Consideration of Critical Material Attributes in Hypromellose Based Hydrophilic Matrices Comprising Drugs of Various Solubility

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Abstract Summary

Two case studies were conducted to evaluate the material attributes of hypromellose (METHOCEL™ K4M premium cellulose ethers) and Starch 1500® partially pregelatinized maize starch on the performance of extended release (ER) matrices. Variations in the properties of hypromellose K4M had minimal effect on theophylline release profiles, but changes in hydroxypropyl substitution levels (% HP) and particle size of the polymer impacted the drug release from hydrochlorothiazide (HCTZ) matrix tablets. Variations in Starch 1500 properties had no significant effect on drug release regardless of drug solubility. In both case studies, coarse Starch 1500 particles resulted in slightly lower tablet strength.

Introduction

Hypromellose is the most commonly used polymer in ER hydrophilic matrix formulations. The effect of hypromellose (METHOCEL K15M PRCR, K100LV PR CR) on the performance of hydrophilic matrix tablets was previously investigated and the critical material attributes (CMA) of METHOCEL were discussed.[1-3] Use of Starch 1500 in hypromellose matrices has been shown to enhance the robustness of drug release from hydrophilic ER tablets.[2,4] The objective of this study was to examine the influence of material attributes on the characteristics of hydrophilic ER matrices comprising METHOCEL K4M and Starch 1500 as the matrix former. Two case studies were conducted using theophylline (water solubility 8.3 mg/mL) or HCTZ (water solubility ~0.7 mg/mL) as model drugs.

Experimental Methods

Quality by Design (QbD) samples of METHOCEL K4M Premium CR were used, the properties are shown in **Table 1**. **Table 2** shows the properties of Starch 1500 samples used in this study. Using these six samples of hypromellose and four Starch 1500 samples, twenty four formulations were prepared, for each model drug. The compositions of both formulations are shown in **Table 3**. Tablets were manufactured at compression forces of 5-20 kN (70-280 MPa) on an instrumented 10-station rotary tablet press (Piccola, RIVA, Argentina) at 30 rpm using standard round 9.5 mm concave tooling. The target drug dose and tablet weight was 100 mg and 330 mg, respectively.

Compressed tablets were examined for physical properties and drug release. Drug dissolution was conducted using USP apparatus II with sinkers at 100 rpm in 1000 mL of DI water for theophylline and 900 mL of pH 6.8 phosphate buffer for HCTZ. The drug release was measured using a UV-Visible spectrophotometer (Agilent Technologies, USA). The similarity factor (f_2) was calculated by comparing two dissolution profiles. The three-point dissolution performance (percent drug dissolved at 2, 6 and 10 hr) was calculated and analyzed using Minitab 16.

Table 1. Properties of METHOCEL™ K4M Premium CR QbD Samples

Hypromellose sample	2% Viscosity (mPa.s)[a]	%through 230 mesh[b]	%HP[c]
High viscosity (HV)	4938	51.0	8.6
Lower viscosity (LV)	3233	54.9	8.4
High % through 230 mesh (HPS)	3300	60.1	8.8
Low % through 230 mesh (LPS)	3528	36.9	8.5
High % HP (HHP)	3410	50.3	10.2
Low % HP (LHP)	3710	55.8	8.0

a Specification range (2% viscosity): 2663 – 4970 mPa.s
b Specification range (% through 230 mesh): 50.0 – 80.0%
c Specification range (% HP): 7.5 - 9.5%

Table 2. Properties of Starch 1500 Samples

Starch 1500 sample (CWS-% through 270 mesh)	CWS[d] (%)	%thru 270 mesh[e]
High -High	14.4	70
High-Low	15.2	30
Low-High	11.2	70
Low-Low	10.2	30

Table 3. Compositions of Matrix Formulations

Ingredients	Quality (% w/w)	
	F1 (Theophylline)	F2 (HCTZ)
Model drug	30.0	30.0
METHOCEL K4M PR CR	20.0	20.0
Starch 1500	20.0	20.0
MCC (Emcocel 90M)	29.0	-
Fast Flo lactose	-	29.0
Silica (Cab-O-Sil M-5P)	0.5	0.5
Magnesium stearate	0.5	0.5
Total	**100**	**100**

Results and Discussion

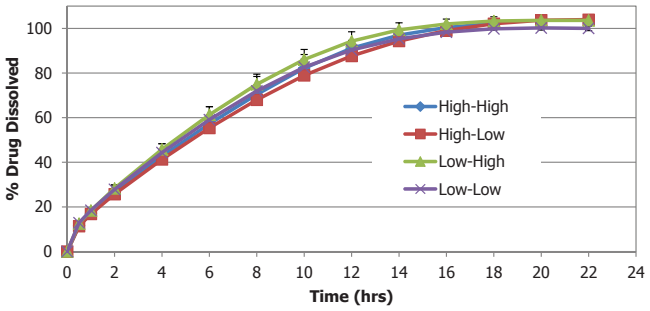
All matrix tablets had excellent mechanical properties with zero friability and tensile strength in the range of 2.5-4.0 MPa (18-23 kp hardness) for theophylline matrices and 1.5-2.1 MPa (8-12 kp hardness) for HCTZ matrices at a compression pressure of 210 MPa (compression force of 15 kN). However, tablets containing coarse Starch 1500 particles showed slightly lower strength.

Case Study 1: Theophylline Matrix Tablets

Figures 1(A & B) show drug release profiles for the theophylline tablets. The drug was released mainly by diffusion (release exponent: 0.5-0.6). **Figure 1(A)** shows that variations in CWS and particle size of Starch 1500 had minimal impact on drug release (f_2 = 81-90). Both **Figure 1(B)** and **Figure 2** indicated that a trend of relatively slower release was found from tablets containing METHOCEL K4M PR CR of low % HP substitution (f_2 = 55). Further statistical analysis indicated HPMC or Starch 1500 had no substantial impact on theophylline release from matrix tablets ($p > 0.1$).

Figure 1. Drug Release Profiles of Theophylline Matrices

(A) Study of Starch 1500 Properties (n = 6)



(B) Study of Hypromellose K4M Properties

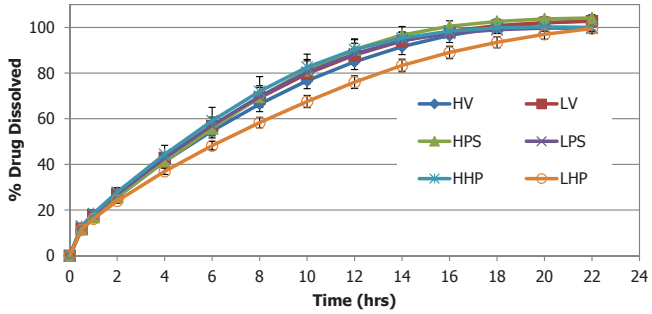
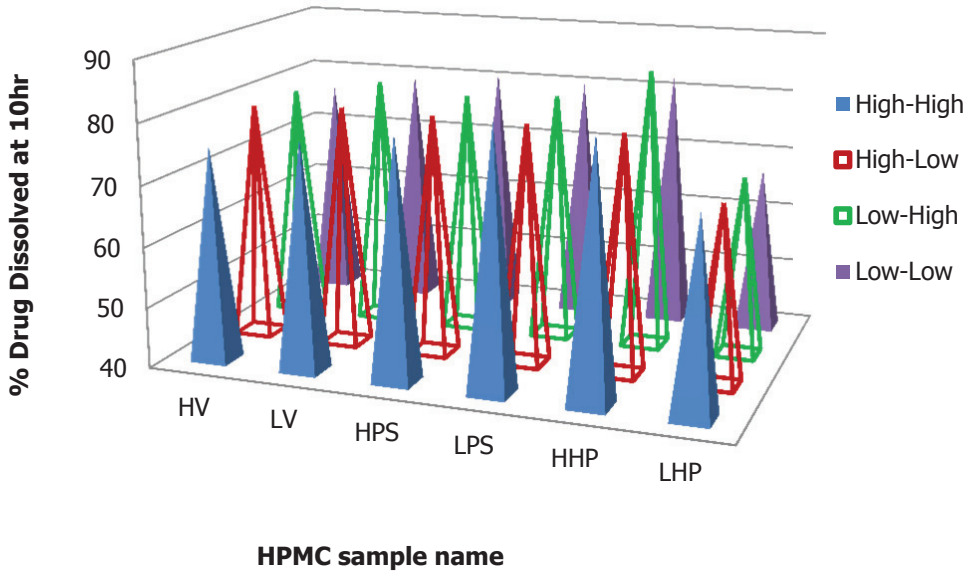


Figure 2. Dissolution Data (% Dissolved at 10hr) of Theophylline Tablets

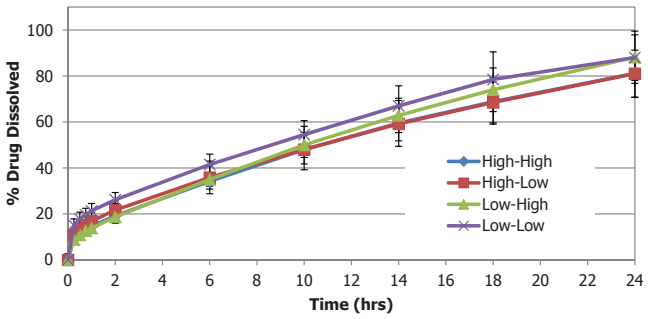


Case Study 2: HCTZ Matrix Tablets

The near zero order drug release profiles of HCTZ matrices are shown in **Figure 3(A)**, indicating that Starch 1500 property had no significant effect on drug release (f_2 = 73-86). **Figure 3(B)** showed that an initial burst release was observed in tablets with coarse hypromellose particles (K4M LPS) and faster release was found from tablets with high %HP level hypromellose (K4M HHP). Both **Figures 3(B)** and **4** show the physicochemical property of METHOCEL K4M PR CR impacted drug release from HCTZ matrices (f_2 = 44-86). Statistical analysis indicates % HP and particle size of HPMC K4M had significant influence on HCTZ dissolution ($p < 0.1$).

Figure 3. Drug Release Profiles of HCTZ Matrices

(A) Study of Starch 1500 Properties (n = 6)



(B) Study of Hypromellose K4M Properties

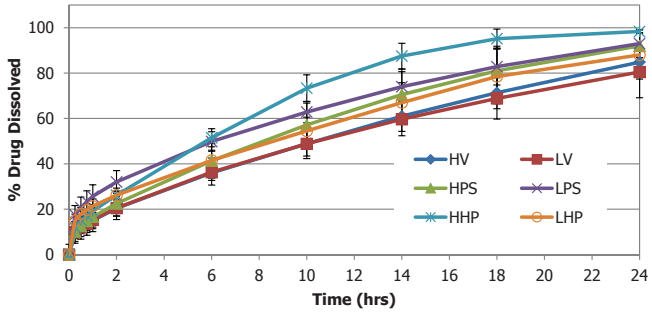
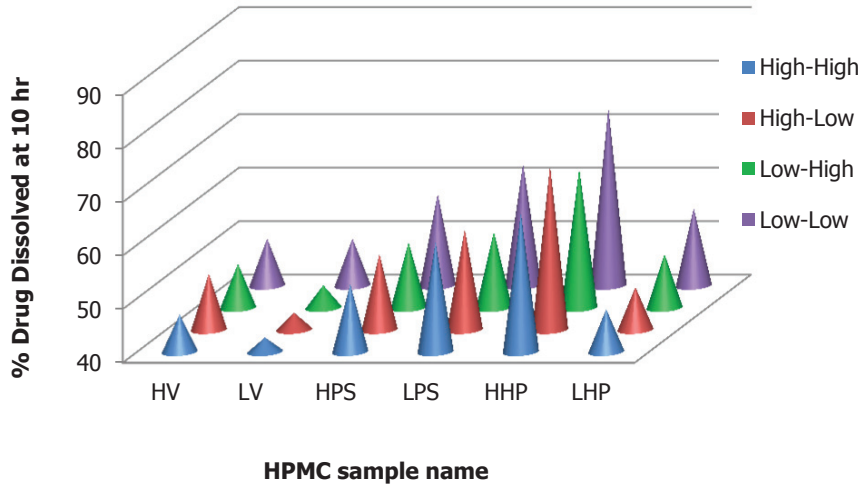


Figure 4. Dissolution Data (% Dissolved at 10hr) of HCTZ Tablets



Conclusions

The CMA of METHOCEL (viscosity, particle size and % HP content) and their impact on hydrophilic matrix tablets were dependent on drug solubility. Results suggest % HP substitution and particle size of hypromellose are the critical material attributes for HCTZ formulations, but may be considered as non-critical for theophylline formulations. Variations in Starch 1500 properties had no significant effect on drug release from either matrix formulation.

References

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2. Deng H, et al. 38th CRS Annual Meeting and Exposition, 2011
3. Deng H., et al. AAPS Annual Meeting & exposition, 2012
4. Levina M, Rajabi-Siahboomi A.R., *J. Pharm. Sci.* 2004. 93(11): 2746-2754