drug, 30% Klucel™ HPC, 49.5% silicified microcrystalline cellulose (MCC) polymer and 0.5% magnesium stearate were prepared on a Manesty Betapress. Additional theophylline formulations were prepared with varied polymer level (20 and 40%) or increased drug dose (40% theophylline), where the MCC levels were reduced.

Theophylline tablet dissolution testing was performed in USP apparatus I in pH 6.8, 0.5M phosphate buffer. For nifedipine, USP apparatus II was modified by placing the tablets on a 7 cm round stainless steel mesh which was located at the bottom of the dissolution flask. This modification was made to prevent poorly soluble tablets or drug particles from accumulating in the stagnant solvent layers at the bottom of the dissolution vessel, as described previously⁽⁶⁾. The dissolution medium was pH 4.6 buffer enriched with 1% sodium lauryl sulfate.

Tablet erosion and uptake of the dissolution medium uptake were determined gravimetrically in the same conditions as used for dissolution testing. Basic calculations are shown below. Additional experimental details have been described previously⁽⁷⁾.

$$\text{Dissolution Medium Uptake (\%)} = \frac{100 (\text{Wet Weight} - \text{Remaining Dry Weight})}{\text{Remaining Dry Weight}}$$

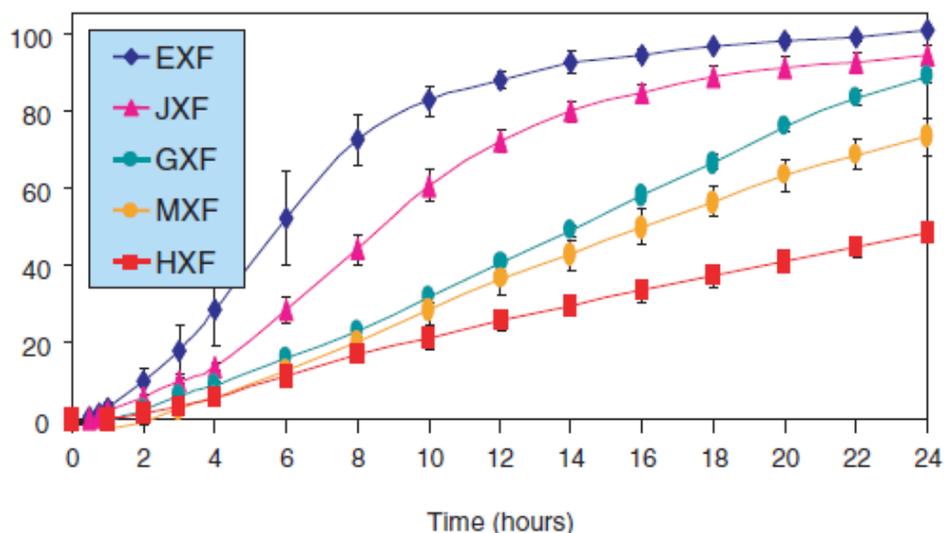
$$\text{Remaining Mass (\%)} = \frac{100 (\text{Remaining Dry Weight})}{\text{Original Dry Weight}}$$

Results

Effect of MW on Insoluble Drug Release (Nifedipine)

Figure 1 shows that the release rate of 20% nifedipine is effectively regulated by varying the MW of fine particle size HPC. After an initial lag time all profiles are relatively linear, with t40% values ranging from 5 hours for EXF to 20 hours for HXF. The lag times can be attributed to the low wettability and low aqueous solubility of nifedipine, resulting in negligible initial diffusion until steady state conditions have been established.

Figure 1
Effect of Fine Particle Klucel™ HPC MW on Nifedipine Dissolution
Formulation: 20% Nifedipine, 30% HPC, 49.5% MCC, 0.5% Mag Stearate
Nifedipine Release (%)



Effect of MW Weight on Erosion and Swelling Behavior of Nifedipine Tablets

The drug release kinetics largely correlates with the tablet erosion rates and are inversely proportional to the rate of water uptake in this matrix system (Figures 2 and 3). The low and intermediate MW grades, EXF, JXF and GFX, achieve complete tablet erosion within the 24-hour test period. High MW HXF and MXF show limited erosion of 20 and 40%, respectively, over a 24 hour period. The trend of lower erodibility with higher MW coincides with greater swelling tendency as indicated by water uptake rate into the matrix. Confirming the MW dependency of swelling and erosion kinetics, lower MW tablets are significantly smaller in volume after 4 hours of dissolution testing as compared to higher MW grades (Figure 4). For low MW, the tablet surface is rougher and grainier in appearance, allowing visual distinction of white MCC interspersed in the intensely yellow-colored drug blend.

Figure 2
Effect of Fine Particle Klucel™ HPC MW on Nifedipine Tablet Erosion
Formulation: 20% Nifedipine, 30% HPC, 49.5% MCC, 0.5% Mag Stearate
Remaining Mass (% of Original Dry Weight)

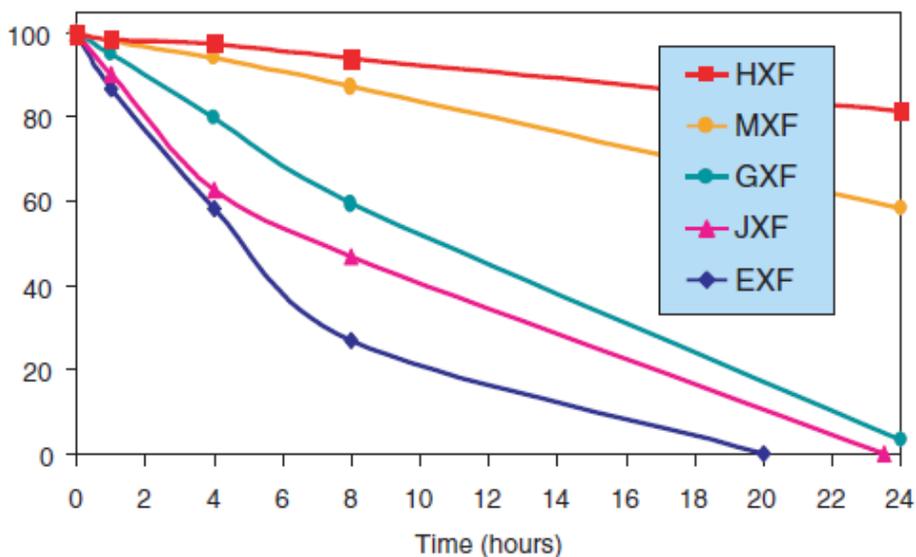


Figure 3
Effect of Fine Particle Klucel HPC MW on Nifedipine Tablet Medium Uptake
Formulation: 20% Nifedipine, 30% HPC, 49.5% MCC, 0.5% Mag Stearate
Dissolution Medium Uptake (% of Original Dry Weight)

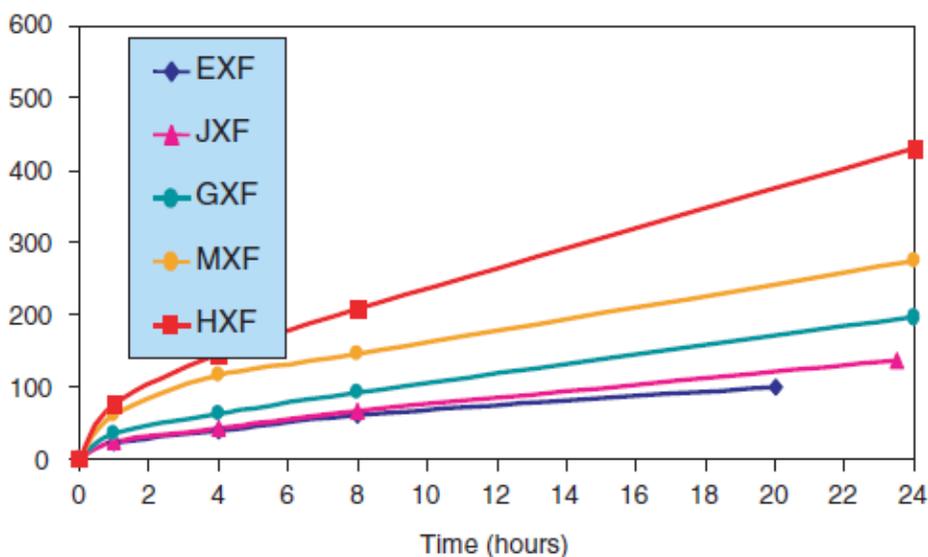


Figure 4
Effect of Fine Particle Klucel™ HPC MW on Erosion and Swelling Behavior
Nifedipine Matrix Tablets Subjected to Dissolution Testing for 4 and 8 Hours
Formulation: 20% Nifedipine, 30% HPC, 49.5% MCC, 0.5% Mag Stearate
(Ruler shows 1mm spacing).



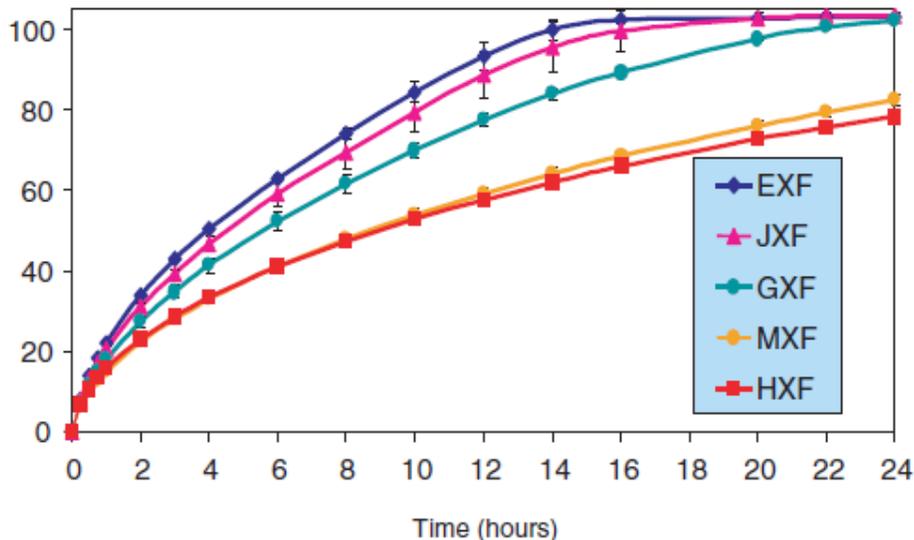
For insoluble drugs such as nifedipine, drug dissolution rate is the rate limiting factor. In addition to the very limited diffusion of dissolved drug through the tablet matrix, low and medium MW grades promote the liberation of undissolved drug particles by surface erosion. These particles can then dissolve more rapidly in the bulk fluid. In contrast, high MW grades have limited erodibility, but cause a substantial increase in overall tablet volume and gel layer thickness with time. Drug release is therefore primarily due to diffusion of dissolved drug through the gel layer. Due to the solubility constraints, a significant amount of undissolved drug remains trapped in the tablet matrix well beyond 24 hours.

A change in release mechanism can therefore be readily achieved by changing the MW of fine particle size HPC in a formulation. The new intermediate fine particle grades of Klucel Pharm HPC can therefore serve as a highly effective tool to control insoluble drug release profiles within physiologically relevant time periods.

Effect of Molecular Weight on Soluble Drug Release (Theophylline)

Figure 5 shows that varying the MW of fine particle size HPC is also effective in regulating the drug release kinetics for a soluble drug such as theophylline. At a 20% drug load, the achievable release rate variation among the HPC grades for theophylline was lower than the variation found for nifedipine. The $t_{60\%}$ values varied from 5.5 hours for EXF to 13 hours for HXF. Noticeably for the higher MW HXF and MXF, a viscosity threshold exists above which further increases in viscosity result in only negligible release duration gains. Similar observations have been made previously for hydroxyethylcellulose and hypromellose^(8, 9). As observed for the nifedipine tablets, the lower MW EXF and JXF tablets eroded completely. In contrast, higher MW grades gradually increased in volume due to swelling.

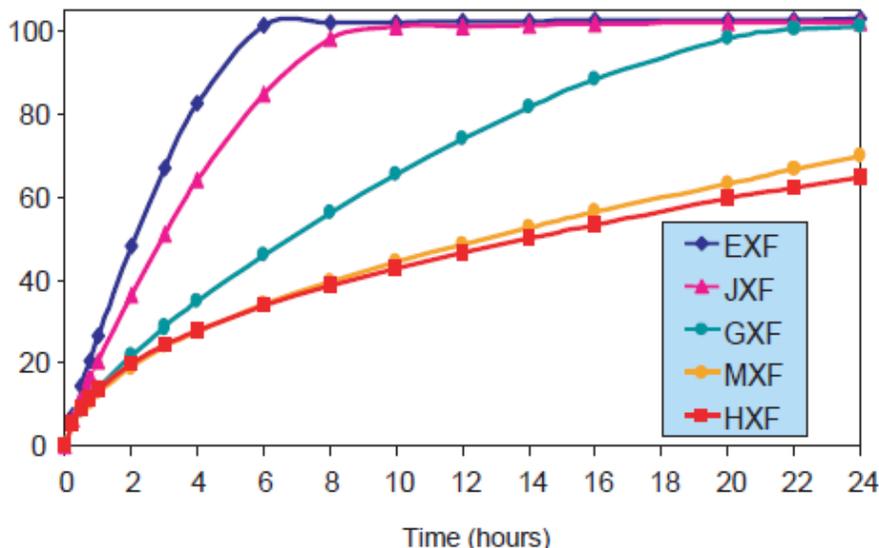
Figure 5
Effect of Fine Particle Klucel™ HPC MW Variation on Theophylline Dissolution
Formulation: 20% Theophylline, 30% HPC, 49.5% MCC, 0.5% Mag Stearate
 Theophylline Release (%)



Effect of MW When Soluble Drug Load is Increased

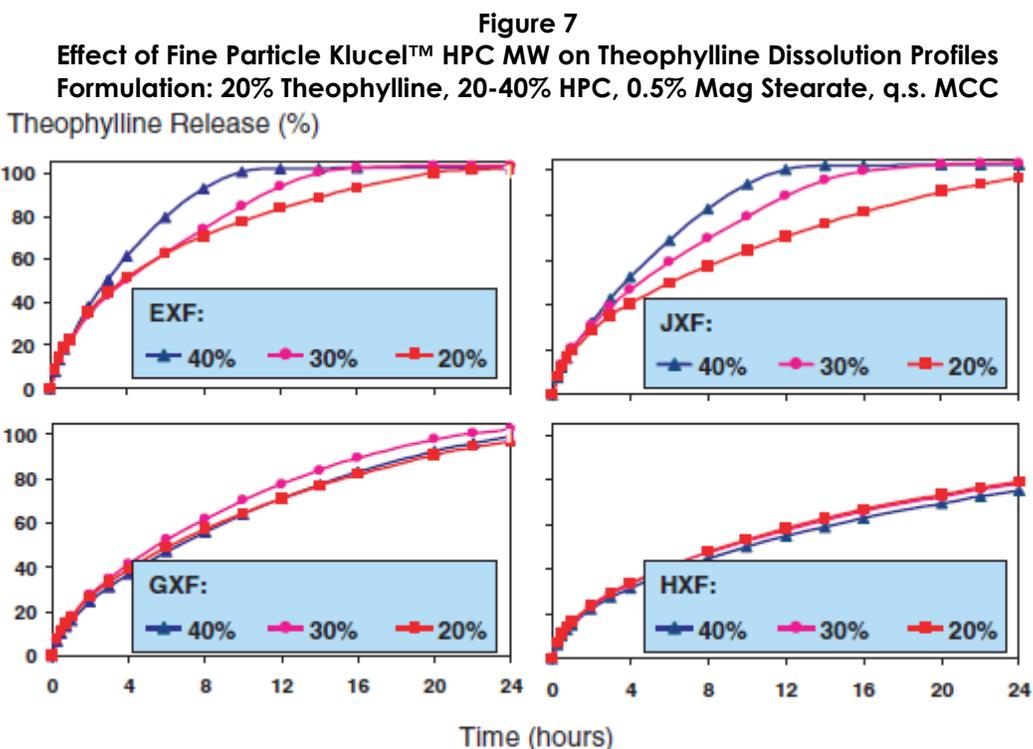
The impact of polymer MW variation increases when theophylline drug load is increased from 20 to 40%, with $t_{60\%}$ values ranging from 2.5 hours for EXF to 18 hours for HXF and MXF. In addition to faster release, the profiles for low viscosity grades EXF and JXF are also more linear at the higher drug load (Figure 6). For higher MW grades, release decreases as drug load increases. As is typical for diffusion mediated release, profiles remain curved, with release rates declining in the late time period. As observed earlier for nifedipine, the change in MW results in a fundamental shift in release mechanism, with diffusion of drug through the gel layers dominating for high viscosity grades, while drug dissolution and matrix erosion are more important at lower MW.

Figure 6
Effect of Fine Particle Klucel HPC MW When Drug Load is Increased
Formulation: 40% Theophylline, 30% HPC, 29.5% MCC, 0.5% Mag Stearate
 Theophylline Release (%)



Effect of MW on Soluble Drug Release When Polymer Level is Increased

The differences in release mechanism are further highlighted when polymer levels are varied from 20 to 30 and 40% HPC. Release rates markedly increase for lower MW EXF and JXF (Figure 7). This can be attributed to the greater solubility and erodibility of lower MW grades, which can be added to a formulation in higher proportions to speed up release. In the case of intermediate MW GFX, changing polymer level has minimal effect indicating a balance between swelling and erosion processes. For higher MW HXF and MXF, there is a slight decrease in release rates as polymer levels are increased, indicating a predominance of swelling mediated diffusion over erosion.



Conclusions

Varying molecular weight (MW) of fine particle HPC over the nominal range of 80 to 1150 kDa provides significant and effective control of in vitro drug release rates for both soluble and insoluble drugs.

Lower MW HPC types up to ~370 kD undergo significant erosion. For MW above this threshold, diffusion through the swelling gel layer becomes more significant.

These grades provide a simple and effective means to vary the release profile and mechanisms and offer the advantage of allowing tablet size, chemical composition and proportion of components to remain constant.

The three new grades of fine particle size Klucel HPC provide a valuable addition to the formulation opportunities for controlling modified release matrix systems.

References

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3. DY Lee, D. Y. and Chen C.M., US Patent 6,103,263, granted 8/15/00, expires 11/17/14.
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8. Versatility of Natrosol™ Hydroxyethylcellulose in Controlled Release Matrix Systems, Ashland Pharmaceutical Technology Report PTR-017.
9. Benecel™ Hypromellose for Use in Modified Release Drug Dosage Forms: Performance Similarity to Competitive Grades, Aqualon Technical Information Bulletin VC-631.

Materials

1. Klucel™ Pharm hydroxypropylcellulose, 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. ProSolv HD* 90 silicified microcrystalline cellulose, NF, marketed by J. Rettenmaier & Söhne GmbH & Co. KG, Rosenberg, Germany.
5. HyQual* magnesium stearate, NF, marketed by Mallinckrodt Inc., a Division of Tyco International, St. Louis, MO.