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Hydrodynamic Robustness of Hypromellose and Methylcellulose Based Modified Release Matrix Systems

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Introduction

Recent studies indicate that the USP I (basket) and USP II (paddle) apparatus are often poorly predictive of *in vivo* release profiles, especially during the fed state, when a dosage form may be retained for 4-6 hours in the stomach, while continuously subjected to 3 to 4 contractions per minute. In contrast, the unconventional method of testing the modified release matrix tablets in the more hydrodynamically aggressive USP disintegration test was highly predictive of *in vivo* behavior[1].

The current study aims to evaluate the hydrodynamic robustness of hypromellose (HPMC) and methylcellulose (MC), taking polymer substitution, polymer molecular weight (MW) and drug solubility into account. For MC and closely related HPMC, the variation in substituent levels affects polymer hydrophilicity (Table 1). The hydrophilic rank order is as follows: HPMC type 2208 > HPMC type 2910 > MC.

Table 1. The Substitution Levels of Benecel™ HPMC and MC Pharm Grades

Type	Methoxyl (%)	Hydroxypropyl (%)	Hydrophilicity
MC	27.5-31.5	0	Low
HPMC Type 2910	28-30	7-12	Medium
HPMC Type 2208	20-24	7-12	High

As the disintegration test is not well suited for precise drug release studies on individual tablets, we chose the closely related USP III reciprocating cylinder dissolution apparatus. A variety of hydrodynamic conditions including the high shear, high fluid flow conditions of the disintegration test (as a model of fed state hydrodynamic conditions) as well as lower shear environments, more reflective of fasted state and intestinal hydrodynamic conditions were simulated by varying the reciprocation rate at 5, 15 and 25 dips per minute (dpm). Dissolution behavior in USP Apparatus I (basket) at 100 RPM was used as the reference and compared to USP Apparatus III at 5, 15 and 25 dips per minute (DPM), using the f_2 similarity factor. Profiles with f_2 values > 50 are generally regarded as similar.

Table 2 lists the polymers which included HPMC Type 2208, Type 2910 and MC spanning high to low hydrophilicity. HPMC type 2208 was studied over a range of MW's spanning low (115-135 kDA) to high (1150-1400) at 30% polymer loading. Medium MW HPMC type 2208, Benecel K4M PH CR HPMC was also compared with analogous MW HPMC type 2910, Benecel E4M PH CR HPMC and Benecel A4M PH MC.

The model drugs were soluble theophylline (solubility 6.9mg/ml in pH 6.8 buffer at 37°C) and low soluble glipizide (solubility 1.8 mg/ ml at pH 7.5 with 0.5% polysorbate 80 at 37°C).

Note: This work was presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, November 16th-November 20th, 2008, Atlanta, GA.

Table 2. Ashland™ Pharmaceutical Grades of Bencel™ HPMC and MC

Grade	2% Viscosity (mPa·s)	Hydrophilicity
Benecel K100LV HPMC	100*	High
Benecel K4M HPMC	3600*	High
Benecel K15M HPMC	15000*	High
Benecel K100M HPMC	100000*	High
Benecel K200M HPMC	200000*	High
Benecel E4M HPMC	3600*	Medium
Benecel A4M MC	3600** 4000***	Low

*EP/ USP Harmonized Nominal Viscosity
**EP Nominal Viscosity
***USP Nominal Viscosity

Experimental Methods

1.5 kg batches comprising 25% drug (theophylline or glipizide), 30% polymer and q.s. microcrystalline cellulose were wet granulated using a high shear mixer. After drying, milling and lubrication with 0.5% magnesium stearate, 400 mg tablets were compressed on an instrumented Manesty Beta press, equipped with an AIM-Metropolitan Computing Company data acquisition system. Dissolution behavior in USP Apparatus I (basket) at 100 RPM was used as the reference and compared to USP Apparatus III (BIO-DIS III Apparatus, marketed by Varian, Inc.) at 5, 15 and 25 dips per minute (DPM), using the f_2 similarity factor. Phosphate buffer (pH 6.8) was used for theophylline. For glipizide a 0.1% solution of polysorbate 80 in pH 7.5 buffer was used. "Hydrodynamic Robustness" was assessed based on similarity of dissolution profiles under different conditions, lack of erratic release patterns and low variability.

Results

Effect of substituents: MC appears generally unsuitable for controlled release due to dose dumping. This effect is most likely due to the low hydrophilicity and slow hydration rate of MC, which prevents a sufficiently strong gel layer from forming in the early time period. Without an appropriate gel layer, the tablets disintegrate and rapidly liberate the drug. When comparing HPMC type 2208 and 2910 for a soluble drug like theophylline, the overall dissolution profiles are similar (figures 1 and 2). However, there is somewhat less variability due to hydrodynamic stress for HPMC type 2910 (Benecel E4M PH CR HPMC) as opposed to type 2208 (Benecel K4M PH CR HPMC).

The differences between the less hydrophilic HPMC substitution type 2910 and the more hydrophilic HPMC substitution type 2208 become more visible in the case of low soluble glipizide. As shown in Figures 3 and 4 and Table 3, HPMC type 2208 results in markedly faster release as compared to HPMC type 2910. These differences are likely attributable to the lower hydrophilicity of HPMC type 2910, resulting in less swelling and thus less dilute, but stronger gel layers which are less susceptible to erosion and hydrodynamic stress.

Molecular Weight Effects: MW is a major determinant of dissolution time, hydrodynamic robustness and erodibility (Table 3). Benecel K100LV PH CR HPMC has significantly faster release profiles but also shows lack of hydrodynamic robustness (Figures 5 and 6). If relatively rapid erosion, but good hydrodynamic robustness is desired, a blend of higher and low MW polymer maybe effective, alternatively we have shown superior hydrodynamic robustness for intermediate MW HPC grades[2].

For soluble theophylline, the higher MW grades of HPMC type 2208 were generally all robust under the hydrodynamic stresses applied in this study, with Benecel™ K100M PH CR HPMC and Benecel K200M PH CR HPMC being the most robust (Figures 7 and 8). However for low soluble glipizide, larger variations generally occurred as hydrodynamic stress increased. While Benecel K200M PH CR HPMC profiles at 25 dpm were still similar to those obtained with USP apparatus I (f_2 >50), the extent of release in 24 hours is too low to be of physiological usefulness.

Conclusion

Our study shows that HPMC MW, drug solubility and hydrodynamic environment are key determinates to drug release whereas substitution has less influence. MC on the other hand is ineffective as a gel matrix former and was highly susceptible to the hydrodynamic stress. Very high hydrodynamic robustness can be achieved for soluble drugs by selecting high and medium MW HPMC grades, whereas for low soluble drugs these grades release slowly necessitating the use of lower MW polymers with low hydrodynamic robustness.

References

[1] International Patent Application, WO 03/035029 A1. Louie-Helm, J. and Berner, B. May 2003.
[2] Ashland Pharmaceutical Technology Report, PTR-037-2, 2006.

Materials

1. Benecel Pharm Hypromellose and Methylcellulose, grades K4M, K15M, K100M, E4M and A4M PH marketed by Ashland Specialty Ingredients, Ashland Inc., Wilmington, DE.
2. Avicel* PH101 microcrystalline cellulose NF, marketed by FMC Corporation, Philadelphia, PA.
3. HyQual* Magnesium Stearate, NF, marketed by Mallinckrodt Corporation, a Division of Tyco International, St. Louis, MO.
4. Theophylline USP, marketed by BASF Corporation, Mount Olive, NJ.
5. Glipizide USP, marketed by RIA International, Whippany, NJ.

Table 3. Benecel HPMC Substitution Type, MW and Hydrodynamic Effects on Drug Dissolution

Hydrophilicity	Benecel HPMC Grade	$T_{60\%}$ (Hrs)				f_2 Value (USP I, 100 RPM as Reference)		
		USP 1 100 RPM	5 DPM	15 DPM	25 DPM	5 DPM	15 DPM	25 DPM
		Theophylline						
High	K100LV PH	5.5	>24	7	3.5	18	44	39
	K4M PH	10	9.5	8	7	84	60	52
	K15M PH	11.5	10	9	7	71	59	50
	K100M PH	14	14	9.5	8.5	83	61	57
	K200M PH	14.5	~10	~10	~10	52	50	49
Medium	E4M PH	8	8	7.5	7	83	70	71
		Glipizide						
High	K100LV PH	~10	8	7	~4	59	61	33
	K4M PH	>24	>24	>24	>24	82	56	44
	K15M PH	>24	>24	>24	>24	74	52	48
	K100M PH	>24	>24	>24	>24	74	60	48
	K200M PH	>24	>24	>24	>24	82	60	33
Medium	E4M PH	>24	>24	>24	>24	45	51	78

*f_2 value in red indicate failure of the dissolution.

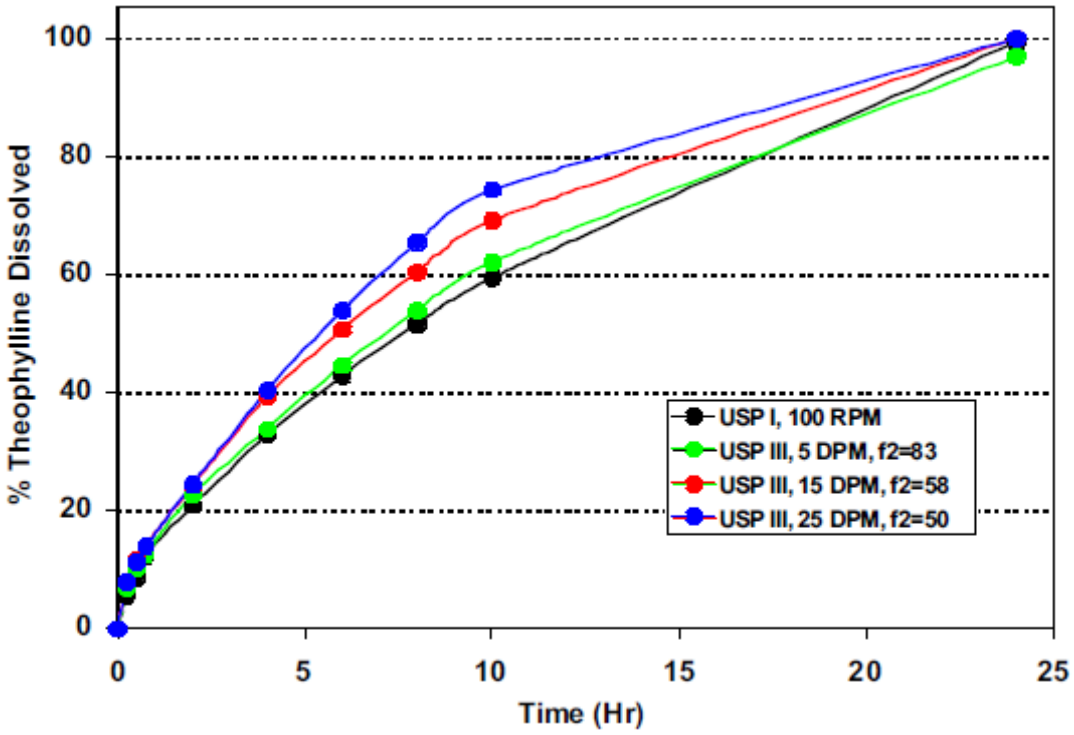

Figure 1
Effect of medium MW Benecel™ K4M PH CR HPMC and hydrodynamic stress on release from soluble theophylline matrix tablets

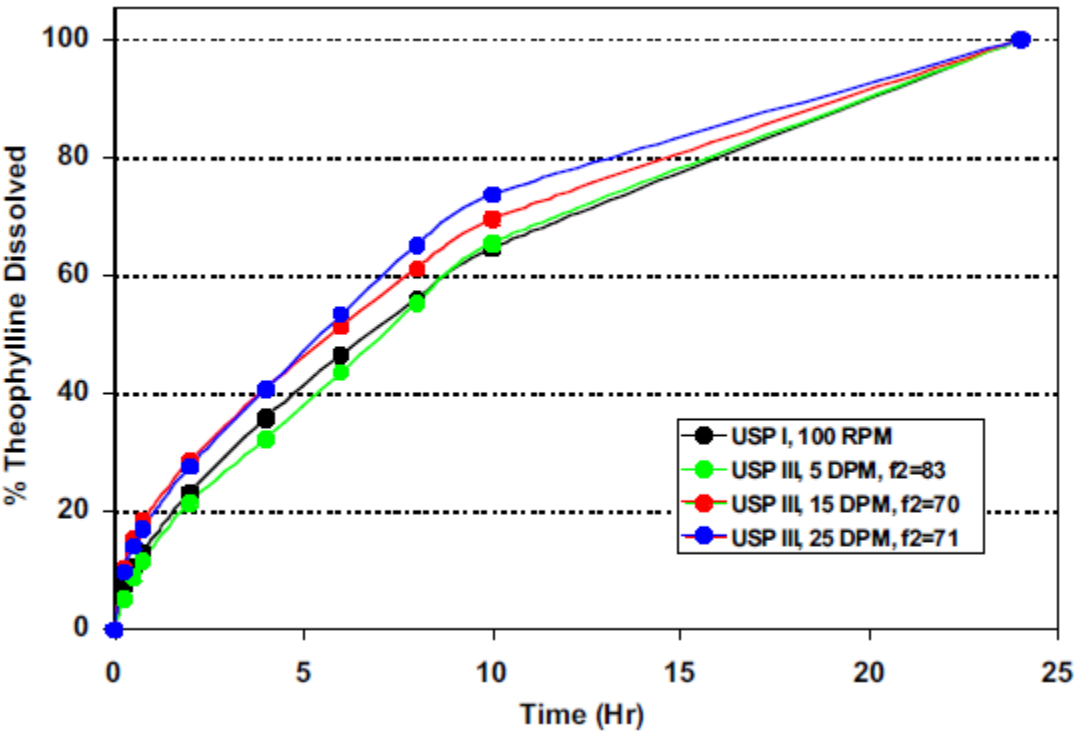

Figure 2
Effect of medium MW Benecel E4M PH CR HPMC and hydrodynamic stress on release from soluble theophylline matrix tablets

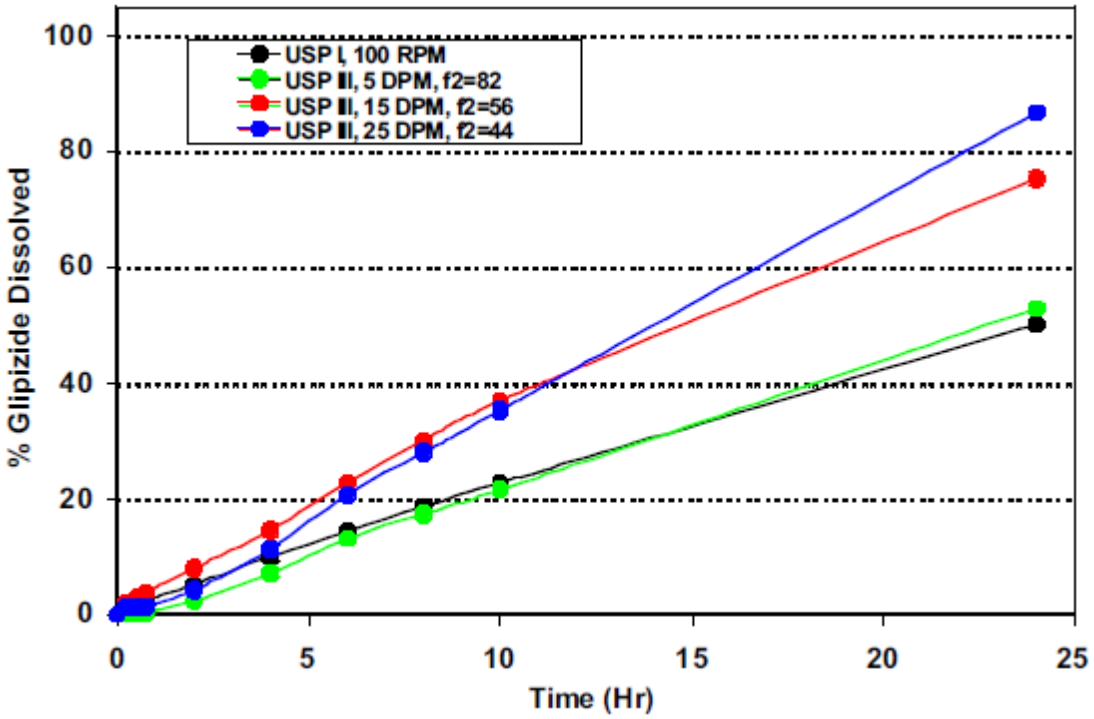

Figure 3
Effect of medium MW Benecel K4M PH CR HPMC and hydrodynamic stress on release from low soluble glipizide matrix tablets

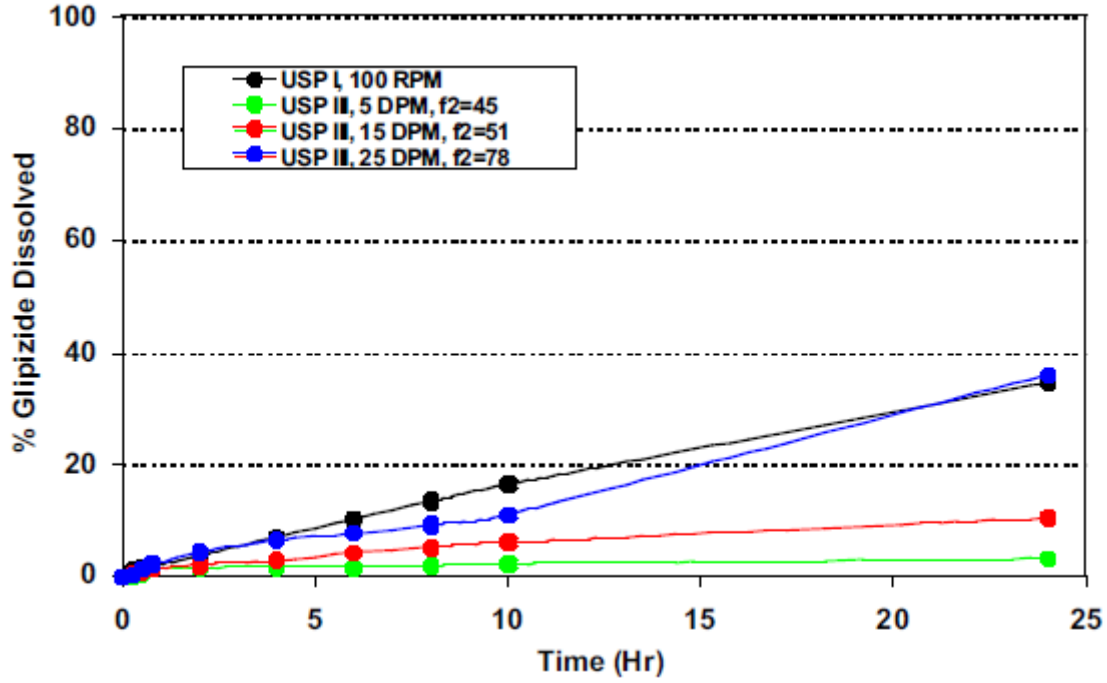

Figure 4
Effect of medium MW Benecel E4M PH CR HPMC and hydrodynamic stress on release from low soluble glipizide matrix tablets

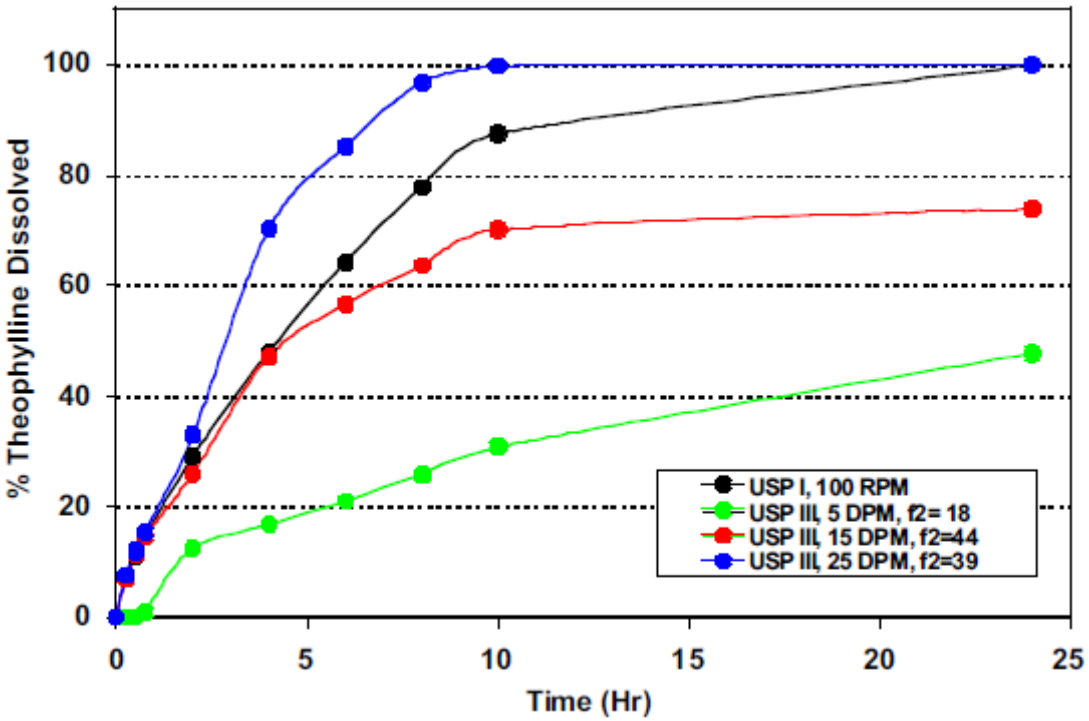

Figure 5
Effect of low MW Benecel K100LV PH CR HPMC and hydrodynamic stress on release from soluble theophylline matrix tablets

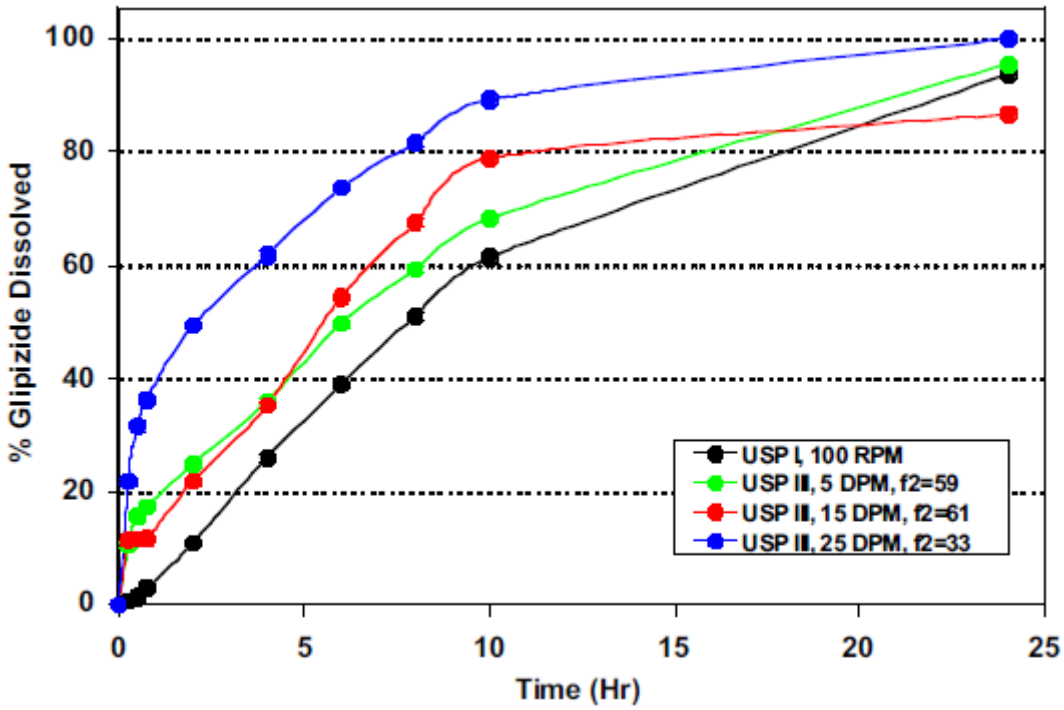

Figure 6
Effect of low MW Benecel K100LV PH CR HPMC and hydrodynamics on release from insoluble glipizide matrix tablets

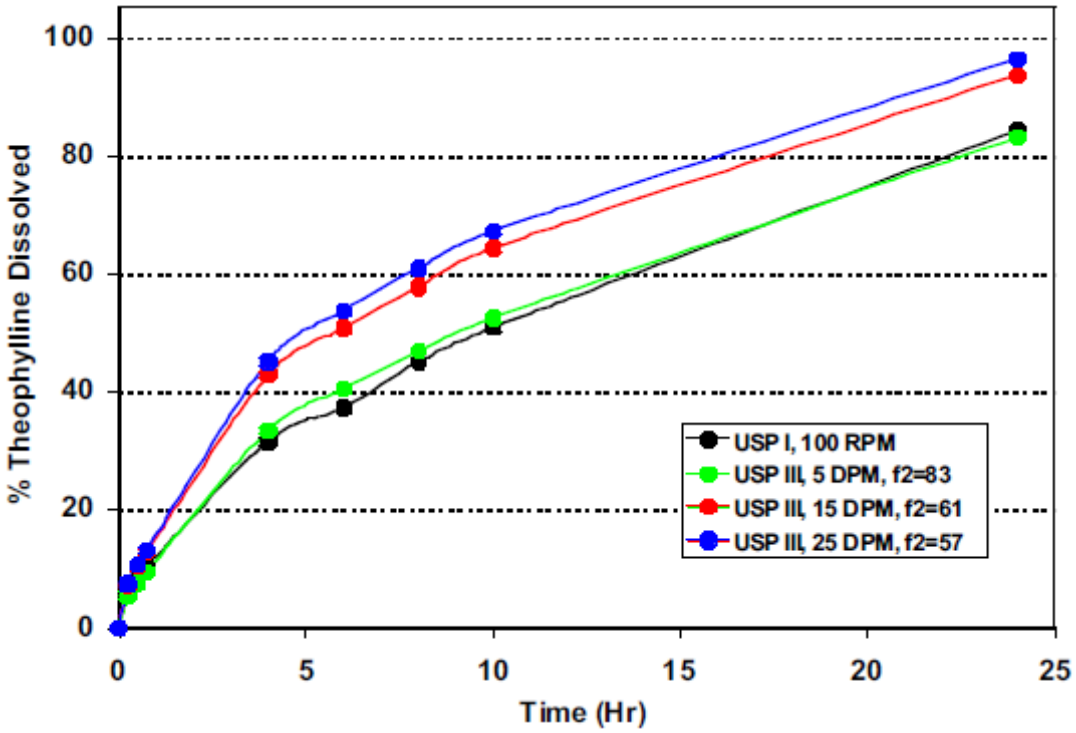

Figure 7
Effect of high MW Benecel™ K100M PH CR HPMC and hydrodynamic stress on release from soluble theophylline matrix tablets

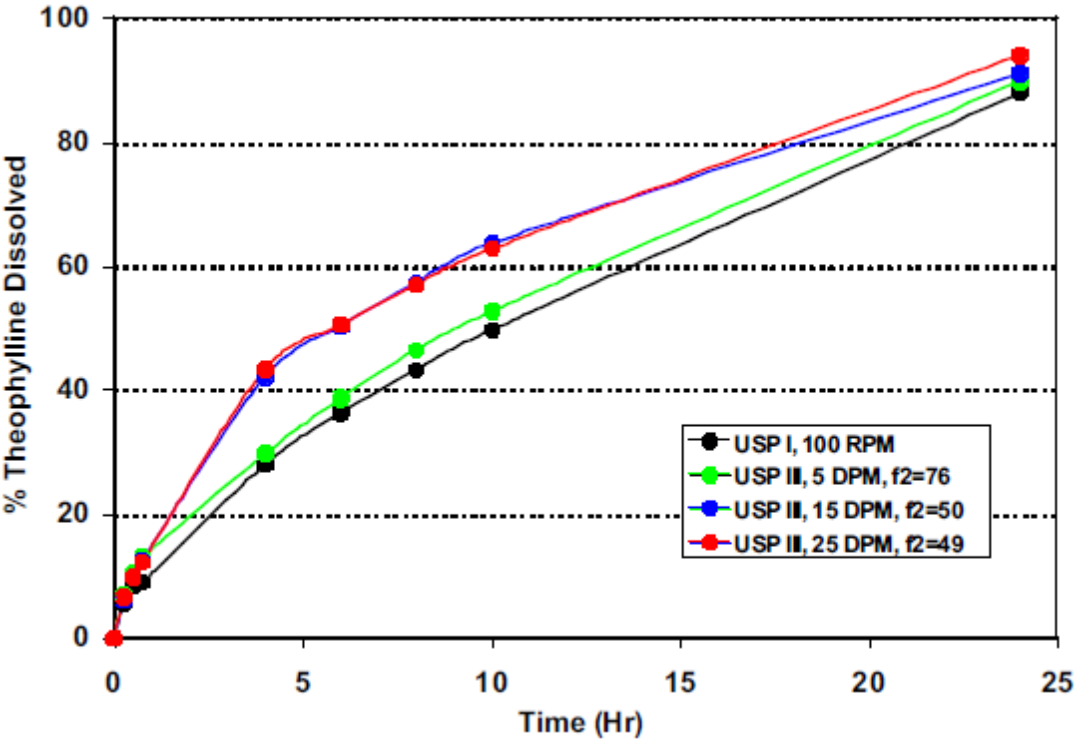

Figure 8
Effect of high MW Benecel K200M PH CR HPMC and hydrodynamic stress on release from soluble theophylline matrix tablets

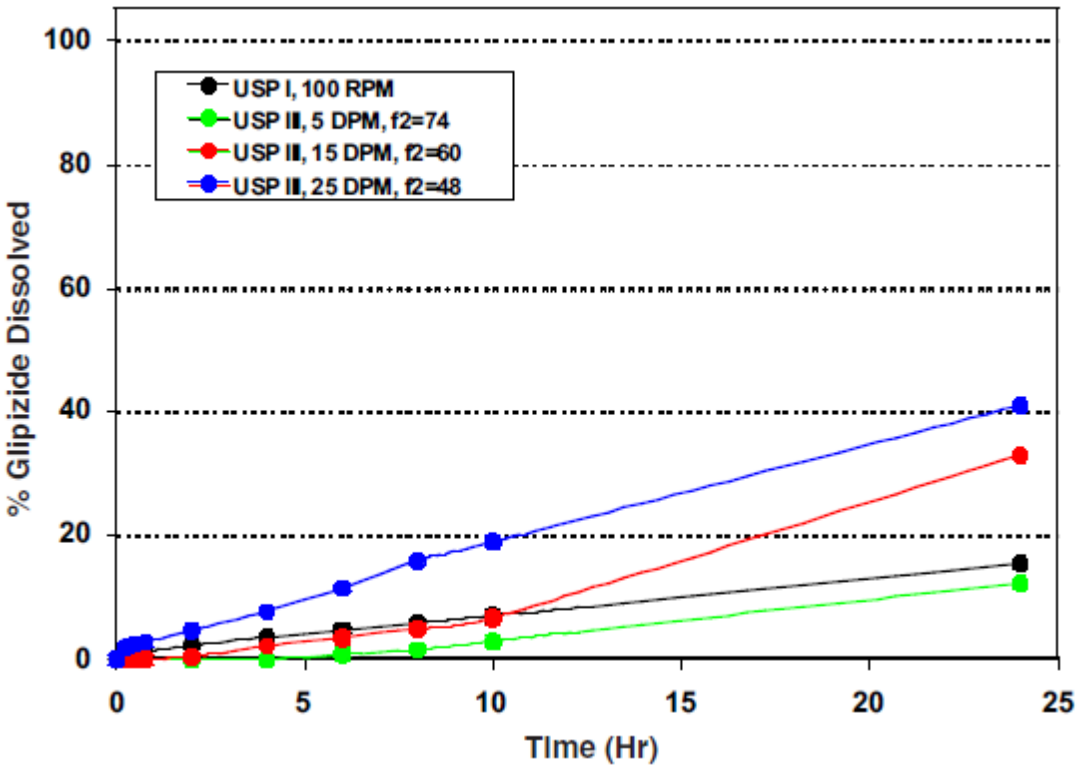

Figure 9
Effect of high MW Benecel™ K100M PH CR HPMC and hydrodynamic stress on release from low soluble glipizide matrix tablets

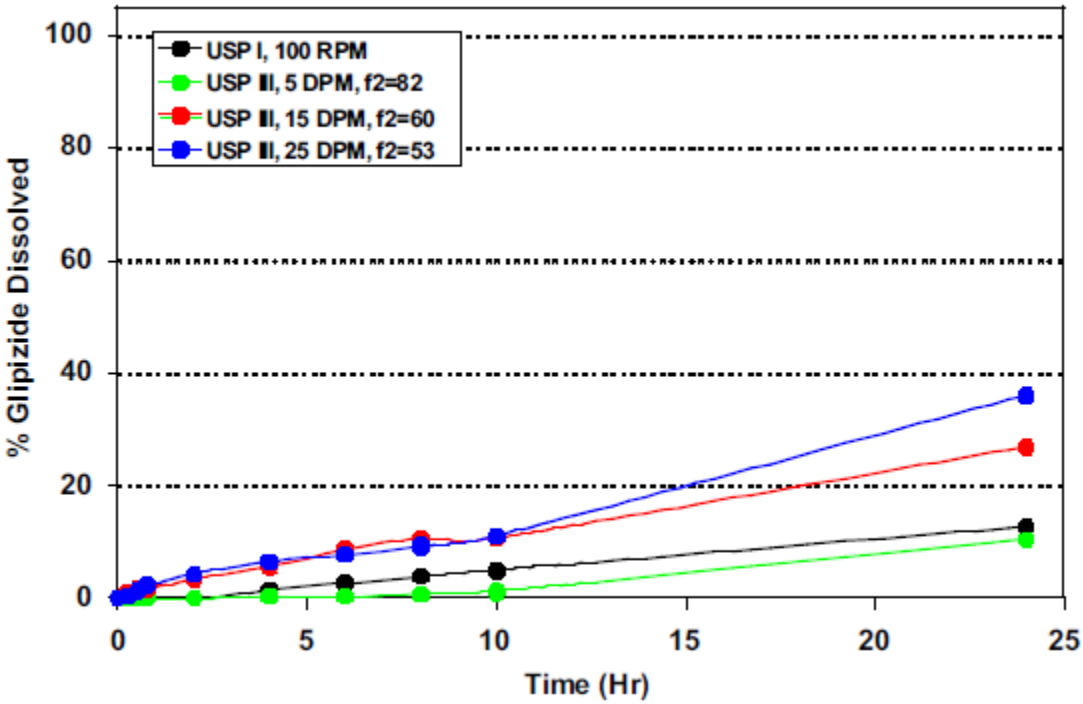

Figure 10
Effect of high MW Benecel K200M PH CR HPMC and hydrodynamic stress on release from low soluble glipizide matrix tablets