Critical Material Attributes Consideration for Extended Release Propranolol HCl Hydrophilic Matrix Tablets

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Purpose

Hypromellose is the most commonly used polymer in extended release (ER) hydrophilic matrix formulations. Our previous studies have shown that hypromellose viscosity, hydroxypropoxyl content (%HP) and particle size are important material attributes that may impact the performance of ER matrix tablets, depending on the drug solubility and formulations.[1-2] The aim of this study was to further examine the influence of critical material attributes (CMA) of hypromellose on tablet physical properties and in vitro drug release profiles from extended release (ER) hydrophilic matrix tablets containing propranolol HCl, as a soluble model drug. Quality by Design (QbD) samples of METHOCEL™ K15M Premium CR was used as the rate controlling polymer, at various levels, and the impact on the performance of ER matrices investigated.

Methods

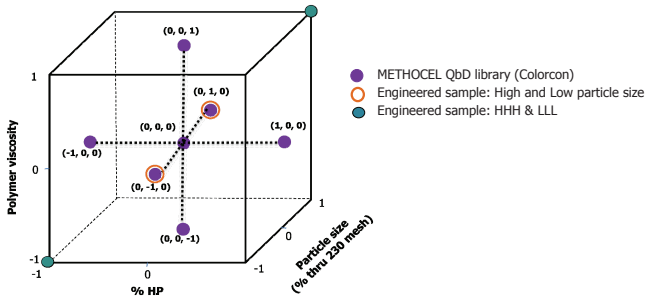
Materials

Model drug: propranolol HCl (Ipca Laboratories LTD., India)

Rate controlling polymer: METHOCEL™ K15M Premium CR (International Flavors and Fragrances Inc., USA). QbD samples are available from Colorcon Inc. The engineered QbD samples were prepared at Colorcon's laboratory by combining standard METHOCEL grades. The physicochemical properties of QbD library samples and the engineered QbD samples are provided in Figure 1 and Table 1.

Other excipients: Microcrystalline cellulose (MCC, Emcocel 90M, JRS Pharm, USA) and Magnesium stearate (Peter Greven, Germany)

Figure 1. Design Space of METHOCEL K15M Premium CR



Note: X, Y, Z indicates polymer viscosity, %HP, particle size (% thru 230 mesh), respectively.
HHH represents samples of High viscosity, High %HP and High % thru 230 mesh;
LLL represents sample of Low viscosity, Low %HP and Low % thru 230 mesh.

Table 1. Physicochemical Properties of METHOCEL K15M Premium CR Samples

(7 samples from METHOCEL QbD library and 4 engineered samples)

Hypromellose Batch	2% Viscosity[a] (mPa.s)	% through #230 mesh[b]	% HP[c]
High viscosity	**24856**	57.5	9.1
Low viscosity	**13413**	55.0	9.6
High % thru #230 mesh	17054	**62.8**	9.5
High % thru #230 mesh-E*	17800	**63.6**	9.5
Low % thru #230 mesh	20156	**52.6**	9.4
Low % thru #230 mesh-E*	21767	**47.0**	9.5
High %HP	16698	56.2	**10.5**
Low %HP	16833	56.2	**8.4**
Center Point	19036	57.5	9.4
Engineered HHH	**24933**	**63.4**	**10.5**
Engineered LLL*	**13833**	**48.5**	**8.4**

[a] Specification range (2% viscosity) 13275 – 24780 mPa·s
[b] Specification range (% through 230 mesh) 50.0 - 80.0%
[c] Specification range (% HP) 8.5 - 10.5%

Table 2. Composition of Propranolol HCl ER Formulations

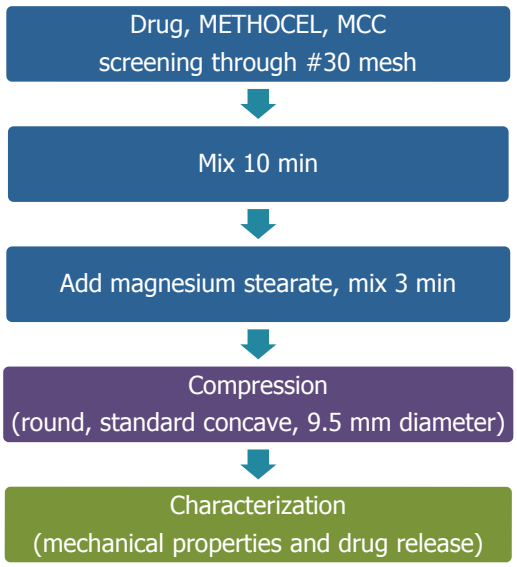
Ingredient	Composition (%)
Propranolol HCl (160mg)	45.7
METHOCEL K15M Premium CR*	15.0, 20.0, 25.0, 30.0
MCC	q.s.
Magnesium stearate	0.5 %
Total (350mg)	100.0

*Case study 1 evaluated 15% and 30% w/w polymer levels using all eleven (11) QbD samples.
Case study 2 investigated 20% and 25% w/w polymer levels using four (4) engineered samples.

Tablet Preparation

Matrix tablets were prepared as shown in Figure 2. Matrix tablets were compressed on a rotary tablet press (Piccola, RIVA, Argentina) at the compression force of 5-20 kN (compression pressure of 70-280 MPa).

Figure 2. Preparation of Propranolol HCl Matrix Tablets Using a Direct Compression Method



Tablet Characterization and Drug Release

Physical properties of tablets (weight, breaking force and dimensions) were measured on an automated Multicheck tablet tester (Erweka, Germany). Tablet friability was examined using a VanKel friabilator at 100 revolutions, 25 rpm (Varian Inc., USA). Drug release testing was performed using USP Apparatus II (VK 7000, Varian, USA) with sinkers at 100 rpm and in 1000 mL of pH 6.8 phosphate buffer at 37 ± 0.5°C. Drug release was detected at a wavelength of 289 nm using a UV Visible spectrophotometer (Agilent 8453, Agilent Technologies, USA).

Data Analysis and Model Fitting

The drug release rate constant (k) and exponent (n) were calculated by fitting the dissolution data to the Power Law equation:[3]

$$Q = k \times t^n$$

where Q is the fractional amount released at time t, k is the kinetic constant, and n is the release exponent. The similarity factor (f_2) was calculated using the center-point sample as the control. The dissolution profiles were further analyzed using Minitab 16.

Results

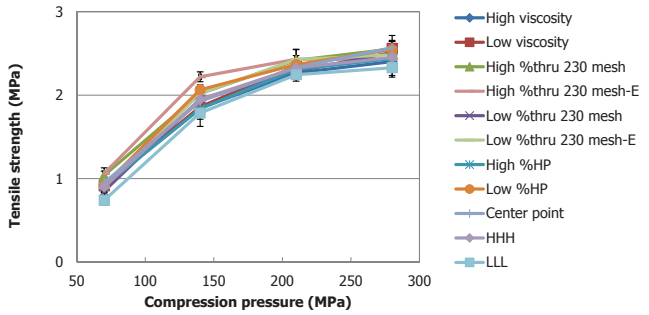
Case Study 1:

This part of the study investigated the performance of propranolol HCl matrix tablets at 15% and 30% w/w polymer levels. Figures 3(A) & 3(B) show comparable mechanical strength obtained from tablets at the same polymer level. Figure 4(A) illustrates that three coarse particle hypromellose samples (low %thru 230 mesh, low %thru 230 mesh-E, LLL) showed similar drug release profiles (f_2 = 70–88), but faster release rates (f_2 = 44–52) when compared

to other samples (f_2 = 67–87) used in the study. Figure 4(B) reveals more robust drug release from the tablets containing 30% w/w polymer level regardless of variations in hypromellose samples (f_2 = 67–94). Therefore, hypromellose particle size was the key factor impacting the drug release at low polymer level. The effect of particle size was more significant at the 15% w/w polymer concentration, which is below the critical percolation threshold of 20% w/w METHOCEL.[4] In addition, there was no difference in the performance of ER matrices when using METHOCEL samples with similar %HP, particle size and viscosity. Therefore, the study results indicated the equivalence of METHOCEL QbD samples whether they were used as manufactured or engineered via mixing in the laboratory.

Figure 3. Tensile Strength of Propranolol HCl Matrix Tablets (n = 20)

(A) 15% Polymer Level



(B) 30% Polymer Level

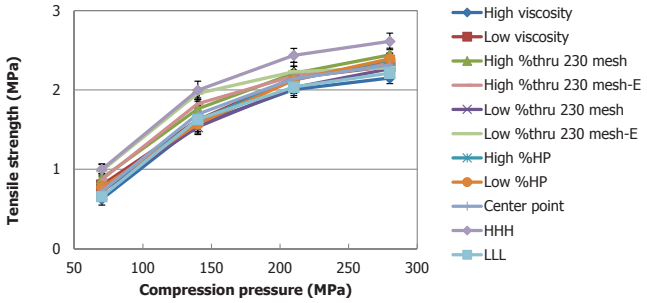
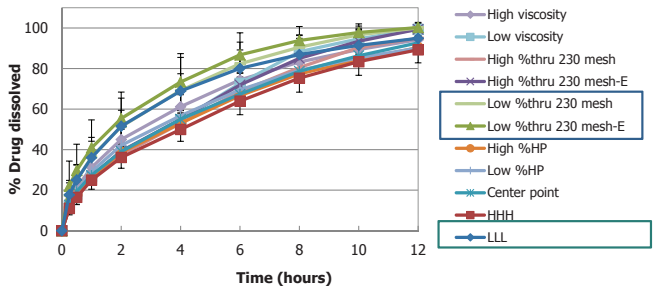
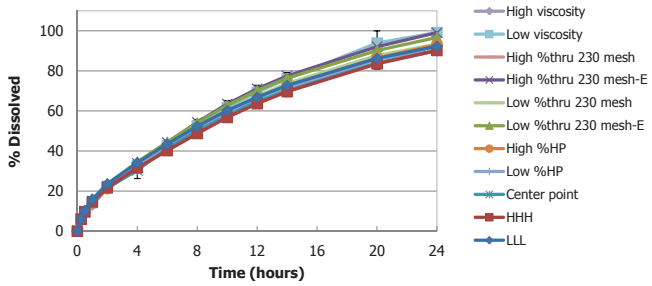


Figure 4. Comparative Propranolol HCl Release Profiles

(A) 15% Polymer Level (f_2 = 44-52, 67-87)



(B) 30% Polymer Level (f_2 = 67-94)

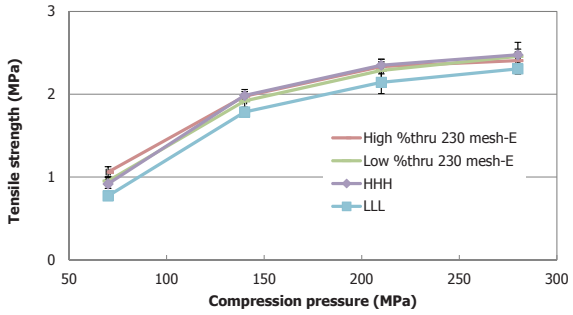


Case Study 2:

This part of the study further investigated the effect of hypromellose particle size on the performance of propranolol HCl ER matrices at 20 or 25% w/w polymer levels. Figures 5(A) & 5(B) show comparable tablet mechanical strength at 20-25% w/w polymer level. Figures 6(A) & 6(B) demonstrate similar drug release profiles from tablets containing 20 or 25% w/w polymer level regardless of variations in hypromellose samples (f_2 = 66-83). Therefore, the results of case study 2 show that hypromellose particle size had a minimal effect on drug release at polymer concentrations equal or higher than the critical percolation threshold of 20% w/w METHOCEL level.[4]

Figure 5. Tensile Strength of Propranolol HCl Matrix Tablets (n = 20)

(A) 20% Polymer Level



(B) 25% Polymer Level

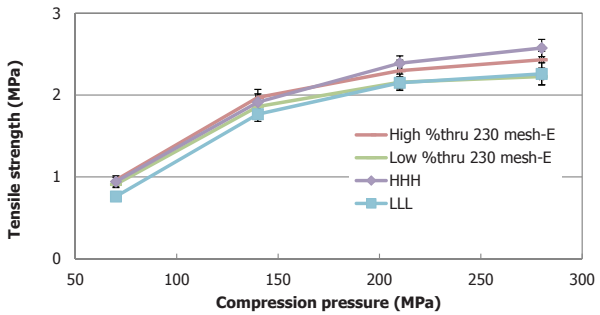
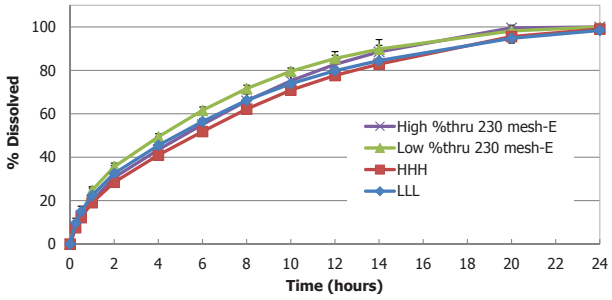
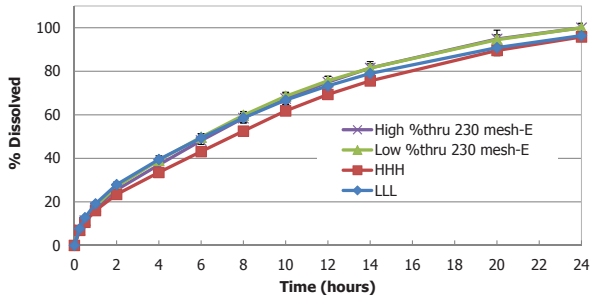


Figure 6. Comparative Propranolol HCl Release Profiles (n = 6)

(A) 20% Polymer Level (f_2 = 66-76)



(B) 25% Polymer Level (f_2 = 66-83)



Statistical Analysis

At 15% w/w METHOCEL level, there was a significant relationship (p-value < 0.1) between the response ($t_{20\%}$, time for 20% drug release) and predictors variables (HPMC viscosity, particle size, %HP and their interactions (viscosity*particle size, viscosity*%HP, particle size*%HP), indicating that the initial phase of drug release might be sensitive to the variations in HPMC physicochemical properties at low polymer levels. At 30% METHOCEL level, the relationships between the responses [release constant (k), time for 20%, 50% drug release ($t_{20\%}$, $t_{50\%}$)] and predictor variables (viscosity, % HP, particle size and their interactions) were statistically significant (p-value < 0.1), indicating that HPMC viscosity, particle size and %HP are the critical material attributes (CMAs) for hydrophilic matrices that should be carefully monitored throughout the formulation design.

Conclusions

Hypromellose CMA had no significant effect on the physical properties of ER matrix tablets, but may impact drug release profiles when the METHOCEL level is low (15% w/w). At low polymer level, METHOCEL particle size was the main factor impacting the drug release. Polymer concentration was the most significant factor impacting the drug release rate. Based on these results, a METHOCEL inclusion level of 20-30% w/w is recommended to ensure robust matrix performance. In addition, study results suggest that the design space of the current METHOCEL K15M QbD library is sufficient to map out the relationships between drug release and CMA. Results of this study indicate that both formulation aspect and CMA of key ingredients should be carefully considered within a QbD approach.

References

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