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

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Purpose

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.[1] In the case of hydrophilic matrix tablets, it is critical to consider the variability in properties of the rate-controlling polymer[2] in addition to the variabilities in API properties and processing conditions. The objective of this study was to investigate the effects of variation in hypromellose physico-chemical properties on powder flow, tablet physical properties and in vitro drug release profiles, from an extended release hydrophilic matrix tablet using QbD principles. Propranolol hydrochloride, a soluble drug (~50 mg/mL in water) was used as a model API, and METHOCEL™, premium cellulose ethers, K15M Premium CR was used as the rate-controlling polymer.

Methods

Materials

Hypromellose (METHOCEL K15M Premium CR; The Dow Chemical Company) batches were selected so that two of the three properties (% hydroxypropoxyl substitution [% HP], particle size and polymer viscosity) approximated nominal production values and the third property was at the "high" or the "low" end of the normal manufacturing range (**Table 1**). Using these 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 will be referred to by the "batch name" listed in **Table 1**.

Table 1. Physicochemical Properties of METHOCEL K15M Premium CR Batches

Hypromellose Batch Name	2% Viscosity[a] (mPa·s)	% through 230 mesh[b]	% HP[c]	% MeO[d]
High Viscosity	24865*	57.7	9.1	23.1
Low Viscosity	13462	55.0	9.6	22.9
High % through 230 mesh	17054	62.8	9.5	22.4
Low % through 230 mesh	20156	52.6	9.4	23.1
High % HP	16698	56.2	10.5	22.5
Low % HP	16833	56.2	8.4**	22.8
Center Point	19036	57.5	9.4	22.6

[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
[d] Methoxyl content, for reference purposes only; not an independent variable in the experimental design
Note: * In most cases, lots selected at manufacturing extremes met all specifications; however, in the case of high viscosity, the batch was slightly outside of specification, but close enough to the limits to be considered an acceptable benchmark for this study. **In the case of low %HP, the batch was slightly outside the normal production range, but was still within USP specification (4%-12%).

Formulations and Tablet Preparation

The composition of propranolol HCl formulations is shown in **Table 2**. Drug, hypromellose and MCC were passed through an ASTM #30 mesh (600 µm), 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) and was added to the powder mixture followed by blending for an additional 3 minutes. The final powder mixtures were compressed at 5 kN-20 kN (compaction pressure of 70 MPa-280 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.

Methods (cont'd)

Table 2. Composition of Propranolol HCl Formulations

Ingredients	% Composition (w/w) Low polymer level	% Composition (w/w) High polymer level
Propranolol HCl (Ipca Laboratories LTD., India)	45.7	45.7
METHOCEL K15M CR (The Dow Chemical Company, USA)	15.0	30.0
Microcrystalline cellulose (MCC) (JRS Pharm, USA)	38.8	23.8
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), flowability using a SOTAX FT300 flow tester (SOTAX, USA) and loss on drying (LOD) by an IR moisture balance (Denver Instrument, Model: IR-200, USA). Tablet weight, breaking force, diameter and thickness were measured with an automated Multicheck tablet tester (Erweka, Germany). Tablet friability was measured using a VanKel Friabilator at 100 revolutions, 25 rpm (Varian Inc., USA). Drug dissolution was tested using USP Apparatus II (VK 7000, Varian, USA) at 100 rpm with sinkers and 1000 mL of pH 6.8 phosphate buffer at 37°C±0.5°C. Propranolol release was detected at a wavelength of 289 nm using an UV-Visible spectrophotometer (Agilent 8453, Agilent Technologies, USA) fitted with quartz flow cells of 2 mm path length.

Data Analysis and Model Fitting

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

$$Q = k \times t^{n} \qquad \text{Equation 1}$$

where Q is the fractional amount released at time t, k is the kinetic constant, and n is the release exponent. In addition, the similarity factor (f_2) was calculated by comparing high vs. low end of the selected physicochemical property.

Results

Physical Properties of Formulated Powder Blends and Matrices

The physical properties of the formulations and matrices at 30% polymer level are depicted in **Tables 3 and 4**. The results indicated that at 30% polymer level, all formulated propranolol blends exhibited comparable bulk/tapped densities, powder flow and moisture levels (**Table 3**). Furthermore, all matrices exhibited comparable tablet hardness, tensile strength and friability values (**Table 4**). Similar results were observed for all formulations with 15% w/w polymer level indicating that physico-chemical properties of METHOCEL K15M CR (% HP, particle size and viscosity) had no or minimal influence on physical properties of formulated powder blends or tablets. All matrices showed low friability (≤0.06%) and consistent content uniformity (97.8%-101.5%).

Results (cont'd)

Table 3. Physical Properties of Formulated Propranolol HCl Blends (30% METHOCEL K15M Premium CR)

Hypromellose Batch	Density (g/mL) Bulk	Density (g/mL) Tapped	Carr's Index (%)	Sotax flow (g/sec)	LOD (%)
High viscosity	0.44	0.64	31	5.2	1.8
Low viscosity	0.45	0.66	32	4.8	1.7
High % through 230 mesh	0.44	0.65	32	5.9	1.8
Low % through 230 mesh	0.43	0.63	32	5.0	2.0
High % HP	0.45	0.64	30	4.8	1.8
Low % HP	0.44	0.64	31	5.2	2.4
Center Point	0.43	0.65	34	5.0	1.7

Table 4. Physical Properties of Propranolol HCl Matrix Tablets (30% METHOCEL K15M Premium CR)

Hypromellose Batch	Hardness (kp)	Tensile Strength (MPa)	Friability (%)	Content Uniformity (%)
High viscosity	14.3 ± 0.7	2.81 ± 0.14	0.00	101.1 ± 0.8
Low viscosity	15.4 ± 0.7	3.02 ± 0.14	0.01	100.9 ± 0.7
High % through 230 mesh	15.5 ± 0.1	3.11 ± 0.20	0.00	100.4 ± 0.8
Low % through 230 mesh	14.4 ± 0.7	2.85 ± 0.14	0.03	100.8 ± 0.9
High % HP	15.0 ± 0.7	2.99 ± 0.14	0.00	100.7 ± 0.8
Low % HP	15.0 ± 1.2	2.99 ± 0.24	0.00	99.2 ± 1.3
Center Point	15.4 ± 0.5	3.00 ± 0.10	0.00	100.7 ± 1.0

Analysis of Drug Release Profiles

Propranolol HCl release profiles were slower when polymer concentration was increased from 15% to 30% w/w (**Figures 1-3**). The effect of hypromellose viscosity on drug release profiles is shown in **Figure 1**. At both 15% and 30% polymer levels, drug release profiles were similar (f_2 of 63 and 68 respectively) despite variations in viscosity. Use of higher polymer level (30% w/w) resulted in lower variability, as indicated by error bars. The effect of hypromellose % HP substitution on drug release profiles is shown in **Figure 2**. At both 15% and 30% polymer levels, drug release profiles were similar (f_2 of 82 and 91 respectively) despite variations in % HP content. The effect of hypromellose particle size on drug release profiles is shown in **Figure 3**. At 30% polymer level, drug release profiles were similar (f_2 = 95) despite variations in particle size. At 15% polymer level though, use of larger particle size (low % through 230 mesh) of the polymer resulted in faster and dissimilar drug release profile than fine particle size (high % through 230 mesh) of the polymer (f_2 = 46). All formulations showed good data fitting to Power Law equation (R^2 > 0.99). The release exponent (n) was in the range of 0.59-0.63 for 30% w/w polymer formulations, and 0.48-0.56 for 15% w/w polymer formulations, indicating drug release mainly by diffusion mechanism.[3]

Figure 1. Propranolol HCl Release Profiles: Effect of Viscosity (n = 6)

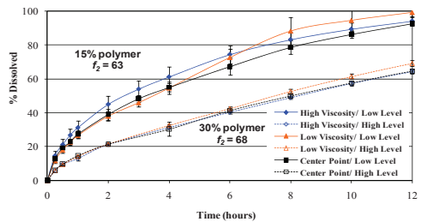


Figure 2. Propranolol HCl Release Profiles: Effect of % Hydroxypropoxy Content (n = 6)

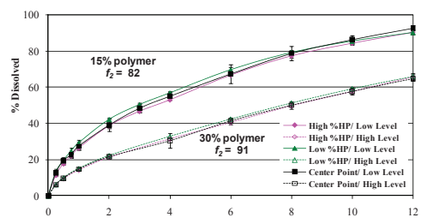
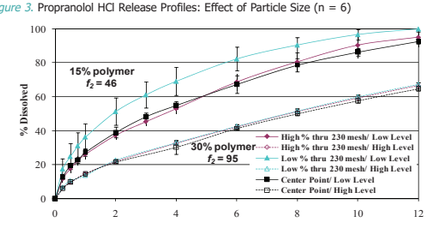


Figure 3. Propranolol HCl Release Profiles: Effect of Particle Size (n = 6)



The multivariate correlations among the three variables (viscosity, % HP and % through 230 mesh) were evaluated, and results showed weak linear relationships ($p > 0.1$) indicating the independent nature of these variables. The linear regression model was also applied to examine the relationship between a response, ie, 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 a statistically insignificant relationship.

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 propranolol HCl formulation blends and tablets. Drug release profiles from hypromellose matrices were slower when polymer concentration was increased from 15% to 30% w/w. At 30% w/w polymer level, drug release profiles were similar (f_2 > 68) despite variations in viscosity, % HP and particle size. At 15% w/w polymer level, drug release profiles were similar (f_2 > 63) despite variations in viscosity and % HP substitution. However, the larger particle size of the polymer at lower polymer inclusion (15% w/w) resulted in faster drug release (f_2 = 46). This QbD case study indicated that robust ER matrix formulations, which were insensitive to variations in polymer viscosity, % HP and particle size and consistent drug release profiles, were achieved when polymer level of ≥ 30% w/w were used.

References

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3. Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P, Peppas, N.A., Mechanism of solute release from porous hydrophilic polymers. *Int J Pharm* 1983;15: 25-35.