

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

Hua Deng, Brad Prusak, Dave Ferrizzi and Ali R. Rajabi-Siahboomi

Poster Reprint
AAPS 2013

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 (The Dow Chemical Company, 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

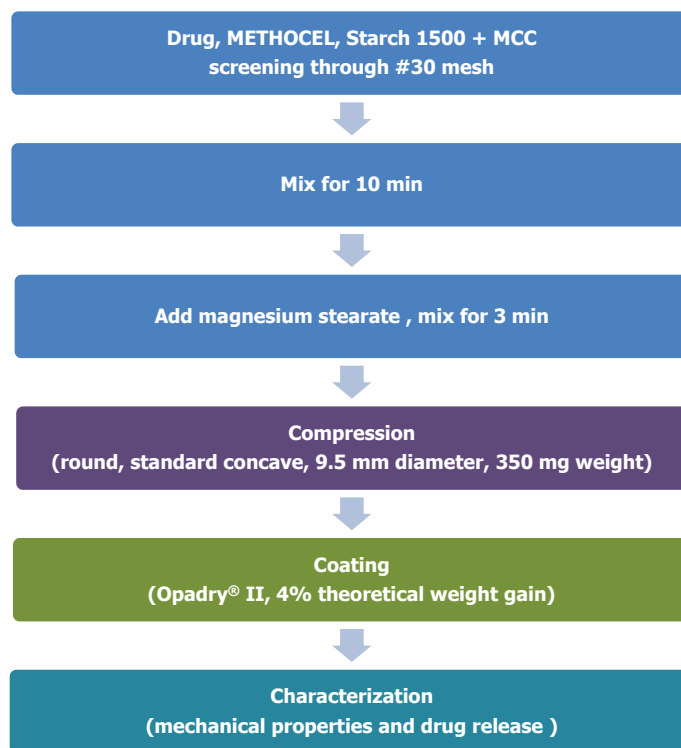
Table 2. Composition of Propranolol HCl ER Formulations

| 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 $37 \pm 0.5^\circ\text{C}$. 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

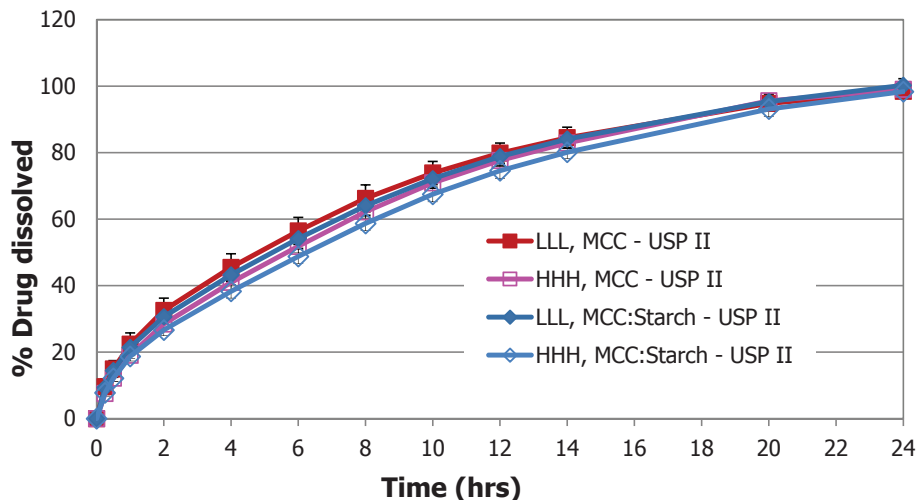
Physical Properties of Matrix Tablets

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 ($\leq 0.14\%$) 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 \pm 0.4 | 1.11 \pm 0.06 | 0.14 | 99.1 \pm 0.8 |
| F1 | LLL | Starch 1500 + MCC | 6.4 \pm 0.2 | 0.92 \pm 0.03 | 0.14 | 98.4 \pm 0.7 |
| F2 | HHH | MCC | 15.7 \pm 0.5 | 2.35 \pm 0.07 | 0.00 | 100.4 \pm 0.8 |
| F2 | LLL | MCC | 14.2 \pm 0.9 | 2.14 \pm 0.14 | 0.00 | 100.8 \pm 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)

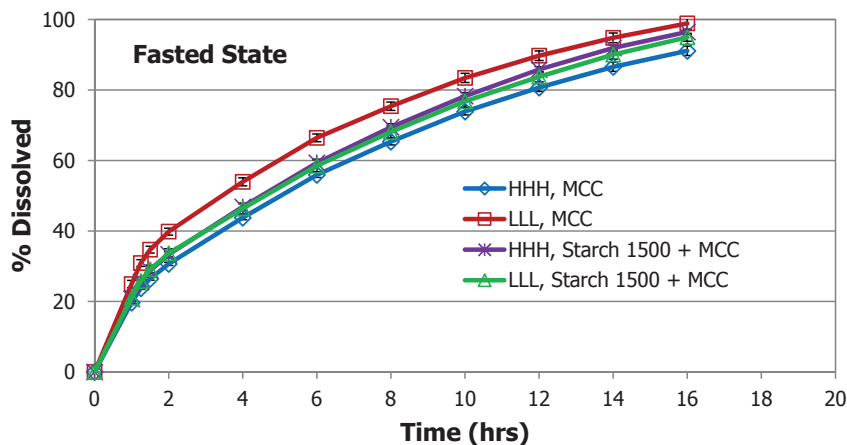
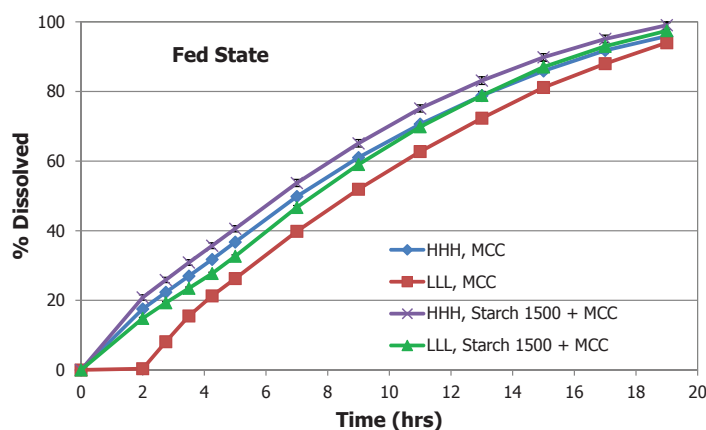


Figure 4. Propranolol HCl Release Profiles of Matrix Tablets: USP Apparatus III, Fed-State Media (n = 6)



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

The information contained herein, to the best of Colorcon, Inc.'s knowledge is true and accurate. Any recommendations or suggestions of Colorcon, Inc. with regard to the products provided by Colorcon, Inc. are made without warranty, either implied or expressed, because of the variations in methods, conditions and equipment which may be used in commercially processing the products, and no such warranties are made for the suitability of the products for any applications that you may have disclosed. Colorcon, Inc. shall not be liable for loss of profit or for incidental, special or consequential loss or damages.

Colorcon, Inc. makes no warranty, either expressed or implied, that the use of the products provided by Colorcon, Inc., will not infringe any trademark, trade name, copyright, patent or other rights held by any third person or entity when used in the customer's application.

For more information, contact your Colorcon representative or call:

North America
+1-215-699-7733

Europe/Middle East/Africa
+44-(0)-1322-293000

Asia Pacific
+65-6438-0318

Latin America
+54-1-5556-7700



©BPSI Holding, LLC 2013

All trademarks, except where noted, are property of BPSI Holdings LLC. The information contained in this document is proprietary to Colorcon, Inc. and may not be used or disseminated inappropriately.

METHOCEL™ is a trademark of The Dow Chemical Company.

METHOCEL™

You can also visit our website at www.colorcon.com

This document is valid at the time of distribution. Distributed 19-Jan-2019 (UTC)

AAPS_2013_Deng_CMA_METH