Application of Quality by Design (QbD) Principles to the Formulation of Extended Release Theophylline Hydrophilic Matrix Tablets

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Abstract Summary

The objective of this study was to investigate the effects of hypromellose physicochemical properties on powder flow, tablet physical properties and in vitro drug release profiles from an extended release hydrophilic matrix tablet using QbD principles. Theophylline, a slightly soluble drug (solubility of ~ 8.3 mg/mL) was used as a model API and METHOCEL™ K15M Premium CR was used as the rate-controlling polymer. Study results indicated that ranges of viscosity, % HP and particle size of METHOCEL™ K15M Premium CR had no significant effect on physical properties of power blends, the tablet physical properties and drug release profiles.

Introduction

Quality by Design (QbD) is a systematic approach to pharmaceutical development. It means designing and developing formulations and manufacturing processes to ensure predefined product quality. In the case of hydrophilic matrix tablets, it is critical to consider the variability in properties of the rate-controlling polymer in addition to the variability in API properties and processing conditions.

The influence of hypromellose physicochemical properties on the physical properties and drug release profiles of extended release hydrophilic matrices containing soluble drugs has been reported.[1-2] The objective of this study was to examine the effect of variations in hypromellose physicochemical properties within normal manufacturing ranges on physical properties of tablets and the drug release profile of a slightly water soluble drug, theophylline from extended release hydrophilic matrices.

Experimental Methods

Materials

Hypromellose (METHOCEL™ K15M Premium CR; International Flavors and Fragrances Inc.) batches were selected, so that six batches had two of three properties [% hydroxypropoxyl substitution (% HP), particle size and polymer viscosity], at approximated nominal production values and the third property at the "high" or the "low" end of the normal manufacturing range. One batch had all three properties close to the nominal production values, denoted as "centre point" (**Table 1**). Using seven batches of hypromellose, a total of 14 extended release (ER) formulations (seven each for 15% and 30% w/w polymer levels) were prepared. The METHOCEL™ K15M Premium CR batches used in this study were referred to by the "batch name" listed in **Table 1**. The Methoxyl content (22.4-23.1%) was not an independent variable in the experimental design.

Formulations and Tablet Preparation

The composition of theophylline formulations is shown in **Table 2**. Theophylline, hypromellose, lactose and Cab-O-Sil were passed through an ASTM #30 mesh (600 µm) screen, and then mixed in a 4-quart V blender (Patterson-Kelley Co., USA) at 26 rpm for 10 minutes. Magnesium stearate was screened through an ASTM #40 mesh (400 µm) screen prior adding to the powder mixture, and followed by blending for an additional 3 minutes. The final powder mixtures were compressed at 15 kN (210 MPa) using an instrumented 10-station rotary tablet press (Piccola, RIVA, Argentina) at 20 rpm using standard round 9.52 mm concave tooling and tablet weight of 350 mg.

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Table 1. Physicochemical Properties of METHOCEL™ K15M Premium CR Batches

Hypromellose Batch Name	2% Viscosity[a] (mPa·s)	% through 230 mesh[b]	% HP[c]
High Viscosity	24865	57.7	9.1
Low Viscosity	13462	55.0	9.6
High % thru 230 mesh	17054	62.8	9.5
Low % thru 230 mesh	20156	52.6	9.4
High % HP	16698	56.2	10.5
Low % HP	16833	56.2	8.4
Center Point	19036	57.5	9.4

[a] Maximum/nominal/minimum USP specification (mPa·s): 24780/17788/13275
[b] Typical maximum/nominal/minimum production range (% through 230 mesh): 70.0/60.0/50.0
[c] Typical maximum/nominal/minimum production range (% HP): 10.5/9.5/8.5

Table 2. Composition of Theophylline Matrix Formulations

Ingredients	% Composition (w/w)	
	Low polymer level (15% w/w)	High polymer level (30% w/w)
Theophylline *(Medilom Co., Belgium)*	45.5	45.5
METHOCEL™ K15M Premium CR (IFF., USA)	15.0	30.0
FastFlo lactose (*Foremost, USA*)	38.5	23.5
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 density using a VanKel density tester (Varian Inc., 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 using USP Apparatus II (VK 7000, Varian, USA) at 100 rpm with sinkers and 1000 mL of deionized water at 37 ± 0.5°C. Theophylline release was detected at a wavelength of 272 nm using a UV-Visible spectrophotometer (Agilent 8453, Agilent Technologies, USA) fitted with quartz flow cells of 2 mm path length. The similarity factor (f_2) was calculated by comparing high vs. low end of the selected physicochemical property. In addition, the release exponent (n) and release rate constant (k) were calculated by fitting the dissolution data to the Power Law equation:[3] $(M_t / M_{inf}) = k\, t^n$.

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Results and Discussion

Physical Properties of Powder Blends and Tablets

The physical properties of theophylline powder blends and compressed tablets at 30% polymer level are shown in **Tables 3 & 4**. Study results indicated that comparable physical properties were obtained for all formulated powder blends and their compressed tablets at both 15% and 30% polymer level. All matrices showed low tablet weight variation (1.0-1.9%), low friability (≤ 0.14%) and consistent content uniformity (94.8-100.0%).

Table 3. Physical Properties of Theophylline Formulations Containing 30% w/w METHOCEL™ K15M Premium CR

Hypromellose Batch	Density (g/mL)		Carr's Index (%)	LOD (%)
	Bulk	Tapped		
High Viscosity	0.38	0.62	39	1.0
Low Viscosity	0.40	0.63	37	1.1
High % thru 230 mesh	0.39	0.63	38	1.1
Low % thru 230 mesh	0.38	0.62	39	1.1
High % HP	0.40	0.63	37	1.8
Low % HP	0.38	0.61	38	1.0
Center Point	0.38	0.62	39	1.0

Table 4. Physical Properties of Theophylline Matrix Tablets Containing 30% w/w METHOCEL™ K15M Premium CR (n = 20)

Hypromellose Batch	Hardness (kp)	Tensile Strength (MPa)	Friability (%)	Content Uniformity (%)
High Viscosity	21.0 ± 5.2	4.6 ± 1.2	0.1	96.8 ± 1.6
Low Viscosity	19.0 ± 4.3	4.1 ± 0.9	0.0	96.2 ± 0.8
High % thru 230 mesh	20.4 ± 3.7	4.6 ± 0.8	0.0	94.8 ± 1.5
Low % thru 230 mesh	20.1 ± 4.1	4.2 ± 0.9	0.1	98.0 ± 1.6
High % HP	20.0 ± 2.6	4.5 ± 0.6	0.1	96.2 ± 0.8
Low % HP	21.3 ± 4.5	4.5 ± 1.0	0.0	97.0 ± 2.5
Center Point	19.8 ± 4.3	4.3 ± 0.9	0.0	96.1 ± 1.5

Drug Release Profiles

Theophylline release rates were lower when polymer concentration was increased from 15% to 30% (w/w) as shown in **Figures 1-3**. At both 15% and 30% polymer levels, drug release profiles were similar ($f_2 > 50$) despite variations in hypromellose viscosity, %HP substitution and particles size. All formulations showed good data fitting to Power Law equation ($R^2 > 0.99$). The release exponent (n) was in the range of 0.50-0.62 for 30% w/w polymer formulations, and 0.39-0.48 for 15% w/w polymer formulations, indicating that diffusion is the principal mechanism of drug release.[3]

The linear regression model was also applied to examine the relationship between a response, i.e. release constant (k), release exponent (n) or time for 80% drug release ($t_{80\%}$) and predictor variables (viscosity, % HP and % through 230 mesh), but results indicated statistically insignificant relationship ($p > 0.1$). It should be noted that hypromellose used in this study were collected based on the normal manufacturing range by International Flavors and Fragrances Inc. The ideal orthogonal experimental design is practically difficult to achieve because of limitations in manufacturing and availability of hypromellose samples.

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Figure 1. **Theophylline Release Profiles: Effect of Viscosity (n = 6)** (Drug Dissolution Using USP Apparatus II, at 100 rpm with Sinkers and 1000 mL of Deionized Water at 37 ± 0.5°C)

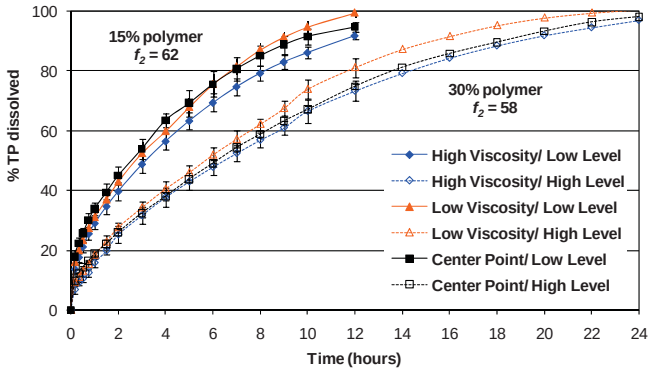


Figure 2. **Theophylline Release Profiles: Effect of % HP Content (n = 6)** (Drug Dissolution Using USP Apparatus II, at 100 rpm with Sinkers and 1000 mL of Deionized Water at 37 ± 0.5°C)

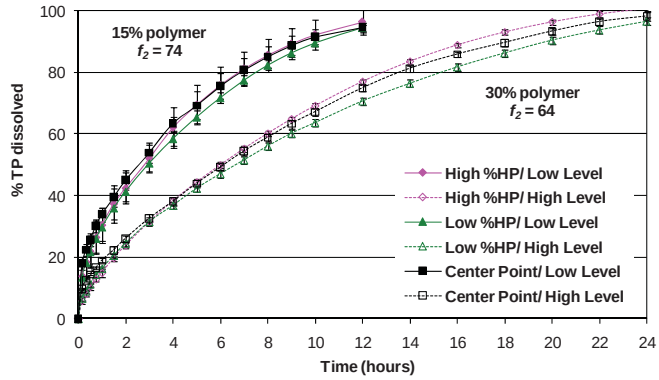
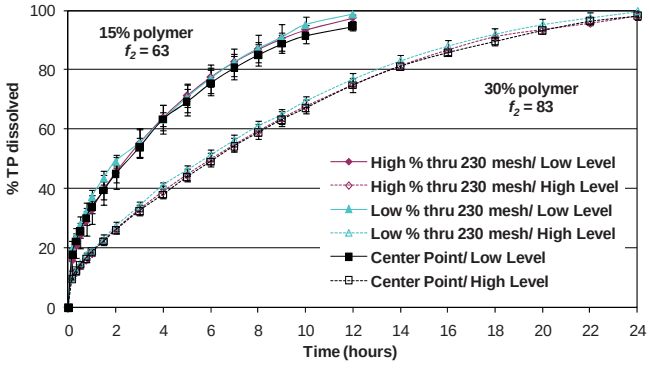


Figure 3. **Theophylline Release Profiles: Effect of Particle Size (n = 6)** (Drug Dissolution Using USP Apparatus II, at 100 rpm with Sinkers and 1000 mL of Deionized Water at 37 ± 0.5°C)



Conclusions

Study results indicated that ranges of viscosity, % HP and particle size of METHOCEL™ K15M Premium CR had no significant effect on physical properties of theophylline formulation blends and tablets. Drug release rates from hypromellose matrices were lower when polymer concentration was increased from 15% to 30% w/w. At both 15% and 30% w/w polymer level, drug release profiles were similar (f_2 > 50) despite variations in viscosity, % HP and particle size within the normal manufacturing ranges. Due to ongoing improvements in manufacturing control for METHOCEL™ Premium CR, results showed a robust matrix formulation of the slightly soluble drug theophylline when formulated with varied physical properties of METHOCEL™ K15M Premium CR.

References

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