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Research Article

Investigation into the Effect of Ethylcellulose Viscosity Variation on the Drug Release of Metoprolol Tartrate and Acetaminophen Extended Release Multiparticulates—Part I

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Abstract. Ethylcellulose is one of the most commonly used polymers to develop reservoir type extended release multiparticulate dosage forms. For multiparticulate extended release dosage forms, the drug release is typically governed by the properties of the barrier membrane coating. The ICH Pharmaceutical Development Guideline (ICH Q8) requires an understanding of the influence of critical material attributes and critical process parameters on the drug release of a pharmaceutical product. Using this understanding, it is possible to develop robust formulations with consistent drug release characteristics. Critical material attributes for ethylcellulose were evaluated, and polymer molecular weight variation (viscosity) was considered to be the most critical attribute that can impact drug release. To investigate the effect of viscosity variation within the manufacturer's specifications of ethylcellulose, extended release multiparticulate formulations of two model drugs, metoprolol tartrate and acetaminophen, were developed using ETHOCEL™ as the rate controlling polymer. Quality by Design (QbD) samples of ETHOCEL Std. 10, 20, and 100 Premium grades representing the low, medium, and high molecular weight (viscosity) material were organically coated onto drug layered multiparticulates to a 15% weight gain (WG). The drug release was found to be similar ($f_2 > 50$) for both metoprolol tartrate and acetaminophen multiparticulates at different coating weight gains of ethylcellulose, highlighting consistent and robust drug release performance. The use of ETHOCEL QbD samples also serves as a means to develop multiparticulate dosage formulations according to regulatory guidelines.

KEY WORDS: acetaminophen; ethylcellulose; extended release; metoprolol tartrate; multiparticulate; quality by design.

INTRODUCTION

Multiparticulate extended release dosage forms are preferred over single unit dosage forms due to their uniform spreading throughout the gastrointestinal tract, which offers major therapeutic benefits of reduced inter- and intrapatient variability (1–3). Extended release multiparticulate dosage forms are generally prepared by application of a barrier membrane coating (3). The extended release characteristic helps to maintain the therapeutic dose of a drug over a prolonged period of time to improve patient compliance, mitigate side effects, and in some cases, allow site-specific drug release (3,4). Many polymers are utilized in the pharmaceutical industry for extended release dosage forms, for example cellulose derivatives such as cellulose acetate and ethylcellulose, and methacrylic acid copolymers. Ethylcellulose has a long history of use as a barrier membrane coating and has been successfully used in a wide range of extended release dosage forms (5–8).

Ethylcellulose is produced by substituting hydroxyl groups with ethoxyl groups on the cellulose backbone chain. The level of substitution (ethoxyl content) and molecular weight of the cellulosic backbone (viscosity) are considered as critical material attributes for ethylcellulose that may affect the barrier membrane coating performance. Ethylcellulose is commercially manufactured with varying viscosity grades, while ethoxyl content is kept within a tight specification range for all grades (9,10).

For each viscosity grade of ethylcellulose, the pharmacopeia specification allows for variation of 80–120% within the stated nominal viscosity, while ethoxyl substitution is kept within a range of 44–51% (11). Better manufacturing process control and consistency of cellulose feedstock help to produce ethylcellulose with minimal viscosity variation as well as tighter ethoxyl substitution. For example, ethylcellulose produced by the Dow Chemical Company with the brand name of ETHOCEL™ consists of viscosity variation within 90–110% of nominal viscosity and ethoxyl substitution variation between 48 and 49.5% (10). Comparison of both critical material

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attributes of ETHOCEL provided a wider range of deviation (10%) of viscosity from the nominal value while a fairly narrow range variation for ethoxyl substitution (1.5%). For a viscosity grade of ethylcellulose (*e.g.*, ETHOCEL 20 cP), 10% viscosity deviation from nominal viscosity value translates to a specification range of 18–22 cP (low-high), whereas the same deviation for a higher viscosity grade (*e.g.*, ETHOCEL 100 cP) converts to a specification range of 90–110 cP (low-high). Because this fixed 10% deviation results in increasingly broad viscosity ranges for higher viscosity grades, the impact of viscosity variation can be considered to be the major critical attribute compared to the more tightly controlled ethoxyl substitution.

According to the Quality by Design (QbD) approach outlined in ICH Pharmaceutical Development Q8 Guideline, the safety and efficacy of any pharmaceutical dosage form depends on the critical material attributes of excipients, drug substances, and critical process parameters (12,13). The risk assessment evaluation of raw material variability and critical process parameters on target drug release profile is necessary to develop a design space and control strategy (14–17). Since the target drug release profile of ethylcellulose barrier membrane-coated multiparticulate system is mainly controlled by the ethylcellulose film, understanding the influence of the critical material attributes of ethylcellulose polymer, *i.e.*, viscosity variation within each viscosity grade and its impact on target drug release profile, was considered to be an essential element to develop the design space.

The objective of this study was therefore to determine the impact of ethylcellulose molecular weight (as measured by viscosity) variation within the manufacturer's specification on the release of two model drugs metoprolol tartrate and acetaminophen. Metoprolol tartrate was selected to represent a model drug with high aqueous solubility, whereas acetaminophen as a model drug with low aqueous solubility. Drug layered sugar spheres were coated with different viscosity grades of ethylcellulose at varying coating weight gains, and their drug release profiles were determined.

MATERIALS AND METHODS

Extended release multiparticulates of metoprolol tartrate and acetaminophen were prepared by drug layering of the inert sugar sphere followed by ethylcellulose coating. Prior to the ethylcellulose coating, screening of drug layered multiparticulates between mesh #16 and mesh #20 was performed to eliminate agglomerates and fines.

Sugar Sphere

Sugar spheres (Suglets® #18–20, 850–1000 μm, Colorcon Inc., USA) were used for drug layering of metoprolol tartrate and acetaminophen. Suglets, made of sucrose and starch, were utilized in this study due to their consistent sphericity, particle size, and narrow size distribution to minimize the influence of substrate on drug release (18,19).

Drug Layering

Uncoated sugar spheres were coated with the model drugs using a hypromellose (HPMC)-based Opadry® (Colorcon Inc., USA) as binder in an Oystar Huttlin Unilab fluid bed (Huttlin GmbH, Germany). The compositions of the drug layered multiparticulates are displayed in Table I.

Different drug to binder ratios were utilized based on the solubility of the drug. For drug layering of metoprolol tartrate (aqueous solubility >500 mg/mL), a drug to binder ratio of 70:30 *w*/*w* was used, while for acetaminophen (aqueous solubility 14 mg/mL), a 50:50 *w*/*w* drug to binder ratio was used (20,21). Metoprolol tartrate formed a homogeneous drug layering solution due to high aqueous solubility of the drug, while acetaminophen formed a drug layering suspension due to limited aqueous solubility. The viscosity of the drug layering solution of metoprolol tartrate was considerably less (100 cP) at 25% solid (*w*/*w*) due to the soluble nature of the drug and low level of binder. Conversely, the acetaminophen drug layering suspension had a viscosity of 426 cP at 22% solids (*w*/*w*) due to the high level of binder in the suspension. A semifine grade of acetaminophen was used to achieve better drug layering efficiency, and the drug layered multiparticulates were screened to remove agglomerates and fines prior to application of the ethylcellulose barrier membrane coating.

Multiple lots of the drug layered multiparticulates were blended using a 16-qt v-blender (O'Hara Technologies, Canada) to form a single lot prior to the application of the ethylcellulose coating. The blending was conducted to ensure the uniformity of drug layered multiparticulates across multiple ethylcellulose coating runs.

Viscosity Measurement

A 5% *w*/*v* solution of each grade of ethylcellulose in 80:20 toluene/ethanol was prepared and its viscosity was measured at 25°C using an Ubbelohde viscometer (Lauda-Brinkmann Model, USA) (22).

Ethoxyl Content

The ethoxyl content of each grade of ethylcellulose was determined by gas chromatography (Agilent Technologies Model 6890, USA) equipped with a flame ionization detector and a packed column injection port. Sample quantity of 50 mg was combined with 60 mg of adipic acid and then dissolved in 2 mL of a 1.2% (*v*/*v*) solution of toluene in *o*-xylene. Subsequently, 2 mL of hydriodic acid was added to this solution and heated to 125°C for 60 min and then cooled to room temperature to form two solution layers. One microliter was extracted from the top layer and injected into the gas chromatograph operating at 200°C with H_2 gas flowing at 40 mL/min and air flowing at 200 mL/min. Ethoxyl results were determined based on ethyl iodide standards prepared and ran in a similar manner described above (21).

Ethylcellulose Sample Selection

ETHOCEL Standard Premium is available in different viscosity grades. The viscosity grades reflect the molecular weight of the ethylcellulose polymer chain; typically, higher viscosity grades of ethylcellulose tend to produce stronger and more durable films (9). The specifications of commercially available ethylcellulose viscosity grades are shown in

Table I. Composition of Drug Layered Multiparticulates

Ingredients	Supplier	% *w/w*	% *w/w*
Metoprolol tartrate	Polydrug, India	7	–
Acetaminophen (semifine grade)	Mallinckrodt, USA	–	7
Suglets NF 18/20 (850–1000 μm)	Colorcon, USA	90	86
Opadry 02A	Colorcon, USA	3	7
Total		100	100

Table II, indicating that ETHOCEL has tighter specifications than the USP monograph.

In this study, the lower viscosity grade of ethylcellulose (ETHOCEL 10 cP), a high viscosity grade (ETHOCEL 100 cP), and an intermediate viscosity grade (ETHOCEL 20 cP) were selected to represent the viscosity range of ethylcellulose products used in extended release multiparticulates. For each selected viscosity grade, the QbD samples representing a complete viscosity range specification of a particular grade of ethylcellulose were used in the study to determine the effect of viscosity variation within specification (Table III).

Preparation of Ethylcellulose Coating Solution

Organic coating solutions of selected ethylcellulose viscosity grades for the study were prepared using isopropyl alcohol and purified water (90:10 *w/w*) as the solvent. Dibutyl sebacate (Vertellus, USA) was used as a plasticizer at a 9:1 *w/w* ratio of polymer to plasticizer. The viscosity of the ethylcellulose coating solutions was determined using a Brookfield Viscometer (Brookfield, DVII+ Pro, Brookfield Engineering, USA) prior to the coating application. The viscosity of the ethylcellulose coating solutions were kept in the range of 75–100 cP to ensure similar droplet size and consistent film formation for all samples. The percent solids of the coating solutions were adjusted accordingly to achieve the targeted viscosity range, as shown in Table IV.

Coating Application of Ethylcellulose

Organic coating trials were carried out using a Glatt GPCG-2 (Glatt Air Techniques Inc., USA) fluid bed equipped with 4-in. Wurster column. The process parameters for applying the ethylcellulose coatings are shown in Table V. Process parameters were identified to achieve coating efficiency greater than 85% and less than 1% multiparticulate agglomeration.

Table II. Ethylcellulose Viscosity and Substitution Specifications

Ethylcellulose viscosity grade (cPs)	Viscosity specification		Ethoxyl (%)	
	DOW	USP	DOW	USP
4	3.0–5.5	3.0–5.6	48.0–49.5	44–51
7	6.0–8.0	5.6–8.4	48.0–49.5	44–51
10	9.0–11.0	8.0–12.0	48.0–49.5	44–51
20	18.0–22.0	16.0–24.0	48.0–49.5	44–51
45	41.0–49.0	36.0–54.0	48.0–49.5	44–51
100	90.0–110.0	80.0–120.0	48.0–49.5	44–51

Process parameters such as product bed temperature, air volume, and solution flow rate were kept constant to ensure consistent film formation. Samples were collected at 2.5, 5, 7.5, 10, 12.5, and 15% *w/w* theoretical coating weight gains.

Drug Assay

The actual coating weight gain and drug assay were determined before conducting the drug release analysis. Drug assay was determined by weighing 1 g of the multiparticulates into a 100-mL flask, followed by addition of 50 mL of methanol to dissolve the content of the multiparticulates. The content was sonicated for 1 h with intermittent shaking. In addition, an extra hour of mechanical shaking was performed to ensure complete dissolution of multiparticulates into methanol. The contents were then further diluted with 100 mL of methanol. The solution was filtered through a 0.45-μm syringe filter and drug content was determined spectrophotometrically at the wavelength of 276 nm for metoprolol tartrate and at the wavelength of 243 nm for acetaminophen.

Quantitative Ethylcellulose Content of Drug Layered Beads

Actual ethylcellulose weight gain was also determined by liquid chromatography. Ethylcellulose-coated multiparticulate samples (200 mg) were weighed into a 20-mL vial. Fifteen milliliters of tetrahydrofuran (THF) was transferred into the vial and the combined weight recorded. The vials were then sealed with PTFE-lined caps and agitated on a flatbed shaker for 4 h. After shaking at ambient temperature, the solutions were filtered into autosampler vials and analyzed with an Agilent 1200 LC with a mixed C-column and equipped with a ShowDEX refractive index detector. Chromatograph signals were collected with PL DataStream high-resolution data acquisition system. Cirrus GPC software was used to analyze the samples against an 11-point linear calibration curve. The ethylcellulose content determined was then used to calculate coating efficiency by taking the ratio of the theoretical weight gain to the actual weight gain.

Drug Release Analysis

In vitro dissolution studies of ethylcellulose-coated acetaminophen and metoprolol tartrate multiparticulates were carried out using USP Apparatus I, with baskets (Agilent Technologies, Cary, USA) at 100 rpm in 1000 mL of DI water at 37°C. The drug release at various weight gains was determined spectrophotometrically at 243 nm for acetaminophen and at 276 nm for metoprolol tartrate. The drug release

Table III. Ethylcellulose (ETHOCEL) Sample Selection for QbD Study

Viscosity grade	Viscosity specification[a] (cP)	QbD sample viscosity (cP)	Ethoxyl (%)
ETHOCEL Std. 10 Premium	9–11	9, 10, 11	48.4, 48.5, 48.5
ETHOCEL Std. 20 Premium	18–22	18, 20, 22	49.1, 49.4, 48.7
ETHOCEL Std. 100 Premium	90–110	90, 100, 110	48.4, 48.9, 49.1

[a] Based on the manufacturer's product specification (certificate of analysis)

analysis was performed using three replicates, and standard deviation was calculated to analyze the variability of drug release.

Drug Release Comparison

Drug release data for all multiparticulates were compared using the similarity factor (f_2) (23). To calculate the value of the similarity factor (f_2), the drug release from multiparticulates coated with ethylcellulose with nominal viscosity was selected as reference and compared with drug release from lower and higher viscosity samples, respectively. This calculation was performed for all the weight gains as per the FDA guidelines and the lowest value of the similarity factor (f_2) was reported (24). As the similarity factor f_2 calculation was sensitive to the number of time points, a total of six time points were selected across the drug release profile to perform the calculations. One point representing >85% drug release and one point <10% drug release were used for the f_2 calculations. In case of drug release <85%, six points were selected across the drug release profile.

Scanning Electron Microscopy

Fracture surfaces of the multiparticulates were prepared following immersion in liquid nitrogen for 10 min and by cutting the beads in half with a sharp single-edge blade. Prior to scanning electron microscopy (SEM) analysis, the fractured samples were analyzed under a light microscope to ensure the cut was across the midway. Samples were mounted and sputter coated with iridium using a Peltier cooled Sputter Coater EMS575X (Electron Microscopy Science, USA) for a total time of 60 s. Surfaces were evaluated in a Hitachi Field Emission Scanning Electron Microscope (FE-SEM, Hitachi High Technologies America, Inc., USA). SEM images were obtained using an applied voltage of 10 kV and various working distances depending on sample height and thickness.

Table IV. Concentration and Viscosity of Ethylcellulose Coating Solutions (in Isopropyl Alcohol/Water, 90:10 (*w*/*w*) Solvent)

Viscosity grade	Coating solids % (*w*/*w*)	Coating solution viscosity (cPs)
ETHOCEL Std. 10 Premium	7	79
ETHOCEL Std. 20 Premium	5	73
ETHOCEL Std. 100 Premium	3	80

Particle Size Analysis

Particle size and sphericity of the multiparticulates coated to different weight gains of ethylcellulose samples (10 g) were measured using a Camsizer (Retsch Technology, Germany) (25).

RESULTS AND DISCUSSION

Physical Characterization

SEM Image Analysis

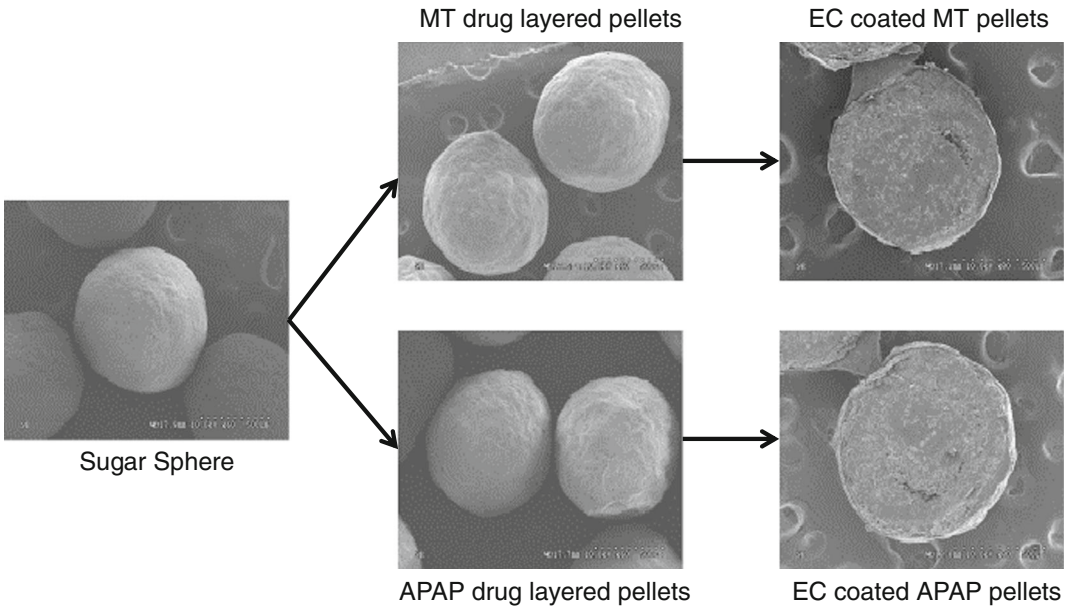
SEM images of multiparticulates were taken at various stages throughout the process from the uncoated sugar sphere to the fully coated samples. The coating surface topography, uniformity, and thickness of the ethylcellulose film, drug layer, and any indication of layer delamination or damage of the samples were analyzed. Figure 1 shows the SEM images of the samples indicating a smooth surface and uniform deposition of drug layer for acetaminophen and metoprolol tartrate and no indication of layer delamination. Additionally, the ethylcellulose film morphology of QbD samples of each viscosity grades (images not shown) was examined and found to be similar, consistent and free from any defects. This observation further suggests the minimal impact of viscosity variation on film morphology.

Particle Size Analysis

The representative particle size analysis of multiparticulates of metoprolol tartrate and acetaminophen coated with ethylcellulose (ETHOCEL) 10-cP grade is shown in Fig. 2a, b. In this study, the particle size analysis was also used as an approach to investigate uniformity of ethylcellulose deposition. Uniform coating thickness was observed at all weight gains, indicating consistent buildup of ethylcellulose films. This observation further indicates that the uniform

Table V. Ethylcellulose Coating Process Parameters

Process parameter	Value
Batch size (g)	750
Inlet temperature (°C)	38–42
Product temperature (°C)	30–32
Outlet temperature (°C)	29–31
Atomizing air (bar)/(psi)	1.3/18.8
Air volume (m^3/h)/(cfm)	45–50/26.5–29.5
Fluid delivery rate (g/min)	5–7
Coating solution viscosity (cP)	70–85



(MT=metoprolol tartrate, APAP= acetaminophen, EC=ethylcellulose)

Fig. 1. SEM images of multiparticulates at various stages. *MT* metoprolol tartrate, *APAP* acetaminophen, *EC* ethylcellulose

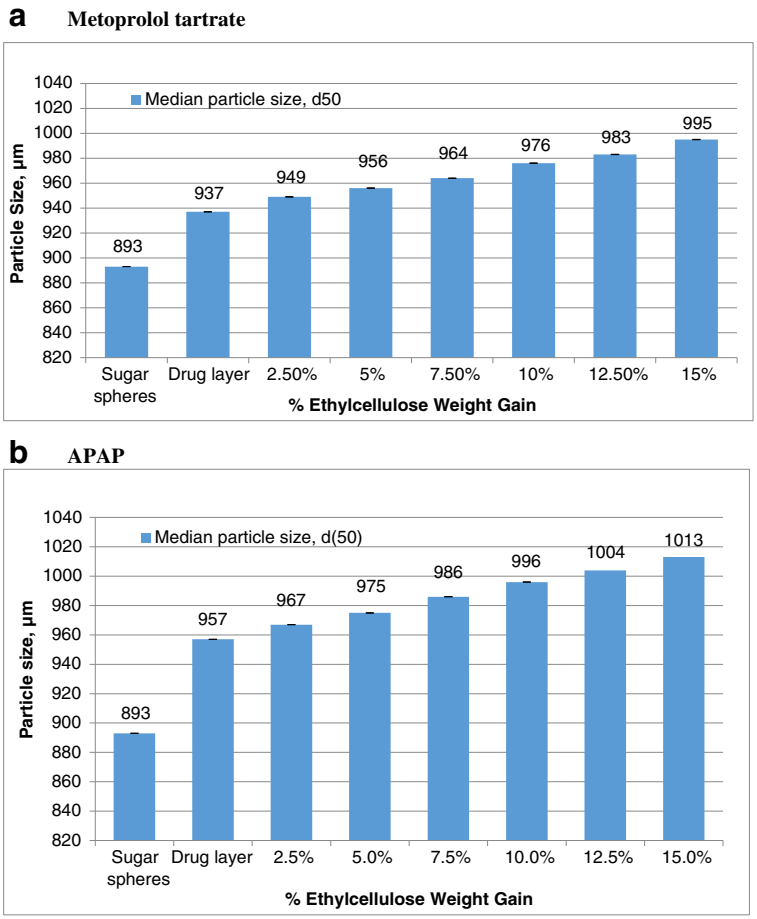


Fig. 2. Particle size growth of extended release multiparticulates. **a** Metoprolol tartrate. **b** APAP

process condition ensures consistent deposition of ethylcellulose and consistent coating thickness irrespective of viscosity grades of the polymer. For examples, the particle size for metoprolol tartrate multiparticulates at 5%, 10%, and 15% weight gain (WG) were 957 ± 3, 975 ± 5, and 998 ± 5 μm, respectively, while equivalent coating weight gains for acetaminophen multiparticulates were 973 ± 2, 994 ± 3, and 1013 ± 4μm, respectively. The larger particle size of the acetaminophen drug layered multiparticulates can be attributed to a higher level of binder used during the layering process.

Process Efficiency of Ethylcellulose Coating on Drug Layered Beads

The coating process efficiency was defined as the ratio of ethylcellulose deposited on the surface of multiparticulates to the amount of ethylcellulose sprayed as a solution. At each coating weight gain, the process efficiency was measured by analyzing ethylcellulose assay of coated multiparticulates. The coating efficiency for all weight gains of ethylcellulose 10 cP was greater than 84% (Table VI, Supplementary data). Coating efficiency decreased with increasing weight gain which could be expected due to the longer processing times for higher weight gains and the potential for fines to be produced or spray drying of ethylcellulose which is captured by the filters. Similar results were obtained (data not shown) for the remaining QbD samples of ethylcellulose (ETHOCEL 20 and 100 cP).

Drug Release Analysis

Effect of Ethylcellulose Coating Weight Gain

The effect of coating weight gain of ethylcellulose 10 cP on drug release for metoprolol tartrate and acetaminophen is shown in panels a and b of Fig. 3, respectively. There was an overall decrease in the drug release, and an increase in initial delay (known as lag time) was noticed with increasing ethylcellulose coating weight gain. A similar trend was observed with other ethylcellulose viscosity grades, with higher viscosity grades exhibiting slower overall drug release and an increase in lag time. The impact of drug solubility on drug release was also apparent, where slower release and increased lag time were observed for the sparingly soluble acetaminophen (APAP), as compared to the soluble metoprolol tartrate.

Evaluation of Ethylcellulose (ETHOCEL) 10 cP QbD Samples

The drug release profiles of metoprolol tartrate and acetaminophen multiparticulates coated with ethylcellulose 10 cP QbD samples are shown in Figs. 4 and 5 at 5%, 10%, and 15% WG, respectively. Drug release comparison was conducted between low, standard, and high viscosity specification for QbD samples. A similarity factor (f_2) analysis was used to compare the drug release profiles from all three QbD samples, and in each case, the lowest value was reported. Metoprolol tartrate drug release profiles are all essentially similar and have similarity factor values of $f_2 > 73$ at 5%, $f_2 > 68$ at 10%, and $f_2 > 60$ at 15% WG. The acetaminophen drug release was

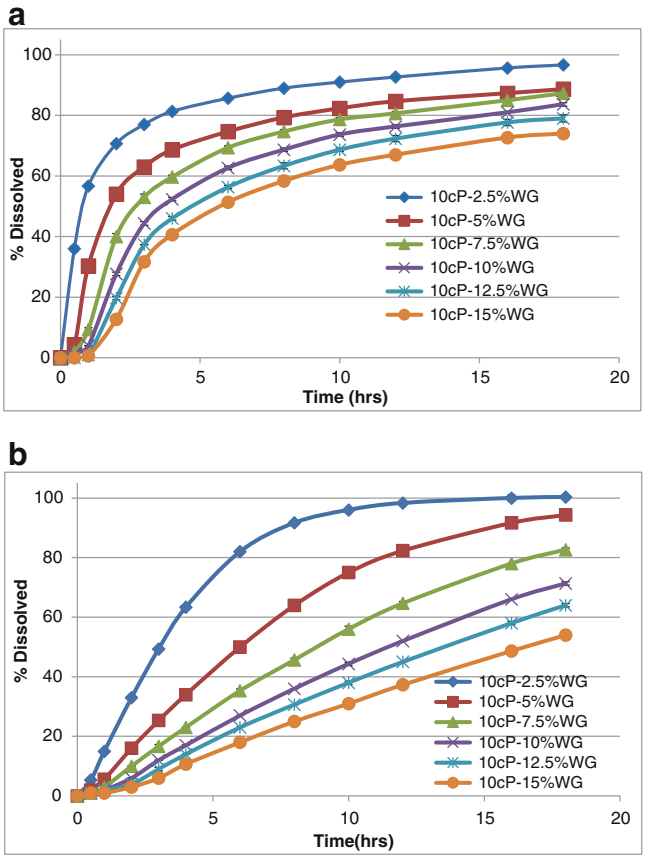


Fig. 3. **a** Effect of coating weight gain on metoprolol tartrate release from multiparticulates coated with ethylcellulose (ETHOCEL 10 cP) QbD samples ($n = 3$). **b** Effect of coating weight gain on APAP release from multiparticulates coated with ethylcellulose (ETHOCEL 10 cP) QbD samples ($n = 3$)

evaluated in the same way, and (f_2) values were $f_2 > 75$, $f_2 > 74$, and $f_2 > 83$ at 5%, 10%, and 15% WG, respectively. This analysis clearly indicates that there is minimal variability in drug release for either model drugs due to variation of viscosity within the ethylcellulose 10-cP grade specification range.

To confirm the reproducibility of the coating application of ethylcellulose, the coating trials of acetaminophen using ethylcellulose 10 cP were repeated. The drug release results at 5%, 10%, and 15% WG were compared, and the similarity factors (f_2) were determined to be 96, 99, and 98, respectively. These values clearly indicate excellent reproducibility of the coating trials and drug release (data not shown).

Evaluation of Ethylcellulose 20 cP QbD Samples

The drug release profiles of metoprolol tartrate and acetaminophen multiparticulates coated with ethylcellulose 20 cP QbD samples are shown in Figs. 6 and 7 at 5%, 10%, and 15% WG, respectively. The same analysis was conducted as previously described for the 10-cP samples. Metoprolol tartrate drug release profiles are all essentially similar and have similarity factor values of $f_2 > 62$, $f_2 > 67$, and $f_2 > 81$ at 5%, 10%, and 15% WG, respectively. The acetaminophen drug release was evaluated in the same way and (f_2) values were $f_2 > 74$, $f_2 >$

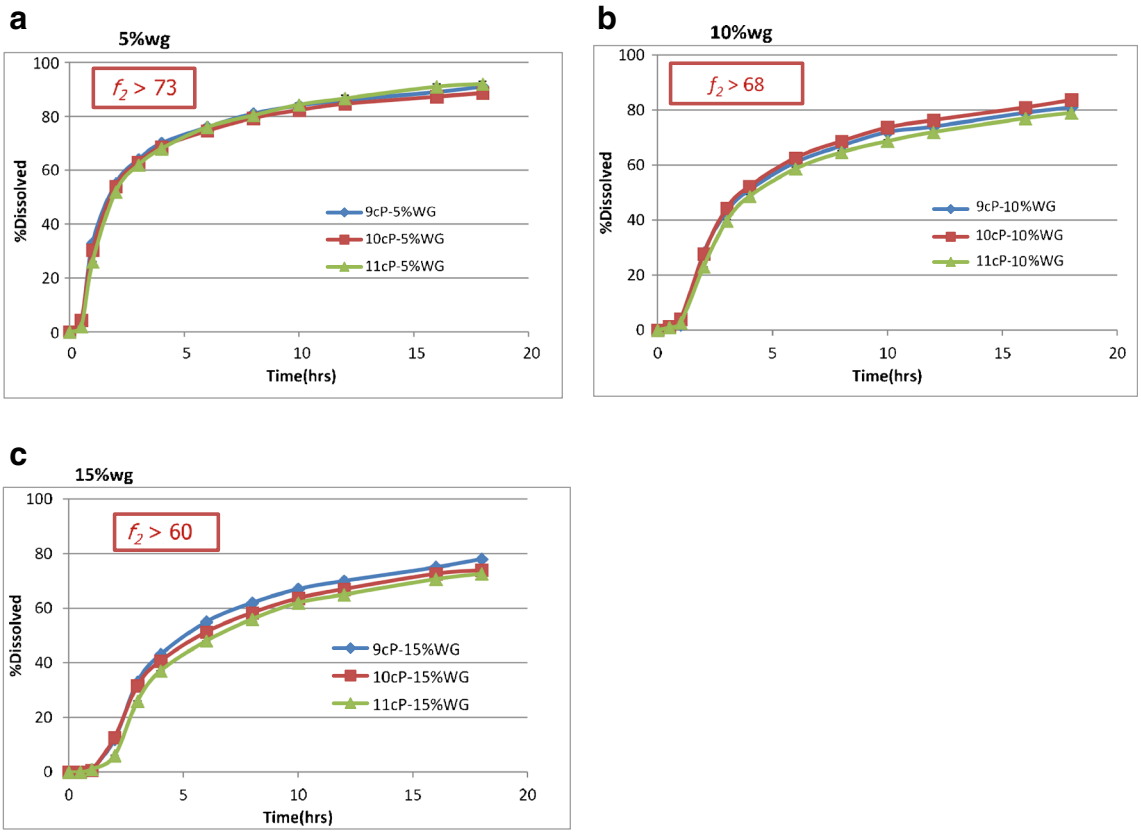


Fig. 4. Metoprolol tartrate release from multiparticulates coated with QbD samples of ethylcellulose (ETHOCEL 10 cP) ($n = 3$). **a** 5% WG. **b** 10% WG. **c** 15% WG

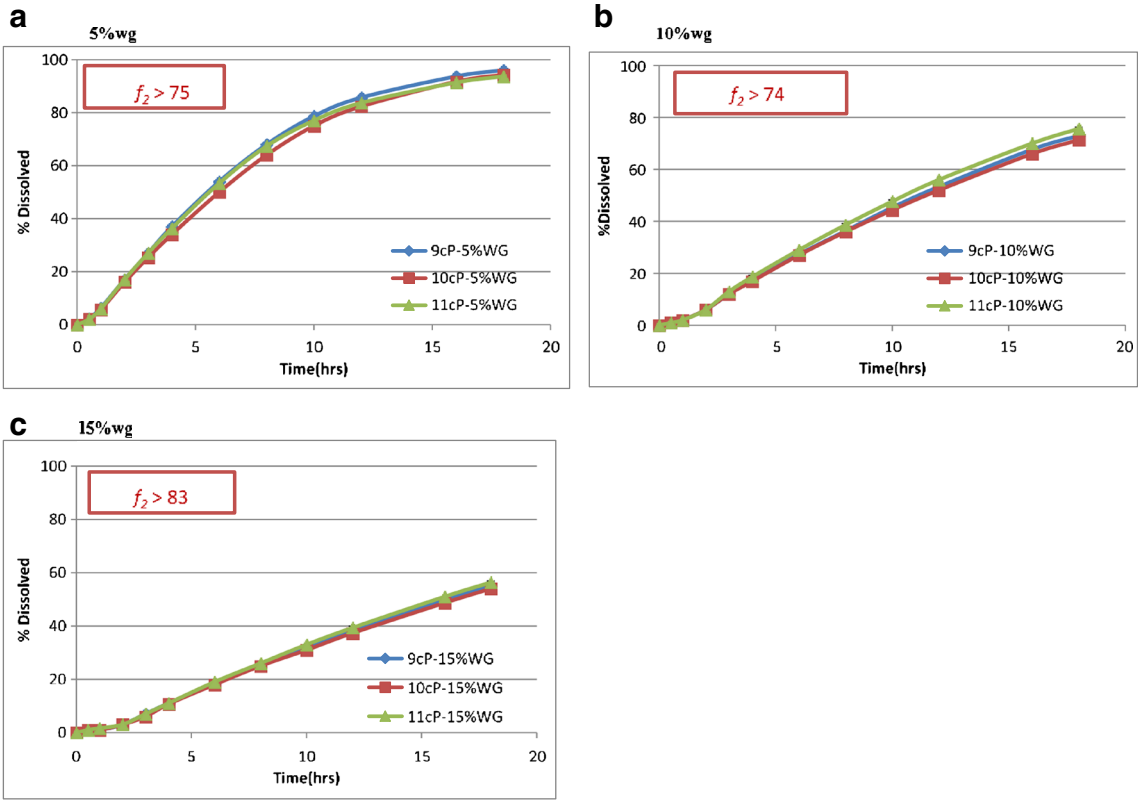


Fig. 5. APAP release from multiparticulates coated with QbD samples of ethylcellulose (ETHOCEL 10 cP) ($n = 3$). **a** 5% WG. **b** 10% WG. **c** 15% WG

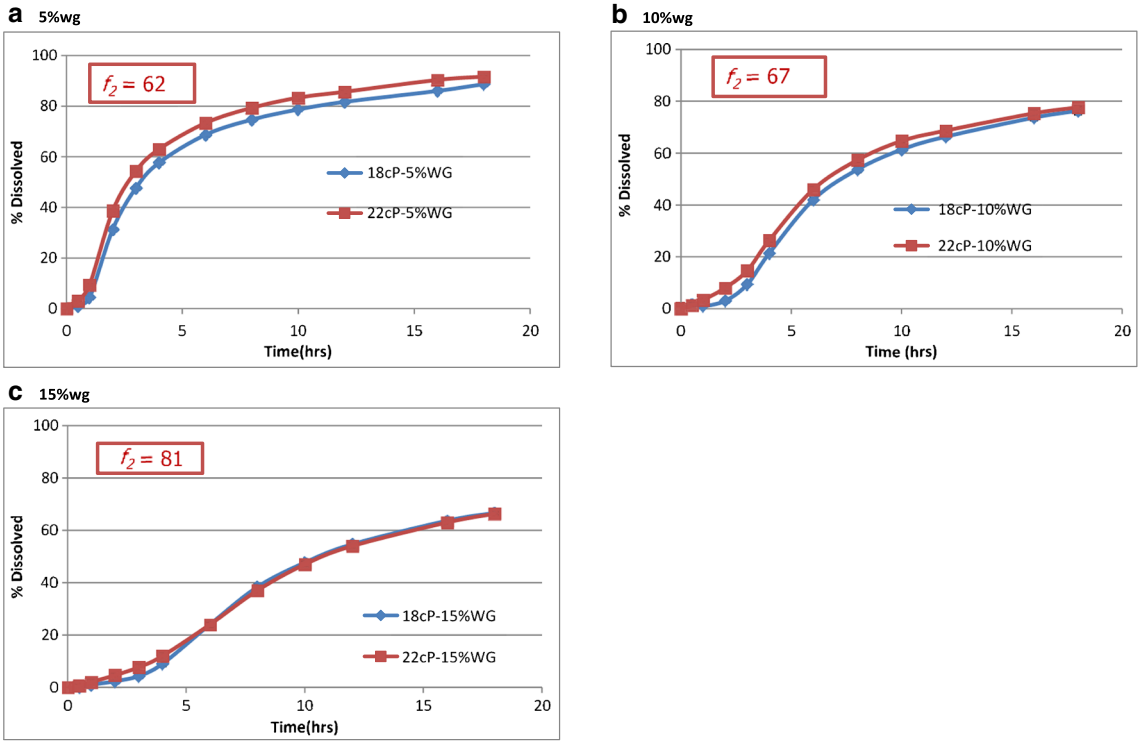


Fig. 6. Metoprolol tartrate release from multiparticulates coated with QbD samples of ethylcellulose (ETHOCEL 20 cP) ($n = 3$). **a** 5% WG. **b** 10% WG. **c** 15% WG

74, and $f_2 > 64$ at 5%, 10%, and 15% WG, respectively. This analysis clearly indicates that there is minimal variability in drug release for either model drugs due to variation of viscosity within the ethylcellulose 20-cP grade specification range.

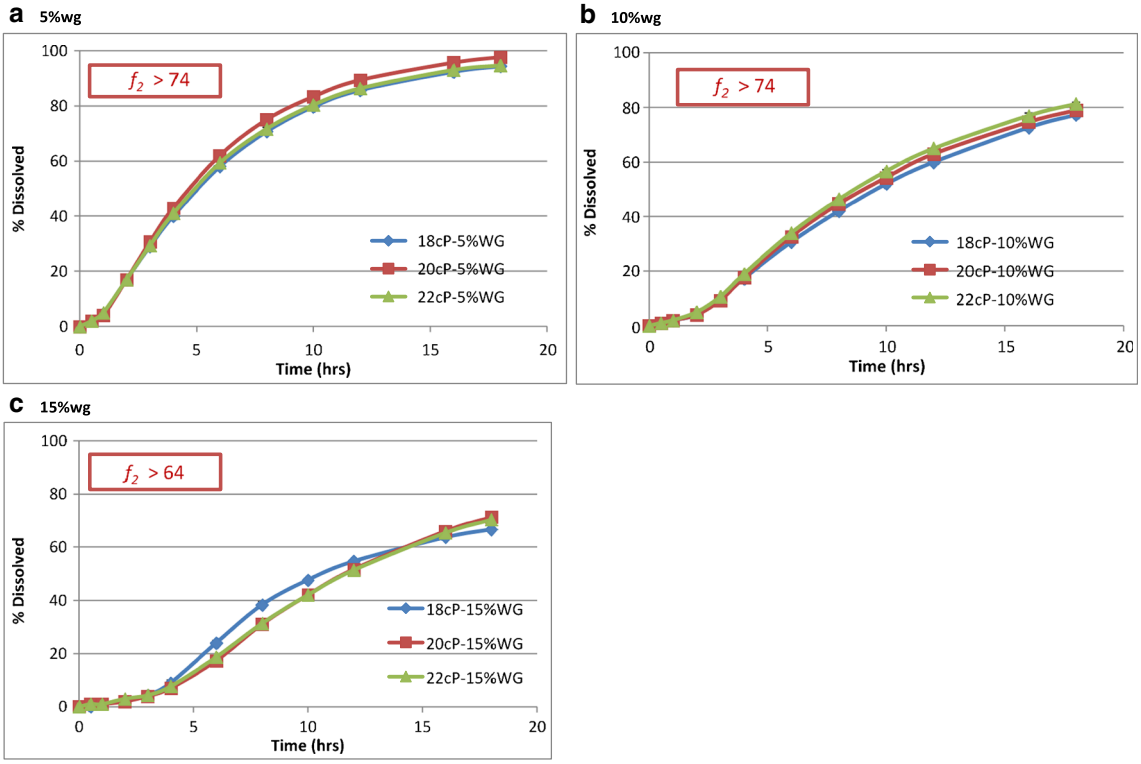


Fig. 7. APAP release from multiparticulates coated with QbD samples of ethylcellulose (ETHOCEL 20 cP) ($n = 3$). a 5% WG. **b** 10% WG. **c** 15% WG

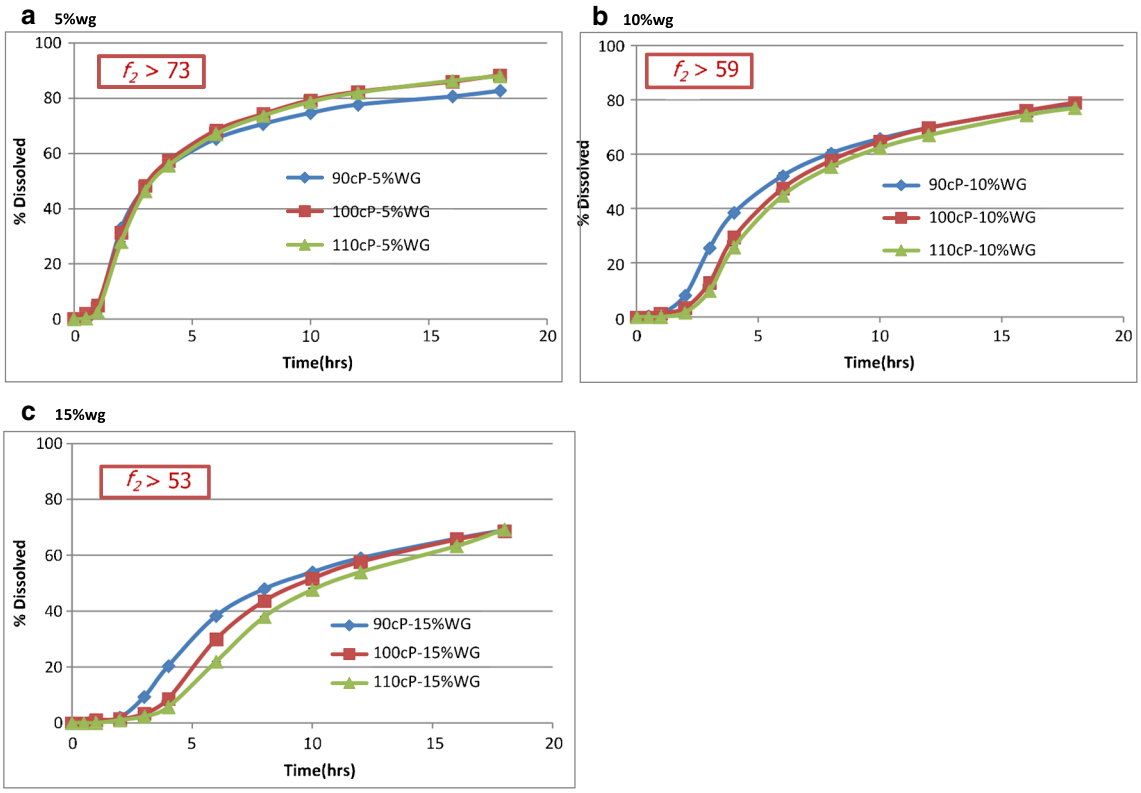


Fig. 8. Metoprolol tartrate release from multiparticulates coated with QbD samples of ethylcellulose (ETHOCEL 100 cP) ($n = 3$). **a** 5% WG. **b** 10% WG. **c** 15% WG

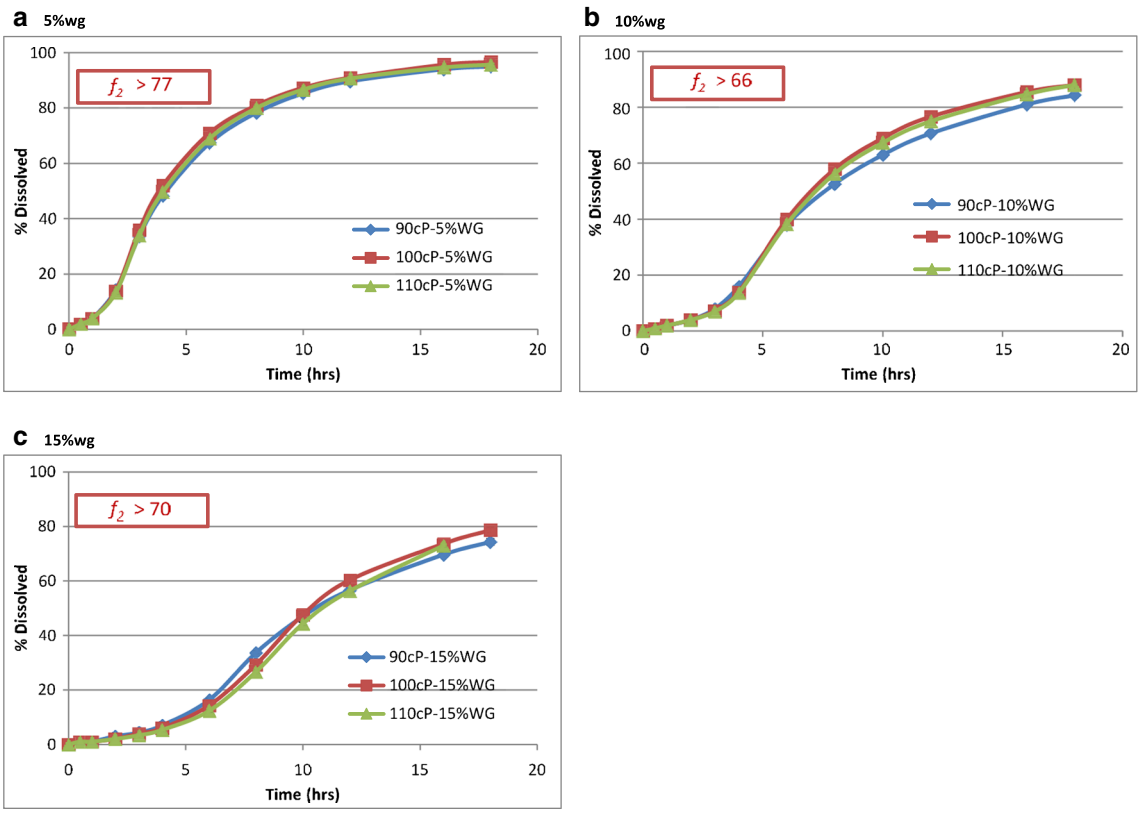


Fig. 9. APAP drug release from MPs coated with QbD samples of ethylcellulose (ETHOCEL 100 cP) ($n = 3$). **a** 5% WG. **b** 10% WG. **c** 15% WG

Evaluation of Ethylcellulose 100 cP QbD Samples

The drug release profiles of metoprolol tartrate and acetaminophen multiparticulates coated with ethylcellulose 100 cP QbD samples are shown in Figs. 8 and 9 at 5%, 10%, and 15% WG, respectively. The same analysis was conducted as previously described for the 10- and 20-cP samples. Metoprolol tartrate drug release profiles are all similar and have similarity factor values of $f_2 > 73$, $f_2 > 59$, and $f_2 > 53$ at 5%, 10%, and 15% WG, respectively. The drug release profiles were found to be similar according to the f_2 similarity criteria; however, more variability was observed at 10% and 15% weight gains. This variability may be attributed to the larger difference in the viscosity range (20 cP) between the lowest and highest viscosity QbD samples of ethylcellulose 100 cP compared to ethylcellulose 10 and 20 cP samples whose viscosity difference is 2 and 4 cP, respectively. The lower f_2 values observed when going from a 5% to 15% WG may potentially be associated with the longer processing times (4 h for 5% WG and 11 h for 15% WG) of 100 cP due to lower solids in the coating solution.

Acetaminophen drug release was evaluated in the same way and (f_2) values were $f_2 > 77$, $f_2 > 66$, and $f_2 > 70$ at 5%, 10%, and 15% WG, respectively. The similarity factor values for acetaminophen were less affected than with metoprolol tartrate even with the wider viscosity specification range of ethylcellulose 100 cP QbD samples. This analysis clearly indicates low variation in drug release for either model drugs due to variation of viscosity within the ethylcellulose 100-cP grade specification range.

CONCLUSION

These studies demonstrated that viscosity variation within the manufacturer's specifications of ethylcellulose (ETHOCEL) 10, 20, and 100 cP grades had a minimal effect on drug release for either model drugs. Among different viscosity grades, the 100-cP samples demonstrated slightly increased drug release variability when compared to 10 and 20 cP viscosity grades, but drug release was still similar based on the f_2 analysis criteria. Acetaminophen-coated multiparticulates exhibited slower drug release and longer lag time when compared to the equivalent metoprolol tartrate multiparticulates, and this can be associated with the lower aqueous solubility of acetaminophen compared to metoprolol tartrate. Based on this study, all grades of ethylcellulose are suitable for organic solvent coating of extended release barrier membrane multiparticulates. The ethylcellulose 10- and 20-cP grades offer the most robust performance with reduced processing time. Viscosity variation within these grades did not contribute a significant variation in the drug release profile.

REFERENCES

1. Ghebre-Selassie I, editor. Multiparticulate oral drug delivery. Vol. 65. Informa Health Care; 1994
2. Bechgaard H, Nielsen GH. Controlled-release multiple-units and single-unit doses. A literature review. Drug Dev Ind Pharm. 1978;4:53–67.
3. Tang ES, Chan LW, Heng PW. Coating of multiparticulates for sustained release. Am J Drug Deliv. 2005;3(1):17–28.
4. Davis SS, Hardy JG, Taylor MJ, Whalley DR, Wilson CG. A comparative study of the gastrointestinal transit of a pellet and tablet formulation. Int J Pharm. 1984;21:167–77.
5. Cole G, Hogan M, Aulton M. Pharmaceutical coating technology. London: Taylor & Francis Books; 1995.
6. Teng Y, Qiu Z. Fluid bed coating and granulation for CR delivery. In: Wen H, Park K, editors. Oral controlled release formulation design and drug delivery: theory to practice. Hoboken: Wiley; 2010.
7. Van Savage G, Rhodes CT. The sustained release coating of solid dosage forms: a historical review. Drug Dev Ind Pharm. 1995;21:93–118.
8. Sakellarious P, Rowe RC. Interaction in cellulose derivative films for oral drug delivery. Prog Polym Sci. 1995;20:889–942.
9. Rekhi GS, Jambhekar SS. Ethylcellulose—a polymer review. Drug Dev Ind Pharm. 1995;21(1):61–77.
10. ETHOCEL ethylcellulose polymers technical handbook, Dow Cellulosic. Available from: http://www.dow.com/dowwolff/en/pdf/192-00818.pdf. Accessed 20 July 2015
11. Rowe RC, Sheskey PJ, Quinn ME, editors. Handbook of pharmaceutical excipients. 6th ed. London: Pharmaceutical Press and American Pharmacists Association; 2009.
12. Guideline, ICH Harmonised Tripartite. Pharmaceutical Development Q8 (R2). ICH Steering Committee, Step 4 (2009). Available from: http://www.fda.gov/downloads/Drugs/Guidances/ucm073507.pdf. Accessed 16 Mar 2015
13. Quality by design for ANDAs: an example for modified release dosage. Available from http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf. Accessed 16 Mar 2015
14. Lawrence XY. Pharmaceutical quality by design: product and process development, understanding, and control. Pharm Res. 2008;25(4):781–91.
15. Lionberger RA, Lee SL, Lee LM, Raw A, Lawrence XY. Quality by design: concepts for ANDAs. AAPS J. 2008;10(2):268–76.
16. Hlinak AJ, Kuriyan K, Morris KR, Reklaitis GV, Basu PK. Understanding critical material properties for solid dosage form design. J Pharm Innov. 2006;1(1):12–7.
17. Moreton RC. Functionality and performance of excipients in quality-by-design world. Part VI: excipient composition. Am Pharm Rev, 2009; (12):48–51.
18. Werner D. Sugar spheres: a versatile excipient for oral pellet medication with modified release kinetics. Pharm Technol Eur. 2006;18(4):35–41.
19. Vass S, Cunningham C, Rajabi-Siahboomi AR. Evaluation of a process relevant method for determining the robustness of sugar spheres as a drug layering substrate. AAPS annual meeting and exposition, San Diego; 2014.
20. Mehta RY, Missaghi S, Farrell TP, Rajabi-Siahboomi AR. Barrier membrane coating of hydrophilic matrices of a very soluble drug, metoprolol tartrate at high dose: a strategy to eliminate the initial burst release. CRS annual meeting and exposition, Quebec City; 2012.
21. Missaghi S, Patel P, Farrell TP, Huatan H, Rajabi-Siahboomi AR. Investigation of critical core formulation and process parameters for osmotic pump oral drug delivery. AAPS PharmSciTech. 2014;15(1):149–60.
22. USP/NF, United States Pharmacopeia/National Formulary, monograph "ethylcellulose" and general chapter <911>, "viscosity", (current version) available from: United States Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852
23. Moore JW, Flanner HH. Mathematical comparison of curves with an emphasis on dissolution profiles. Pharm Technol. 1996;20:64–74.
24. Guidance for Industry: SUPAC-MR modified release solid oral dosage forms, scale-up and post-approval changes: chemistry, manufacturing and controls, in vitro dissolution testing and in vivo bioequivalence documentation. US Food and Drug Administration, Rockville, MD, USA, 1997
25. Larsen CC, Sonnergaard JM, Bertelsen P, Holm P. Validation of an image analysis method for estimating coating thickness on pellets. Eur J Pharm Sci. 2003;18(2):191–6.