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Hydrodynamic Robustness of Hypromellose and Hydroxypropyl Cellulose Based Modified Release Matrix Systems

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Abstract Summary

Factors impacting the "hydrodynamic robustness" of hypromellose and hydroxypropylcellulose matrix systems were investigated using the USP III reciprocating apparatus. Drug release from systems with low (10%) polymer level, low drug solubility or erosion dependent release mechanisms were generally found to vary significantly with change in hydrodynamics.

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]. Hypromellose (HPMC) and hydroxypropyl cellulose (HPC) are widely used hydrophilic matrix polymers, however most published data on systems utilizing these two polymers is based on the conventional USP I or II dissolution apparatus. The current study aims to evaluate hydrodynamic robustness of HPMC and HPC matrix systems, taking polymer level, polymer molecular weight (MW) and drug solubility into account. 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.

Experimental Methods

Table 1 lists the HPMC Type 2208 and HPC grades studied. Each polymer type was studied at two MW levels spanning intermediate (300-370 kDA) to high MW (1000-1300 kDA). Polymer loading was 10 and 30%. The model drugs were soluble theophylline (THEO, solubility 6.9mg/ml in pH 6.8 buffer at 37°C) and low soluble glipizide (GLIP, solubility 1.8 mg/ ml at pH 7.5 with 0.5% polysorbate 80 at 37°C). 400 mg Tablets comprising 25% drug (THEO or GLIP), 30% or 10% polymer (2 polymers at 2 molecular weights each), 0.5% magnesium stearate and q.s. microcrystalline cellulose were prepared by compression on a instrumented rotary tablet press. Hydrodynamic robustness was assessed based on similarity of dissolution profiles under different conditions, lack of erratic release patterns and low variability as measured by maximum standard deviation at individual dissolution time points.

Table 1.
Ashland Pharmaceutical Grade Cellulose Ether Polymers used in this Study.

Grade	Viscosity (mPa·s)	Nominal MW (kDa)
Benecel™ HPMC K4M PH CR	3,600 [(a)]	340
Benecel HPMC K100M PH CR	100,000 [(a)]	1000
Klucel™ HPC GXF	150-400 at 2% [(b)]	370
Klucel HPC HXF	1500-3000 at 1% [(b)]	1150

[(a)] Viscosity measured according to EP Monograph
[(b)] Viscosity measured according to USP Monograph

Results and Discussion

General Observations: Factors which predispose a system toward diffusional release and minimize erosional contributions increase the likelihood of achieving a hydrodynamically robust system. These factors include high drug solubility and high gel strength, which can be achieved through increasing polymer MW and polymer loading. In contrast, lower MW and lower polymer loadings and lower drug solubility increase the erosional contributions to total drug release, leading to greater hydrodynamic sensitivity.

Soluble Drug Dissolution, 30% Polymer Level: For soluble THEO, the USP I basket apparatus dissolution conditions at 100 rpm were generally similar to the USP III reciprocating cylinder apparatus at 5 dpm. Due to superior gel strength, formulations with 30% high MW HPC and HPMC were the most hydrodynamically robust, with no significant dissolution effect even at 25 dpm (Table 2 and Figures 1 and 2). In these systems drug is primarily released via diffusion through the hydrated gel matrix with negligible matrix erosion. High MW HPC had the longest release duration ($t_{60\%}$ 14-15 hours). For high MW HPMC the $t_{60\%}$ values varied form 9-11 hours depending on hydrodynamic conditions. Similarly, THEO formulations comprising 30% medium MW HPC or HPMC were hydro-dynamically robust up to 15 dpm, but release profiles accelerated markedly under extreme shear conditions of 25 dpm (f_2 values <50). Figures 3 and 4 illustrate the dissolution behavior of Medium MW HPC and HPMC systems.

Soluble Drug Dissolution, 10% Polymer Level: At low polymer levels, high MW HPC is not as effective as HPMC with $t_{60\%}$ ranging from 3.5-4 hours as opposed to 5-6 hours for HPMC (Table 2 and Figures 1 and 2. At the 10% polymer level the variability of individual tablets increases markedly as hydrodynamic stress increases (Table 3). Low polymer loadings were also problematic for THEO formulations comprising intermediate MW polymer grades. Medium MW HPC was ineffective ($t_{60\%}$ <1.5 hours under all dissolution conditions). For medium MW HPMC release times were longer, but extreme hydrodynamic sensitivity even at the lowest reciprocating cylinder frequency of 5 dpm was seen. (Table 3 and Figures 3 and 4). Based on these findings, 10% polymer levels should generally be avoided for soluble drugs.

Insoluble Drug Dissolution, 30% level: With the exception of high MW HPC and HPMC at 30%, insoluble GLIP formulations were not as hydrodynamically robust as THEO formulations. However high MW HPMC and HPC at 30% are of limited use due to the physiologically unrealistically long dissolution times ($t_{60\%}$>>24 hours, Table 2). This can be attributed to the fact that erosion is required for GLIP release as diffusion alone is limited by low drug solubility. Medium MW HPC profiles were linear and had low variability under a specific hydrodynamic condition (Figure 5). This was not the case for medium MW HPMC which was more variable and erratic (Figure 6 and Table 3).

Insoluble Drug Dissolution, 10% level: High MW HPC GLIP tablets were extremely sensitive to hydrodynamic changes even when switching from USP Apparatus I to USP Apparatus III at 5 dpm. (f_2 = 39). 10% High MW HPMC was robust at 5 dpm, but release and variability in individual tablets markedly increased at 15 and 25 dpm. Medium MW HPC was ineffective at 10% polymer levels with t_{60}% ranging from 0.25 to 1 hour (Tables 2 and 3 and Figures 5 and 6).

Conclusion

Our study shows that low (10%) polymer levels were generally problematic for both soluble and insoluble drugs, resulting variably in insufficient release retardation, high variability or poor hydrodynamic robustness. At 30% polymer levels, hydrodynamically robust matrix tablets can be achieved for soluble drugs. However it was not possible to achieve hydrodynamic robustness beyond 5 dpm for low soluble, erosion dependent drug matrix systems, while simultaneously achieving release durations less than 24 hours.

It is important to select dissolution conditions that provide physiologically relevant levels of shear, especially with respect to fed state conditions. The USP apparatus III set at 15 dpm appears highly suitable for this purpose.

References

[1]International Patent Application, WO 03/035029 A1. Louie-Helm, J. and Berner, B. May 2003.

Table 2.
Matrix Polymer, Polymer level and Hydrodynamic Effects on Drug Dissolution

MW	Polymer Type, Level	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	HPMC, 30%	13	10	11	9	63	66	53
	HPMC, 10%	4	6	6	5	62	66	74
	HPC, 30%	19	15.5	15.5	14	77	71	59
	HPC, 10%	4	3.5	4	3.5	87	74	80
Medium	HPMC, 30%	10	9	7.5	6	72	54	42
	HPMC, 10%	3	6	6	3.5	42	41	71
	HPC, 30%	8	8	8	6	83	81	40
	HPC, 10%	1.5	1	0.50	0.50	59	41	38
		Glipizide						
High	HPMC, 30%	>24	>24	>24	>24	66	86	56
	HPMC, 10%	24	19	12	9	60	34	32
	HPC, 30%	>24	>24	>24	>24	67	78	79
	HPC, 10%	>24	15.5	9	9	40	26	26
Medium	HPMC, 30%	>24	>24	16	17	79	43	41
	HPMC, 10%	19	18.5	14	9	85	60	40
	HPC, 30%	17.5	14.5	10	9	65	40	34
	HPC, 10%	0.75	0.8	<0.25	<0.25	42	22	27

*f_2 value in red indicate failure of the dissolution.

Table 3.
Matrix Polymer, Polymer Level and Hydrodynamic Effects on Variability of Individual Time Points

MW	Polymer Type, Level	USP 1 100 RPM	Maximum Standard Deviation 5 DPM	15 DPM	25 DPM
			Theophylline		
High	HPMC 30%	0.24	1.47	0.82	0.70
	HPMC 10%	4.12	1.35	4.12	6.48
	HPC 30%	1.44	1.38	0.57	0.39
	HPC 10%	0.5	1.71	5.23	3.21
Medium	HPMC 30%	1.86	1.10	3.17	2.31
	HPMC 10%	7.15	2.82	1.59	4.20
	HPC 30%	1.19	1.45	3.17	0.92
	HPC 10%	3.63	2.46	6.04	1.73
			Glipizide		
High	HPMC 30%	3	0.93	2.66	3.03
	HPMC 10%	2.95	4.00	1.63	4.25
	HPC 30%	0.5	0.27	1.44	1.39
	HPC 10%	1.0	2.26	4.34	2.78
Medium	HPMC 30%	1.7	1.90	0.86	6.94
	HPMC 10%	3.47	3.60	3.70	5.65
	HPC 30%	4.76	7.81	0.84	2.90
	HPC 10%	3.47	2.13	0.51	0.5

*S.D values in red indicate high standard deviation

Figure 1.
Effect of high MW HPC levels and hydrodynamics on release from soluble theophylline matrix tablets.

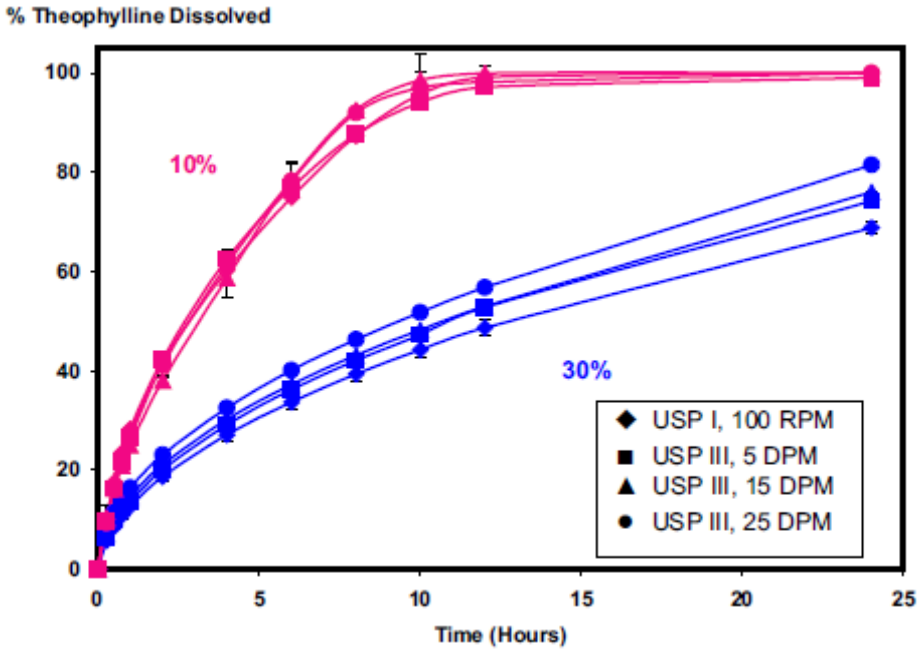

Figure 2.
Effect of high MW HPMC Type 2208 levels and hydrodynamics on release from soluble theophylline matrix tablets.

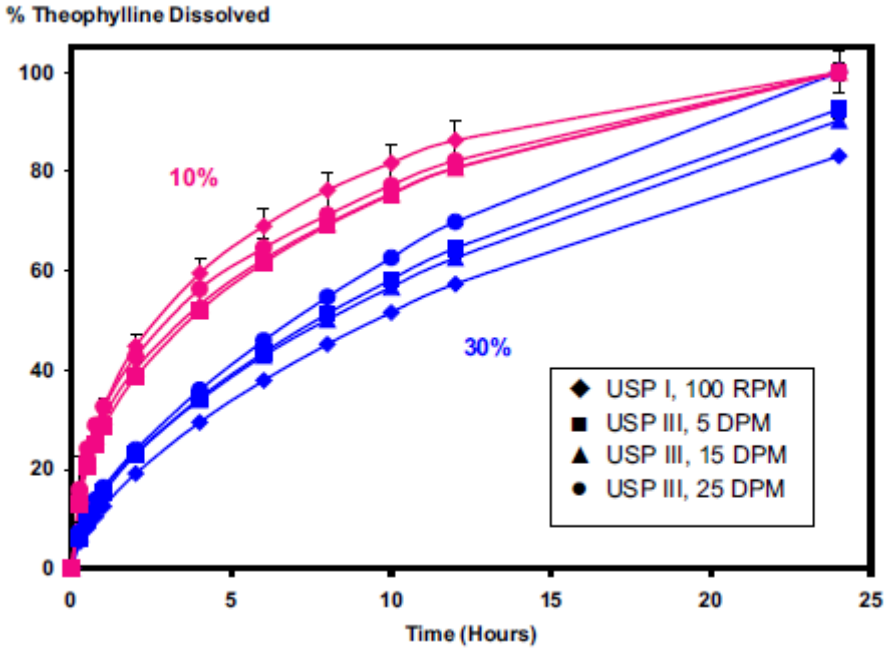

Figure 3.
Effect of medium MW HPC levels and hydrodynamics on release from soluble theophylline matrix tablets.

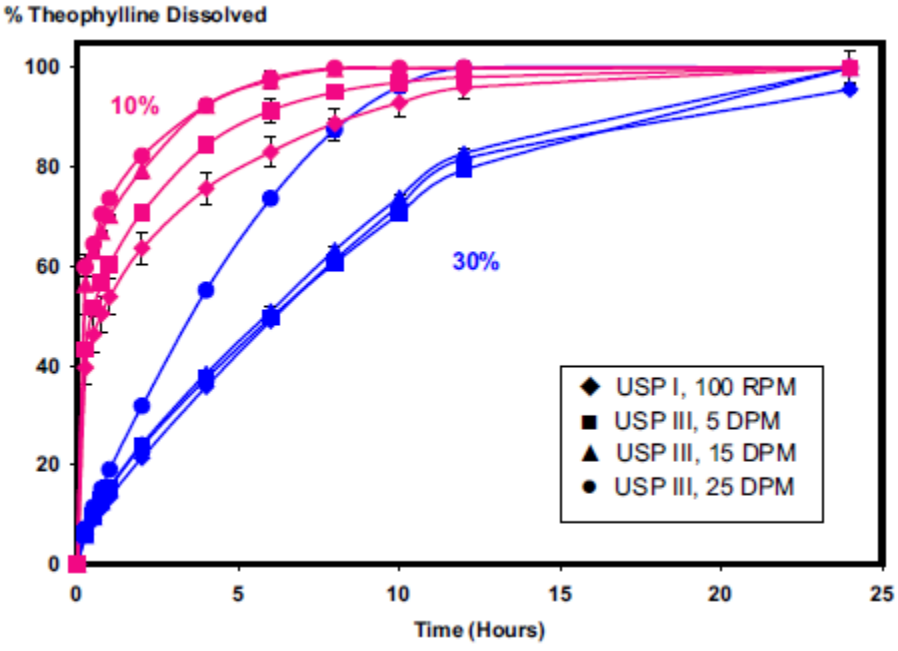

Figure 4.
Effect of medium MW HPMC levels and hydrodynamics on release from soluble theophylline matrix tablets.

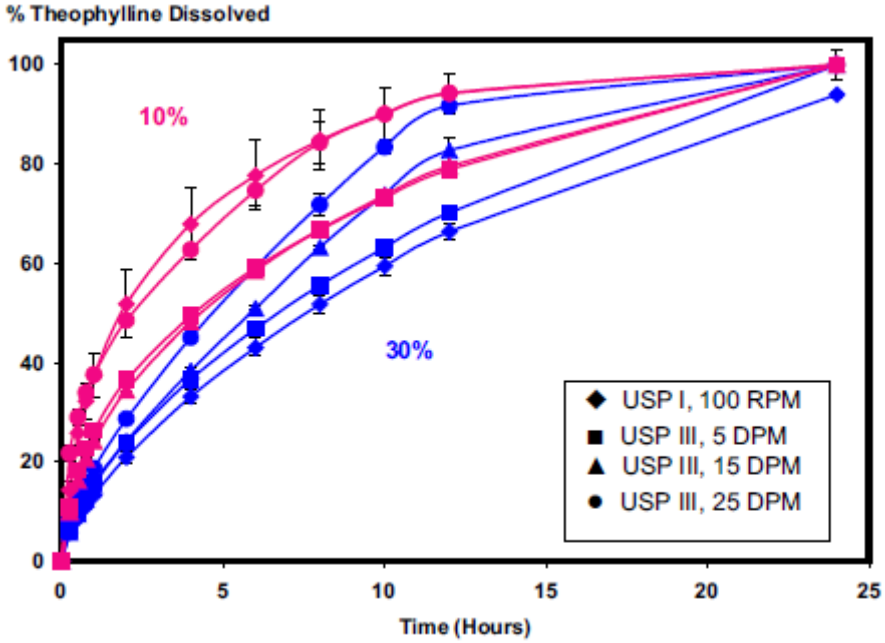

Figure 5.
Effect of medium MW HPC levels and hydrodynamics on release from insoluble glipizide matrix tablets.

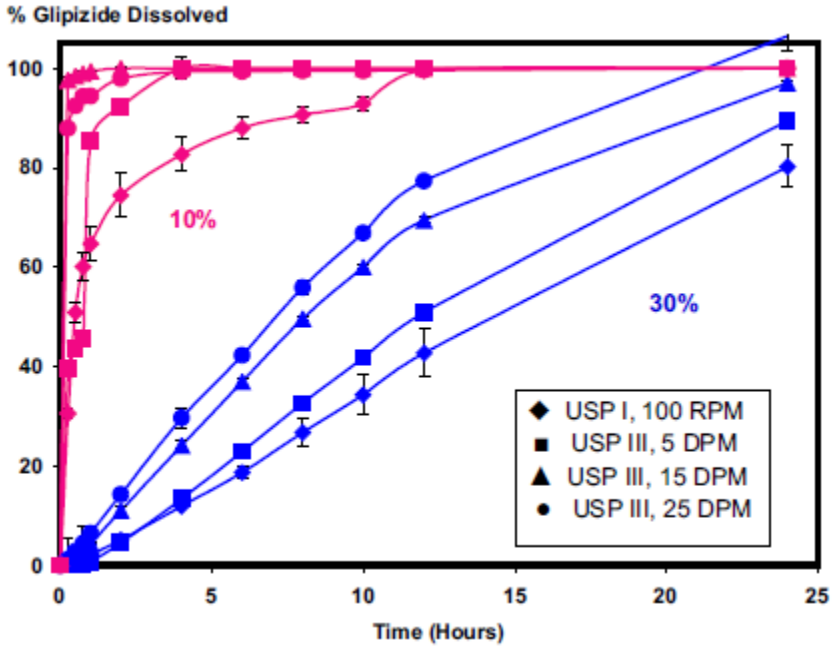

Figure 6.
Effect of medium MW HPMC levels and hydrodynamics on release from insoluble glipizide matrix tablets.