

Use of Starch 1500® to Minimize Variability on Drug Release from Hypromellose Matrices

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Abstract Summary

In the present study, Starch 1500® partially pregelatinized maize starch or lactose was used as filler in extended release (ER) hydrophilic matrix formulations. Hypromellose (METHOCEL™ K100LV Premium CR) was used as the rate-controlling polymer, and hydrochlorothiazide a drug with low solubility was used as the model drug. The hypromellose samples studied were prepared by a sample engineering approach and consisted of polymer viscosity that was kept at near low USP specification (~ 80 MPa.s), while particle size or % hydroxypropoxyl substitution (%HP) was maintained at "high", "medium" or "low" level of the normal production range. Study results showed that the choice of filler had no significant impact on physical properties of powder blends and tablets regardless of the variation in hypromellose properties (%HP and particle size). The use of Starch 1500® as filler provided significantly more robust ER matrices indicated by similar release profiles despite variations in hypromellose properties. By comparison, matrices containing lactose as filler demonstrated dissimilar release profiles as hypromellose properties varied.

Introduction

It has been reported that hypromellose (METHOCEL™ K15M Premium CR) parameters had no significant effect on properties of matrix tablets and drug release performance from ER matrices containing a slightly soluble to very soluble drug, when 30% w/w polymer level was used in formulations.¹⁻³ The objective of this study was to examine the effect of filler choice in hypromellose matrices comprising METHOCEL™ K100LV (30% w/w) and a low water soluble drug, hydrochlorothiazide (0.7-1.0 mg/mL). In addition, the effect of variation in hypromellose properties on tablet characteristics and drug release profiles was also evaluated.

Experimental Methods

Materials

Hypromellose (METHOCEL™ K100LV Premium CR) batches used in this study had polymer viscosity at low USP specification, while particle size or %HP substitution approximated minimal, nominal or maximum normal production values (**Table 1**). METHOCEL™ K100LV samples (with respect to viscosity, % HP, particle size) were prepared by sample engineering approach. Using these 5 batches of hypromellose, a total of 10 ER formulations (five each for Starch 1500® and lactose as filler) were prepared. The hypromellose batches used in this study were referred to by the "batch name" listed in **Table 1**.

Formulations and Tablet Preparation

The composition of hydrochlorothiazide formulations is shown in **Table 2**. Drug, hypromellose, filler (lactose or Starch 1500®) and silica were passed through an ASTM #30 mesh (600 µm), and then mixed in a 4-quart V blender (Patterson-Kelley Co., USA). Magnesium stearate was added to the powder mixture and blended for additional 3 minutes. The final powder mixtures were compressed at 5-20 kN (70-280 MPa) using an instrumented 10-station rotary tablet press (Piccola, RIVA, Argentina) at 20 rpm using standard round 9.5 mm concave tooling and tablet weight of 400 mg.

Table 1. Physicochemical Properties of engineered METHOCEL™ K100LV Premium CR Samples

Hypromellose Batch Name (Low Viscosity)		2% Viscosity (mPa·s)	% thru 230 mesh	% HP	% MeO
Medium %HP	Low % thru 230 mesh	82.7	50.0	8.9	22.6
	Medium % thru 230 mesh	78.9	60.0	8.9	22.6
	High % thru 230 mesh	80.4	70.0	8.9	22.6
Medium % thru 230 mesh	Low %HP	80.6	60.0	7.9	22.7
	High %HP	80.3	60.0	10.2	22.2

Table 2. Composition of Hydrochlorothiazide Formulations

Ingredients	% Composition (w/w)	
	F1	F2
Hydrochlorothiazide (HCTZ) (Hubei Maxpharm, China)	50.0	50.0
METHOCEL™ K100LV Premium CR (The Dow Chemical Company, USA)	30.0	30.0
FastFlo lactose (Foremost, USA)	19.0	-
Starch 1500® (Colorcon Inc., USA)	-	19.0
Cab-O-Sil M-5P (Cabot Co., USA)	0.5	0.5
Magnesium stearate (Peter Greven, Germany)	0.5	0.5
Total	100.0	100.0

Powder and Tablet Characterization

The formulated powder blends were analyzed for bulk and tapped densities using a VanKel density tester (Varian Inc., USA), powder flow using a vibratory funnel-type powder flow tester (SOTAX, USA) and loss on drying (LOD) (Model: IR-200, Denver Instrument, USA). All tablets were examined for physical properties including weight variation, thickness, hardness (Multicheck, Erweka, Germany), and friability (VanKel Industries, USA). Drug release was measured at a wavelength of 272 nm using USP Apparatus II with sinkers (VK 7000, Varian, USA) at 100 rpm and 900mL of pH 6.8 phosphate buffer at 37±0.5°C. The similarity factor (f_2) was calculated by comparing the release profile when two out of three selected physicochemical properties of hypromellose were varied.

Results and Discussion

Physical Properties of Powder Blends and Matrices

The physical properties of hydrochlorothiazide powder blends and compressed tablets are shown in **Tables 3 & 4**. Study results indicated that comparable physical properties were obtained for all powder blends and compressed tablets. The matrix tablet hardness and tensile strength increased with increasing compression force. At compression force of 15 kN, all tablets exhibited excellent mechanical strength regardless of filler choice. All matrices had low tablet weight variation (0.4-0.8 %), low friability values ($\leq 0.5\%$) and good content uniformity (98.7-101.6%).

Table 3. Physical Properties of Formulated Hydrochlorothiazide Blends

Hypromellose Batch (Low Viscosity)		Filler	Density (g/mL)		Carr's Index (%)	Sotax Flow (g/sec)	LOD (%)
			Bulk	Tapped			
Medium %HP	Low % thru 230 mesh	Lactose	0.49	0.70	29	6.5	1.5
		Starch 1500®	0.52	0.75	30	5.8	3.1
	Medium % thru 230 mesh	Lactose	0.51	0.72	29	6.4	1.5
		Starch 1500®	0.52	0.75	30	5.5	2.9
	High % thru 230 mesh	Lactose	0.51	0.73	30	6.1	1.6
		Starch 1500®	0.54	0.78	31	5.3	2.9
Medium % thru 230 mesh	Low %HP	Lactose	0.50	0.70	28	6.2	1.3
		Starch 1500®	0.54	0.74	27	5.3	2.8
	High %HP	Lactose	0.49	0.70	29	6.3	1.4
		Starch 1500®	0.52	0.73	29	5.1	2.6

Table 4. Physical Properties of Hydrochlorothiazide Matrix Tablets Formulated at Compression Force of 15 kN (210 MPa compaction pressure) (n = 20)

Hypromellose Batch (Low Viscosity)		Filler	Hardness (kp)	Tensile Strength (MPa)	Thickness (mm)	Friability (%)
Medium %HP	Low % thru 230 mesh	Lactose	16.8 ± 0.7	3.4 ± 0.1	5.0 ± 0.0	0.0
		Starch 1500®	13.3 ± 0.5	2.6 ± 0.1	5.2 ± 0.0	0.0
	Medium % thru 230 mesh	Lactose	18.7 ± 0.9	3.8 ± 0.2	5.0 ± 0.0	0.3
		Starch 1500®	12.4 ± 0.5	2.3 ± 0.1	5.2 ± 0.0	0.0
	High % thru 230 mesh	Lactose	18.1 ± 1.0	3.7 ± 0.2	5.1 ± 0.0	0.2
		Starch 1500®	11.2 ± 2.7	2.2 ± 0.5	5.2 ± 0.1	0.5
Medium % thru 230 mesh	Low %HP	Lactose	17.3 ± 0.8	3.5 ± 0.2	5.1 ± 0.0	0.0
		Starch 1500®	13.4 ± 0.6	2.6 ± 0.1	5.2 ± 0.0	0.0
	High %HP	Lactose	18.2 ± 1.0	3.7 ± 0.2	5.1 ± 0.0	0.0
		Starch 1500®	15.0 ± 1.2	3.0 ± 0.2	5.1 ± 0.0	0.3

Drug Release Profiles

The drug release profiles of hydrochlorothiazide matrix tablets are shown in **Figures 1 & 2**. For formulations containing lactose as filler (F1), both %HP substitution and particle size of hypromellose significantly influenced drug release profiles from low viscosity hypromellose tablets {**Figures 1(A) & 2(A)**}, as indicated by the similarity value $f_2 < 50$, as shown in **Table 5**. In comparison, for formulations containing Starch 1500® as filler, similar drug release profiles were obtained for low viscosity hypromellose tablets regardless of variations in hypromellose properties {**Figures 1(B) & 2(B)**}, indicated by the similarity value $f_2 > 50$, as shown in Table 5. Therefore, use of Starch 1500® in hypromellose formulations greatly overcame the particle size effect on drug release profiles {**Figures 1(A) & 1(B)**}, while measurable enhancement was obtained for effect of %HP on drug release profiles {**Figures 2(A) & 2(B)**}.

Figure 1. Hydrochlorothiazide Release Profiles: Effect of Particle Size: (A) F1, lactose as a filler; (B) F2, Starch 1500® as a filler (n = 6) (Drug Dissolution Using USP Apparatus II with Sinkers, at 100 rpm and 900 mL of pH 6.8 Phosphate Buffer at 37 ± 0.5°C)

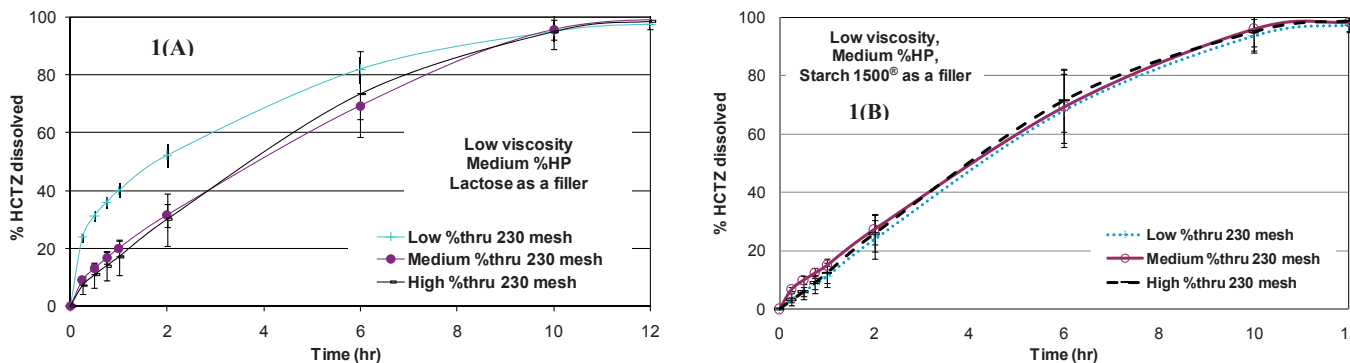


Figure 2. Hydrochlorothiazide Release Profiles: Effect of % HP substitution: (A) F1, lactose as a filler; (B) F2, Starch 1500® as a filler (n = 6) (Drug Dissolution Using USP Apparatus II with Sinkers, at 100 rpm and 900 mL of pH 6.8 Phosphate Buffer at 37± 0.5°C)

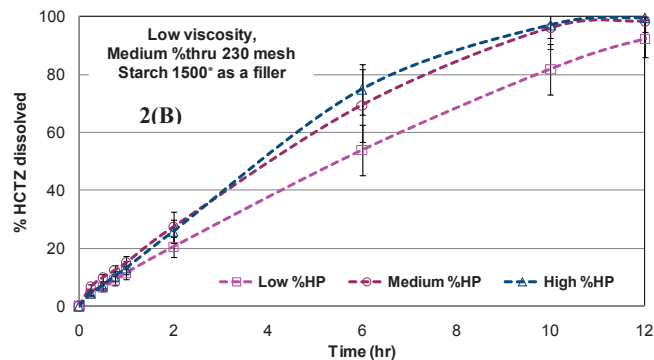
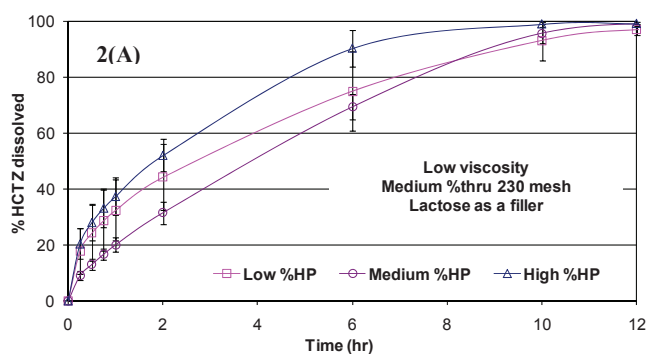


Table 5. Similarity (f_2) of Dissolution Profiles

f_2 calculation	Particle size		% HP	
	Lactose	Starch 1500®	Lactose	Starch 1500®
High vs. Low	40	81	59	55
High vs. Medium	59	87	42	87
Low vs. Medium	42	77	53	59

Conclusions

Study results indicated that use of Starch 1500® as filler in hypromellose formulations could minimize differences in drug release profiles ($f_2 > 50$) despite variations in hypromellose properties. The impact on drug release resulting from hypromellose properties (%HP and particle size) could be effectively overcome by replacing lactose with Starch 1500® as a filler, resulting in more robust ER formulations. This case study indicated that incorporation of Starch 1500® in ER formulation design can provide benefits in supporting Quality by Design (QbD) study and minimizing formulation variability.

References

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