Investigation of Drug Release Performance of Hydrophilic Extended Release Formulations in Bio-Relevant MediaInvestigation of Drug Release Performance of Hydrophilic Extended Release Formulations in Bio-Relevant Media

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Purpose

The purpose of this study was to examine the effect of formulation variables on the robustness of hydrophilic extended release matrix tablets in both compendial media per the USP monograph and in biorelevant media (fed vs. fasted state) using USP apparatus III dissolution method. Propranolol HCl was used as a soluble model drug. METHOCEL™ K15M Quality by Design (QbD) samples with critical material attributes (CMA), i.e. polymer viscosity, hydroxypropoxyl content and particle size, at high or low end of specifications were used as the rate controlling polymer. Starch 1500® and microcrystalline cellulose were used as filler.

Methods

Materials and Formulations

Model drug:

Propranolol HCl (Ipca Laboratories LTD., India)

Rate controlling polymer:

Hypromellose, METHOCEL K15M Premium CR (International Flavors and Fragrances Inc., USA) Two QbD samples of METHOCEL K15M were used, each at the high (HHH) or low (LLL) extremes of the sales specifications for all three CMA. The physicochemical properties of the QbD samples are provided in Table 1.

Other excipients:

Starch 1500 (Colorcon Inc, USA), microcrystalline cellulose (Emcocel 90M, JRS Pharm, USA) and magnesium stearate (Peter Greven, Germany) were used in the formulations (Table 2).

Table 1. Physicochemical Properties of METHOCEL K15M Premium CR, QbD Samples

Hypromellose Batch	2% Viscosity[a] (mPa.s)	% through #230 mesh[b]	% HP[c]
HHH	**24933**	**63.4**	**10.5**
LLL	**13833**	**48.5**	**8.4**

a Viscosity specification range (mPa•s): 13275 - 24780
b Particle size specification range (% pass 230 mesh): 50 - 80
c Hydroxypropoxyl content specification range (% HP): 8.5 – 10.5

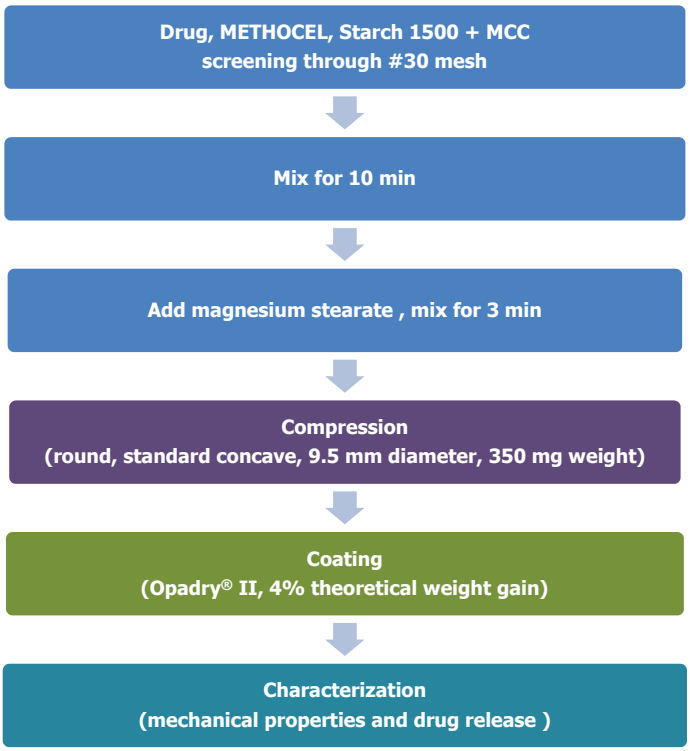
Table 2. Composition of Propranolol HCl ER Formulations

Ingredient	% Composition	
	F1	F2
Propranolol HCl (160 mg)	45.7	45.7
METHOCEL K15M Premium CR	20.0	20.0
Starch 1500	16.9	-
Microcrystalline cellulose (MCC)	16.9	33.8
Magnesium stearate	0.5	0.5
Total	100.0	100.0

Tablet Preparation

The scheme of matrix tablet preparation is shown in Figure 1.

Figure 1. Preparation of Propranolol HCl Matrix Tablets Using a Direct Compression Method



Evaluation of Physical Properties

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 Release Testing

Dissolution testing was conducted per the USP monograph, i.e. USP Apparatus II (paddles) (VK 7000, Varian, USA) at 100 rpm with sinkers and 1000 mL of pH 6.8 phosphate buffer at 37 ± 0.5°C. Drug release testing was also carried out using USP Apparatus III (reciprocating cylinder) in fasted or fed dissolution media at 37°C. The reciprocating cylinder was operated at 10 DPM with multiple steps of media changeover to simulate the human gastrointestinal environment. The composition of fed and fasted state media and residence time was considered according to the physiological relevance as shown in Table 3.[1] The dissolved drug was measured using HPLC.

Table 3. Dissolution Method in Biorelevant Media

Fasted State		Fed State	
Media	**Time (min)**	**Media**	**Time (min)**
FaSSGF 1.8	60	Ensure Plus 6.4	120
FaSSIF 6.5	15	FeSSIF 5.0	45
FaSSIF 6.8	15	FeSSIF 6.5	45
FaSSIF 7.2**	30	FeSSIF 6.5**	45
Blank FaSSIF 7.5	120	Blank FaSSIF 7.5	45
Blank FaSSIF 6.5	720	Blank FaSSIF 6.5	840

Results

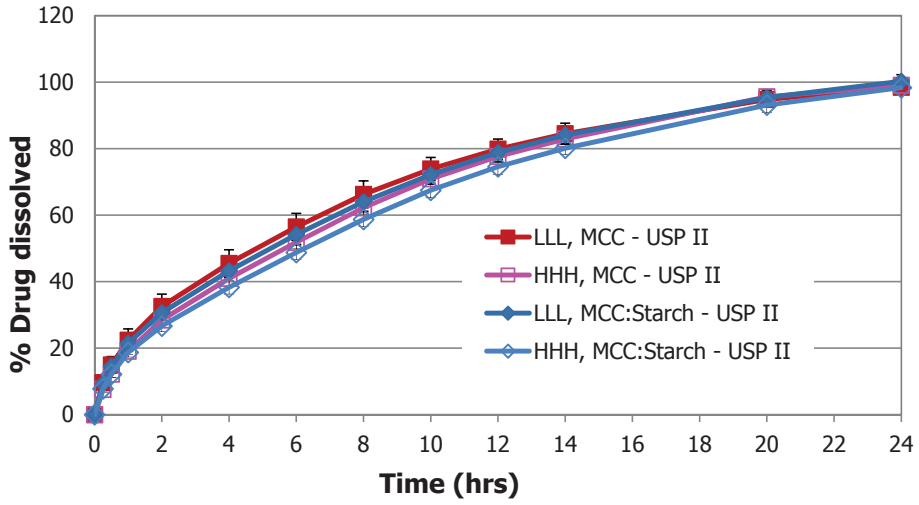
Physical Properties of Matrix Tablets

The physical properties of the matrices prepared at the compression force of 15 kN (compression pressure of 210 MPa) are listed in Tables 4. All matrices exhibited acceptable tablet hardness, tensile strength and friability values. Results also indicated that variations in physicochemical properties of METHOCEL K15M CR (% HP, particle size and viscosity) had minimal influence on tablet physical properties. All matrices showed low friability (≤ 0.14%) and consistent drug content uniformity (98-101%). Tablets with MCC as filler had higher tensile strength/hardness (2.1-2.4 MPa / 14-16 kp) than those with MCC/Starch 1500 (0.8-1.1 MPa / 6-8 kp).

Table 4. Physical Properties of Propranolol HCl Matrix Tablets

Formulation #	METHOCEL CMA (High or Low)	Filler Type	Hardness (kp)	Tensile Strength (MPa)	Friability (%)	Content Uniformity (%)
F1	HHH	Starch 1500 + MCC	7.7 ± 0.4	1.11 ± 0.06	0.14	99.1 ± 0.8
F1	LLL	Starch 1500 + MCC	6.4 ± 0.2	0.92 ± 0.03	0.14	98.4 ± 0.7
F2	HHH	MCC	15.7 ± 0.5	2.35 ± 0.07	0.00	100.4 ± 0.8
F2	LLL	MCC	14.2 ± 0.9	2.14 ± 0.14	0.00	100.8 ± 0.9

Figure 2. Propranolol HCl Release Profiles: USP Apparatus II, pH 6.8 Phosphate Buffer (n = 6)



Drug Release Profiles of Matrix Tablets

Dissolution results (Figure 2) indicated similar drug release (f_2 > 80) for all formulations when tested in pH 6.8 phosphate buffer using USP Apparatus II. Figure 3 shows that all formulations had similar (f_2 = 61-90) drug release profiles when tested in fasted-state media. Figure 4 shows three formulations had similar (f_2 = 59-69) drug release when tested in fed-state media, except f_2 formulation (f_2 = 41) containing METHOCEL K15M LLL as the rate controlling polymer and MCC as a filler. Use of Starch 1500 in the hydrophilic matrix formulations decreased the sensitivity of drug release to biorelevant media and the reciprocating motion of the dosage form within Apparatus III. The slower release in the fed state might be explained by the limited polymer hydration due to high fat and low water concentration available in the Ensure Plus media, pH 6.4. Therefore, the use of Apparatus III may offer more discriminating results in determining the robustness of the hydrophilic matrix tablets.

Figure 3. Propranolol HCl Release Profiles of Matrix Tablets: USP Apparatus III, Fasted-State Media (n = 6)

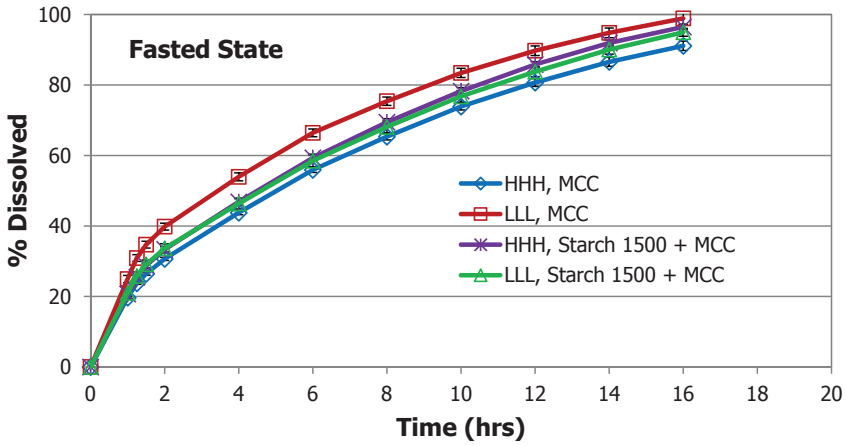
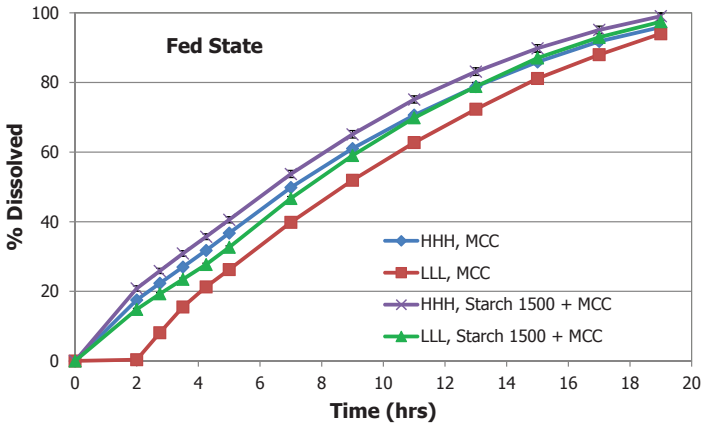


Figure 4. Propranolol HCl Release Profiles of Matrix Tablets: USP Apparatus III, Fed-State Media (n = 6)



Conclusions

Formulation variables such as METHOCEL property (CMAs) and filler choice showed impact on drug release in bio-relevant media, but had minimal influence on drug release under the compendial testing condition. Therefore, drug dissolution testing in biorelevant media using USP Apparatus III can be a valuable tool to further examine and discriminate the robustness of hydrophilic matrices. Study results also indicated that use of Starch 1500 in METHOCEL based hydrophilic extended release formulations provided drug release profiles with minimal sensitivity to the biorelevant media and the reciprocating motion of the dosage form using Apparatus III. The similarity between release profiles in fed and fasted state media indicated robust and consistent performance offered for propranolol HCl matrices using a combination of METHOCEL K15M CR and Starch 1500.

References

1. Dressman, J., Kramer, J., Pharmaceutical Dissolution Testing, Taylor & Francis, 2005

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