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Effect of Hypromellose and Methylcellulose Substitution Type, Molecular Weight and Drug Solubility on Release Kinetics from Matrix Tablets

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Abstract Summary

This study attempts to rationalize the effect of polymer molecular weight (MW), hydrophilicity and drug solubility on drug release kinetics from matrices containing methylcellulose (MC) or hypromellose (HPMC).

Introduction

Variation in degree of substitution and cellulose ether substituent chemistry has a significant effect on polymer hydrophilicity. For the most common cellulose ethers the hydrophilic rank order is hydroxyethyl cellulose (HEC) > HPMC > hydroxypropyl cellulose (HPC). We have previously investigated the role of polymer hydrophilicity for the above mentioned cellulose ethers in conjunction with three different MW levels and three different drug solubilities (ranging from typical BCS class I to typical BCS class II drug solubilities)[(1)]. For low soluble compounds, increased polymer hydrophilicity was found to have a similar effect to lowering MW. In both cases erosional contributions to drug release were increased, resulting in faster drug release overall. In the case of MC and MC derivatives such as HPMC the variation in substitution levels also affects hydrophilicity. The hydrophilic rank order for the most common types of MC and HPMC can be expressed in cloud point temperature and is shown in Table 1.

Table 1
Hydrophilicity of MC and HPMC Grades

Polymer	Cloud Point (°C)	Hydrophilicity
MC	55-60	Low Medium
HPMC Type 2910	60-70	High
HPMC Type 2208	70-80	

While numerous studies have addressed the roles of HPMC substitution, drug solubility or molecular weight separately, few have addressed combined effect of MC and HPMC hydrophilicity, MW and drug solubility. The aim of this study was therefore to simultaneously assess the impact of polymer hydrophilicity, MW (viscosity was used as a surrogate) and drug solubility on the interconnected processes of matrix swelling, erosion and drug dissolution. Table 2 lists the HPMC and MC types used in this study. The three model drugs chosen for this study were highly soluble metformin (METF), intermediate soluble theophylline (THEO) and a low soluble glipizide (GLIP).

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Note: This work was presented at the Controlled Release Society Meeting, July 12-16, 2008, New York.

Table 2
Benecel™ HPMC and MC Grades Used

Grade	Chemistry	Substitution % OCH3	Substitution % POOH	2% Viscosity (mPa·s)
Benecel E4M PH	HPMC	28-30	7-12	3,600*
Benecel K100LV PH CR	HPMC	20-24	7-12	100[a]
Benecel K4M PH CR	HPMC	20-24	7-12	3,600[a]
Benecel K15M PH CR	HPMC	20-24	7-12	18,000[a]
Benecel K100M PH CR	HPMC	20-24	7-12	100,000[a]
Benecel K200M PH CR	HPMC	20-24	7-12	200,000[a]
Benecel A4M PH	MC	27.5-31.5	—	3,600[b] 4,000[c]

[a]EP/ USP Harmonized Nominal Viscosity
[b]EP Nominal Viscosity
[c]USP Nominal Viscosity

Experimental Methods

1 Kg batches comprising 25% drug (METF, GLIP or THEO), 30% polymer and 44.5% microcrystalline cellulose were wet granulated in a high shear mixer. After drying, milling and lubrication, 400 mg tablets were compressed on an instrumented Manesty Beta Press. Dissolution, erosion and swelling studies were done in USP apparatus I. Phosphate buffer (pH 6.8) was used for METF and THEO. For GLIP, 0.5% solution of polysorbate 80 in pH 7.5 buffer was used.

Results and Discussion

Highly Soluble Drug Dissolution: For highly soluble METF, HPMC viscosity (MW) variation is relatively ineffective as a release modulator (Figure 1a). Variation in HPMC viscosity from 200,000 to 4,000 mPa·s resulted in almost superimposable profiles (f_2>70). A somewhat faster profile was achieved for the 100 mPa·s HPMC grade (f_2>50). Drug diffusion rate exceeded polymer swelling and erosion rates (data not shown), hence HPMC MW variation has little effect on drug release. Variation in HPMC substitution (hydrophilicity) levels was similarly ineffective, in modulating METF release (Figure 1b). However more hydrophobic, underivatized MC resulted in almost immediate release, due to poor gel formation. The methoxy groups tend to hydrophobically associate with each other, thus excluding water.

Medium Soluble Drug: For medium soluble THEO a large effect is seen when HPMC viscosity is increased from 100 mPa·s to 4,000 mPa·s (Figure 2a). Limited molecular weight effects are seen for variations between 4,000 and 200,000 mPa·s (f_2>60). Variation in HPMC hydrophilicity has a negligible effect (Figure 2b). The greater hydrophobicity of MC again resulted in poor matrix swelling and negligible release retardation.

Low Soluble Drug: Both MW and hydrophilicity have the most pronounced effect on the release rate of low soluble GLIP (Figure 3a and Figure 3b). The low drug solubility results in only minor diffusional release. Drug release is thus mainly dependant on polymer swelling and subsequent matrix erosion. Release is therefore directly correlated to polymer structural features that affect swelling and erosion (chain disentanglement).

Overall Effect of Molecular Weight: Many physical polymer properties are MW dependant, typically reaching an asymptotic plateau as a certain MW threshold is crossed. This is also true for drug release from HPMC matrix tablets. Figure 4 shows that beyond 4,000 mPa·s very little change occurs in release rates with increasing viscosity. Moreover, below this viscosity threshold, the MW dependence of drug release is strongest for low solubility drug.

Conclusions

Molecular weight had a more significant effect on release than substitution for HPMC based matrix tablets. Molecular weight dependence is greater for low soluble erosion based drugs and for HPMC grades with the viscosity greater than 4,000 mPa·s. Polymer hydrophilicity is significant only for low solubility erosion based systems. More hydrophobic MC was seen to be largely ineffective as a gel matrix former. Further practical implications from these results are that for highly soluble drug combination with high viscosity HPMC, viscosity specification can be wider.

References

[1]D. Tewari, et al, Ashland Pharmaceutical Technology Report, PTR-34-2, 2005.

Materials

1. Benecel™ pharm hypromellose, marketed by Ashland Specialty Ingredients, Ashland Inc., Wilmington, DE.
2. Microcrystalline cellulose: Avicel* PH-102 Microcrystalline cellulose, NF, marketed by FMC Corporation, Philadelphia, PA.
3. HyQual* magnesium stearate, NF, marketed by Mallinckrodt Inc., a Division of Tyco International, St. Louis, MO.
4. Cab-O-Sil* amorphous fumed silica (colloidal silicon dioxide), NF, marketed by Cabot Corporation, Tuscola, IL.
5. Metformin hydrochloride, USP, marketed by Ria International, Whippany, NJ.
6. Theophylline USP, marketed by BASF Corporation, Mount Olive, NJ.
7. Glipizide USP, marketed by Ria International, Whippany, NJ.

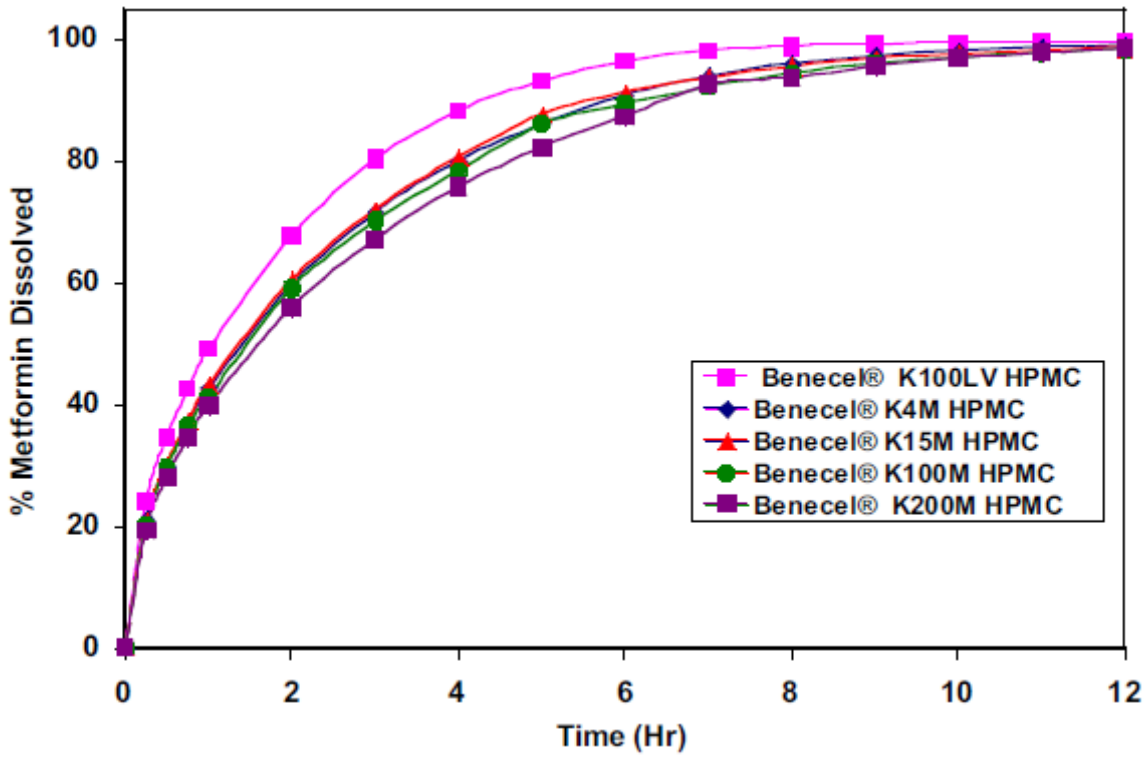

Figure 1a: Effect of Molecular Weight of Benecel HPMC Type 2208 on release of highly soluble metformin

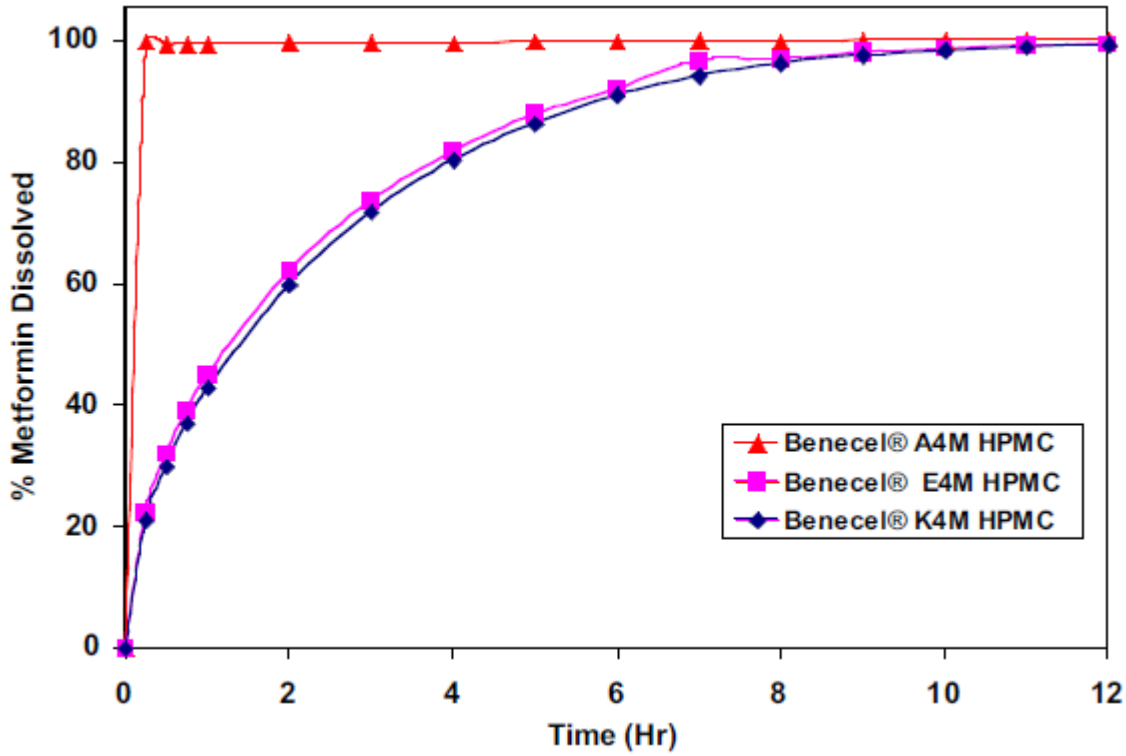

Figure 1b: Effect of Substitution Type of Benecel™ HPMC on release of highly soluble metformin

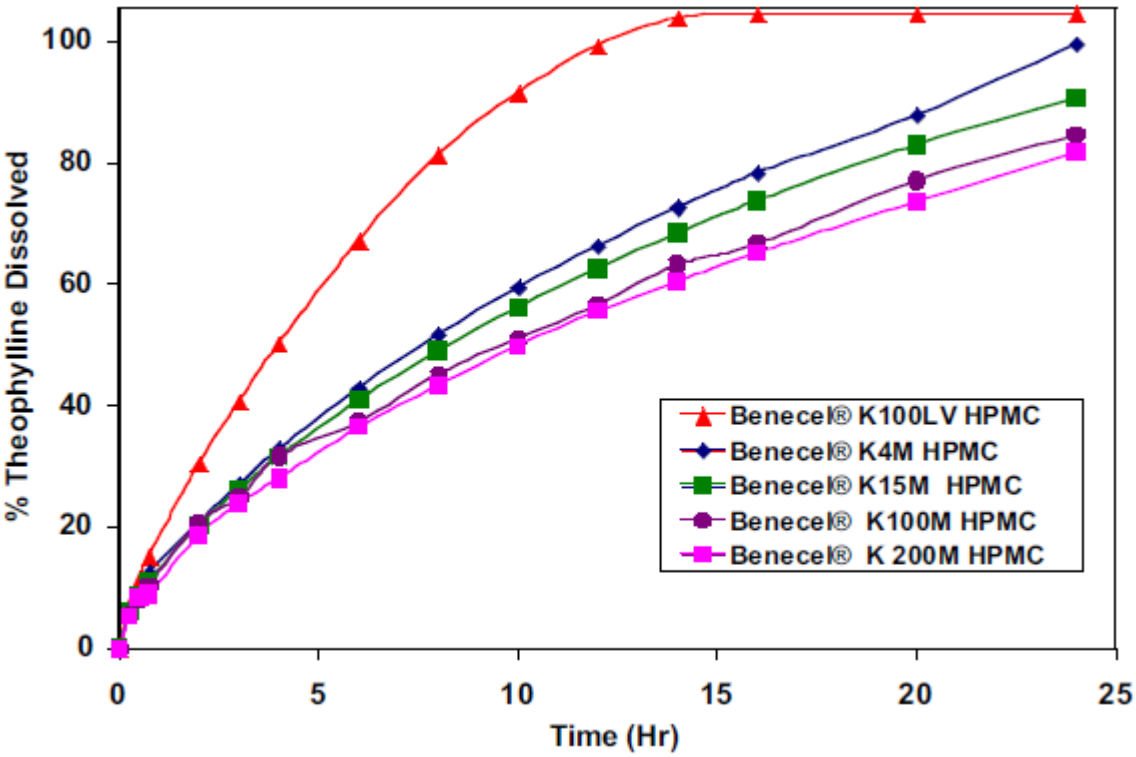

Figure 2a: Effect of Molecular Weight of Benecel HPMC Type 2208 on release of medium soluble theophylline

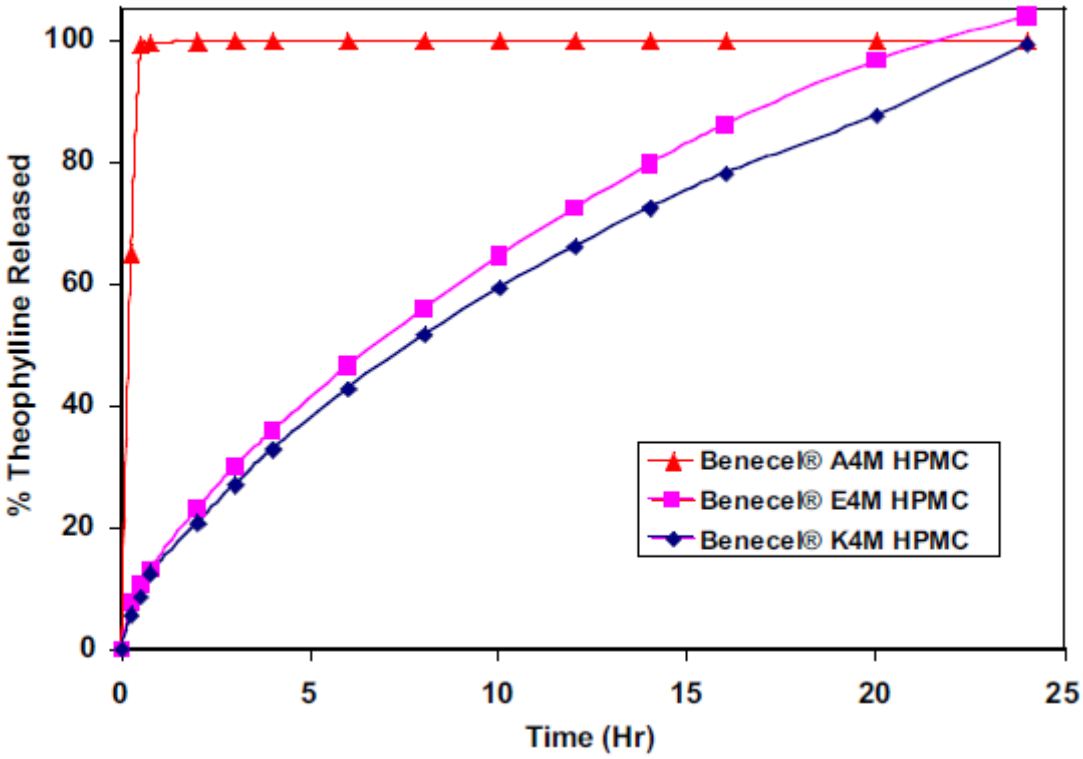

Figure 2b: Effect of Substitution Type of Benecel™ HPMC on release of medium soluble theophylline

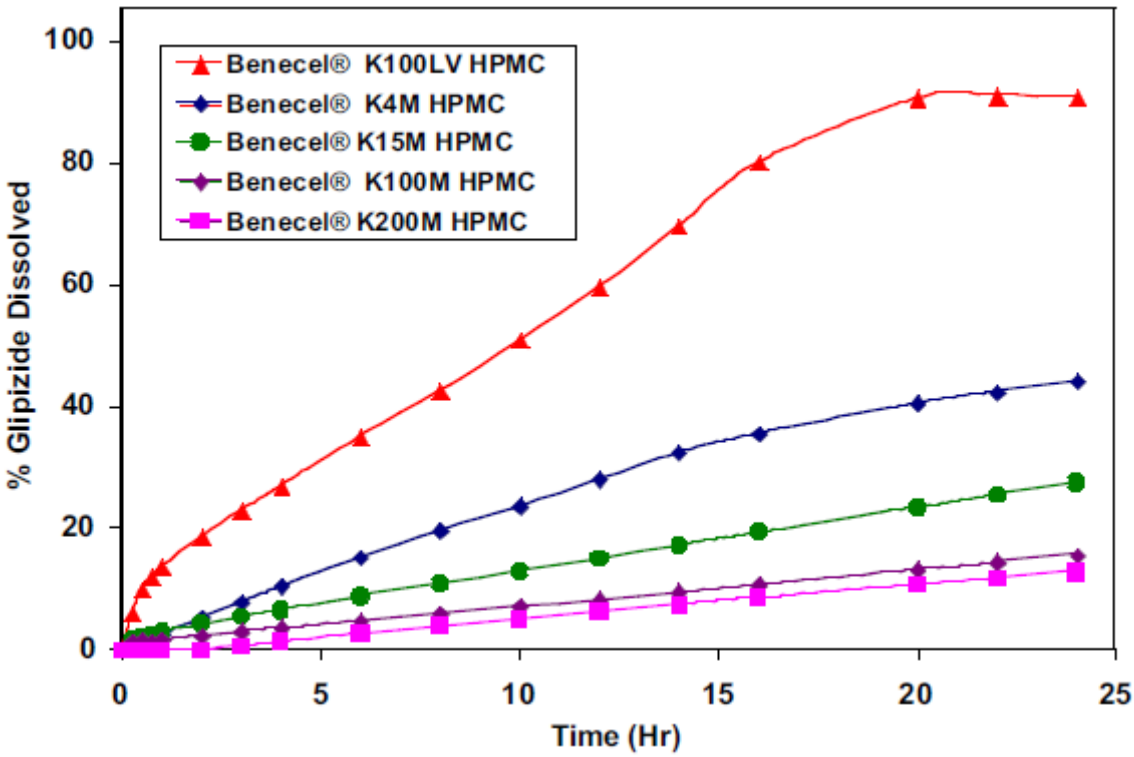

Figure 3a: Effect of Molecular Weight of Benecel HPMC Type 2208 on release of low soluble drug glipizide

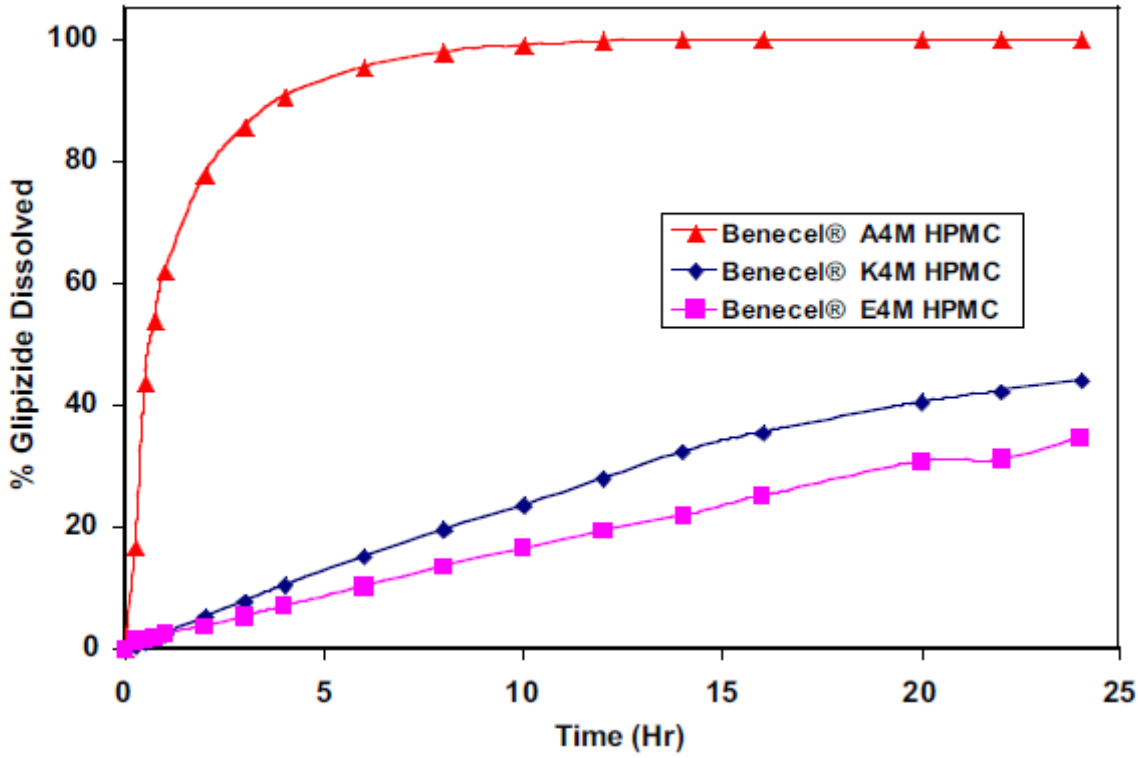

Figure 3b: Effect of Substitution Type of Benecel™ HPMC on release of low soluble drug glipizide

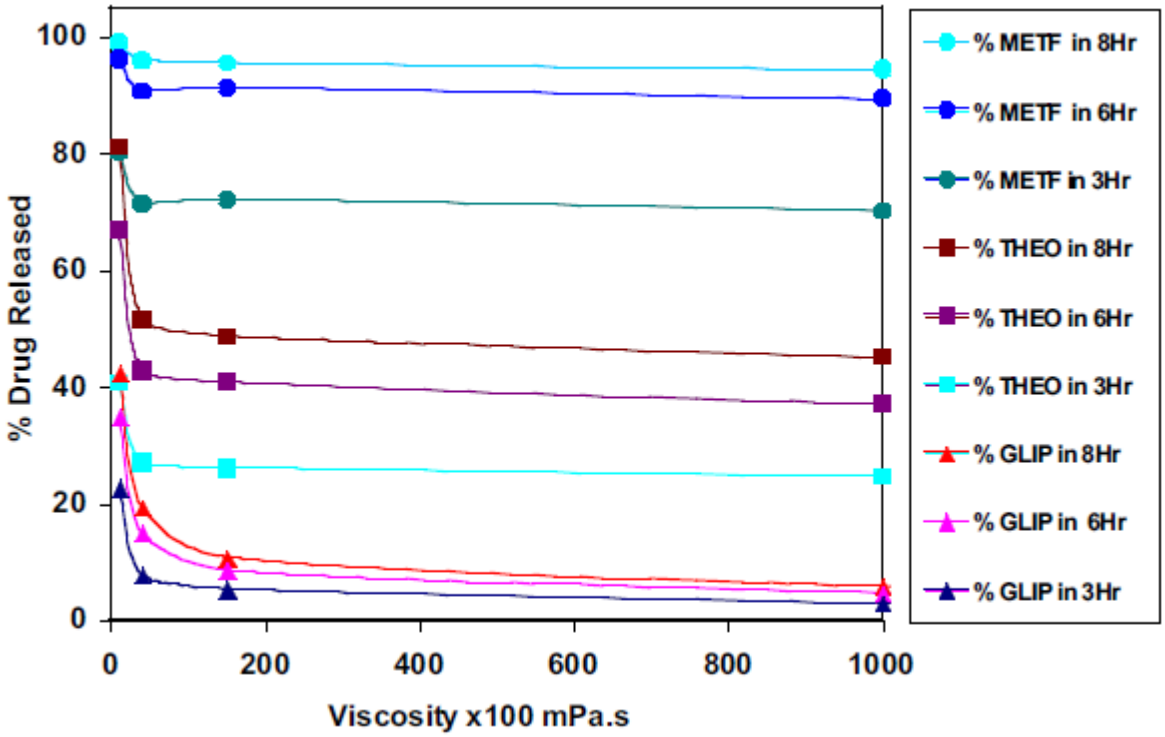

Figure 4: Effect of molecular weight and drug solubility on release rate (METF: 728 mg/ml in pH 6.8 phosphate buffer, THEO: 6.9 mg/ml in pH 6.8 phosphate buffer and GLIP: 1.8 mg/ml in pH 7.5 with 0.5% Tween 80)