A QbD Investigation into the Effect of Ethylcellulose Viscosity Variation on the Drug Release of Metoprolol Tartrate Extended Release Multiparticulates

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Purpose

Ethylcellulose is one of the most commonly used polymers to develop extended release (ER) multiparticulate (MP) formulations, due to its excellent barrier membrane coating properties, global regulatory acceptance and safety. The drug release rate is typically controlled by the properties of the barrier membrane coating. It was previously determined that the most critical material attribute of ethylcellulose that may influence drug release is viscosity.[1-2] To evaluate the effect of ethylcellulose viscosity variation on drug release, metoprolol tartrate (MT), a very soluble drug was selected as a model active. Extended release MPs were prepared using ETHOCEL™ Premium (ethylcellulose, International Flavors and Fragrances Inc. , USA) as a rate controlling barrier membrane coating polymer. Quality by Design (QbD) samples of ETHOCEL Std. 10, 20 and 100 Premium grades were coated organically using a fluid bed coater onto drug layered MPs up to a 15% weight gain (WG). The objective of the study was to investigate the effect of viscosity variation, within the manufacturer's specification of ETHOCEL, on in vitro drug release performance.

Methods

Drug Layering

The composition of the drug layered MP is displayed in Table 1. Uncoated sugar spheres (SUGLETS® PF011, 840-1000 µm, Colorcon Inc., USA) were coated in an Oyster Huttlin Unilab fluid bed (Huttlin GmbH, Germany) using metoprolol tartrate (Polydrug, India) and an HPMC based Opadry® complete film coating system (Colorcon Inc., USA) as a binder. A drug to binder ratio of 70:30 w/w was maintained and the drug layered MPs were screened to remove agglomerates and fines before application of the barrier membrane coating.

Application of Ethylcellulose

The ETHOCEL QbD samples used in the study are shown in Table 2. Dibutyl sebacate (Vertellus, USA) was used as a plasticizer at a 9:1 w/w ratio of polymer to plasticizer. The organic coating solutions of ethylcellulose were prepared using isopropyl alcohol and purified water (90:10 w/w) as the solvent. The ETHOCEL coating solution viscosity was kept in a range of 75-100cP toensure similarity of droplet size and the percent (%) solids were adjusted to achieve the targeted viscosity (Table 2). Organic coating trials were carried out using a Glatt GPCG-2 (Glatt Air Techniques Inc., USA) fluid bed. The process parameters for applying the ethylcellulose coatings are listed in Table 3.

Dissolution Studies

In vitro dissolution studies were carried out using USP Apparatus I (baskets) at 100 rpm in 1000 ml of purified water. Drug release was determined spectrophotometrically at a wavelength of 276 nm. Drug release data for all MP were compared using f_2 similarity factor.

Table 1. Composition of Drug Layer MP

Ingredients	Supplier	% w/w
Metoprolol tartrate	Polydrug Laboratories Pvt. Ltd., India	7
Suglets, PF011 850-1000 µm	Colorcon Inc., USA	90
Opadry	Colorcon Inc., USA	3
Total		100

Table 2. ETHOCEL QbD Samples Used in the Study

Viscosity Grade	Viscosity Specification cP	QbD Sample Viscosity cP	Coating Solids % (w/w)
ETHOCEL Std. 10 Premium	9-11	9, 10, 11	7
ETHOCEL Std. 20 Premium	18-22	18, 20, 22	5
ETHOCEL Std. 100 Premium	90-110	90, 100, 110	3

Table 2. ETHOCEL QbD Samples Used in the Study

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 (m3/hr) / (cfm)	45 - 50 / 26.5 - 29.5
Fluid delivery rate (g/min)	5 – 7
Coating solution viscosity (cP)	70-85

Results and Discussion

The drug release profiles of MP coated with Ethocel Std. 10 Premium QbD samples are shown in Figure 1 and Figure 2 at 5% and 15% WG, respectively. The (f_2) similarity factor values were >73 at a 5% WG and >60 at 15% WG. This indicates there is minimal variability of drug release due to variation of viscosity within the ETHOCEL Std. 10cP Premium grade specification.

The drug release for MP coated with ETHOCEL Std. 20 Premium QbD samples are shown in Figures 3 and 4, while the MP coated with ETHOCEL Std. 100 Premium QbD samples are shown in Figures 5 and 6.

Figure 1: Metoprolol Tartrate Release from ETHOCEL Std. 10 Premium QbD Samples at 5% WG

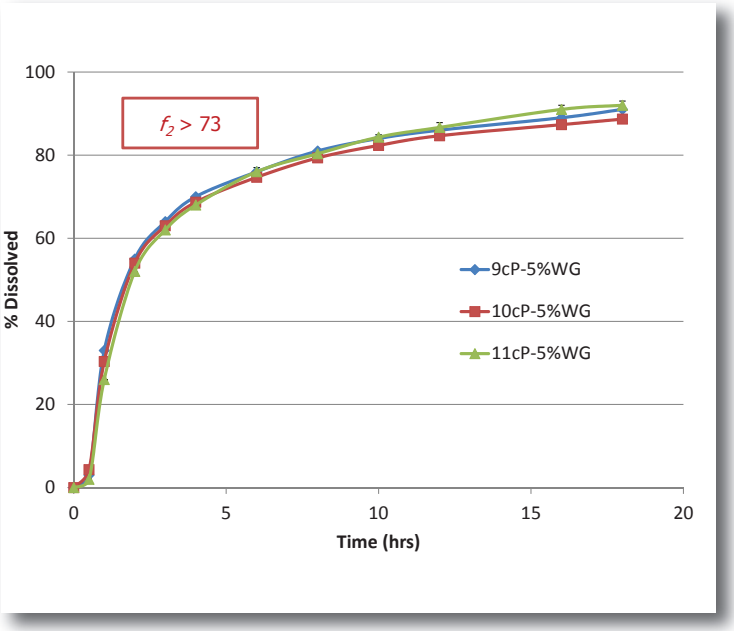


Figure 2: Metoprolol Tartrate Release from ETHOCEL Std. 10 Premium QbD Samples at 15%WG

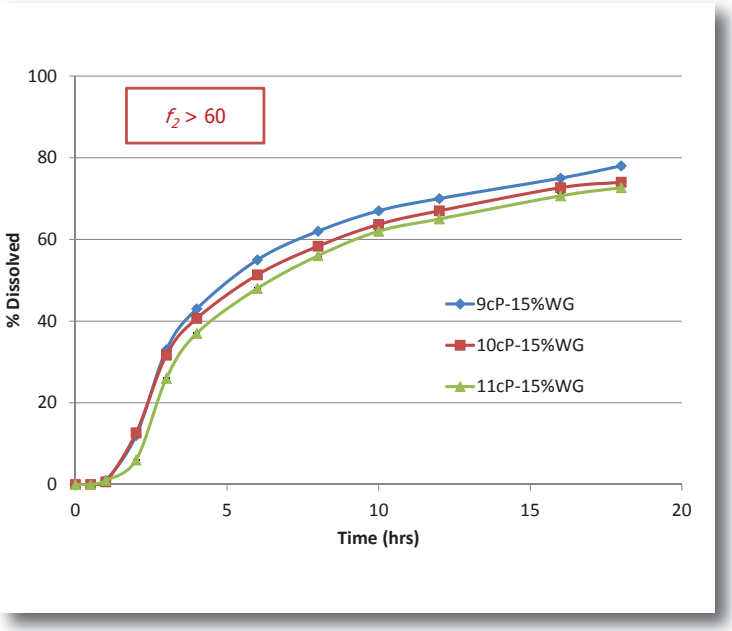


Figure 3: Metoprolol Tartrate Release from ETHOCEL Std. 20 Premium QbD Samples at 5% WG

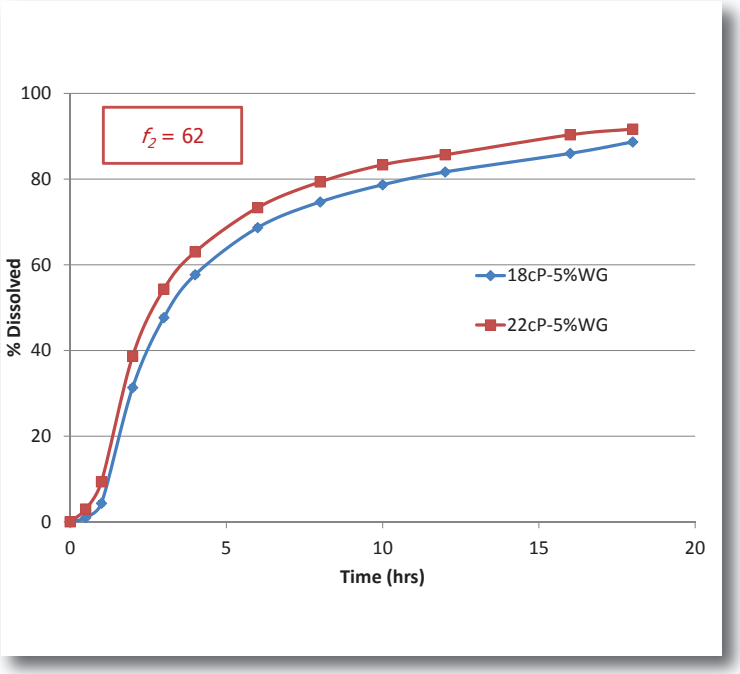
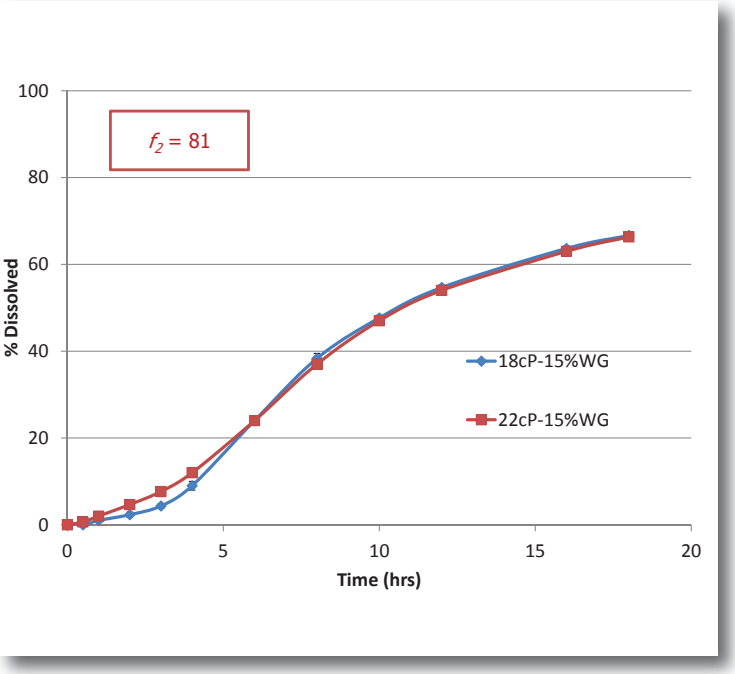


Figure 4: Metoprolol Tartrate Release from ETHOCEL Std. 20 Premium QbD Samples at 15% WG



The drug release f_2 values for 5% WG and 15% WG ETHOCEL Std. 20 Premium samples were 74 and 81, respectively. This indicates there is minimal variability of drug release due to variation of viscosity within the ETHOCEL grade specifications for ETHOCEL Std. 20 Premium.

Application of equivalent coating weight gains of the ETHOCEL Std. 100 QbD Premium samples (90, 100 and 110 cP) provided f_2 >73 and f_2 >53, respectively. The drug release profiles were found to be similar according to the f_2 similarity criteria, but more variability was observed with the higher weight gain sample. ETHOCEL Std. 100 Premium is not generally recommended for ER coating applications. In a previous study[3] with a lower water soluble drug, acetaminophen (APAP), less drug release variability was observed at higher weight gains than in this study.

In all cases, increased weight gain of the ethylcellulose barrier membrane coating resulted in slower drug release, while use of higher viscosity grades resulted in longer initial lag times.

Figure 5: Metoprolol Tartrate Release from ETHOCEL Std. 100 Premium QbD Samples at 5% WG

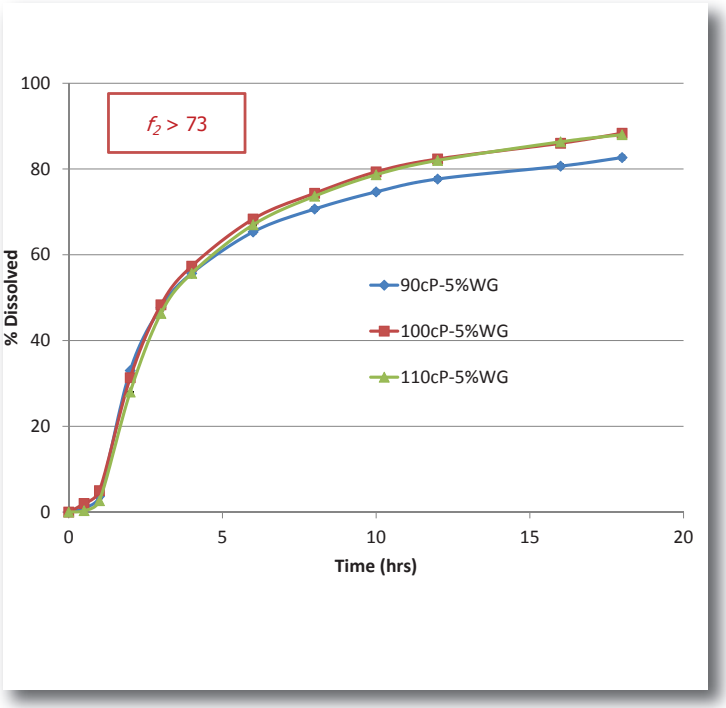
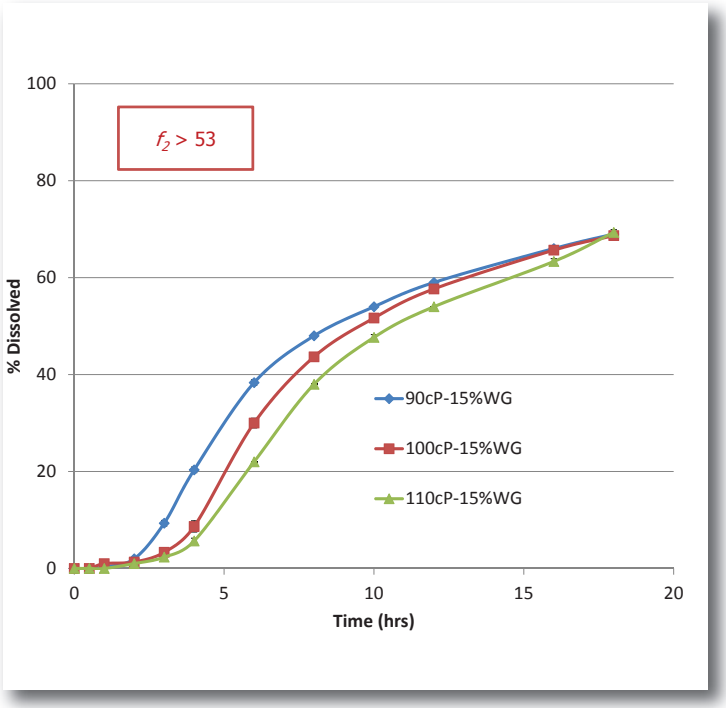


Figure 6: Metoprolol Tartrate Release from ETHOCEL Std. 100 Premium QbD Samples at 15% WG



Conclusions

This study shows that viscosity variation, within the manufacturer's specifications for ETHOCEL Std. 10, 20 and 100 Premium grades, has minimal impact on drug release for ER MPs at both low (5%) and high (15%) weight gains. These results highlight the consistency of the ETHOCEL product and utility of ETHOCEL QbD samples as a means to develop robust ER MP dosage forms.

References

1. ETHOCEL Product Information Brochure, accessed on January 17, 2014 www.colorcon.com
2. Yu LX, Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control. *Pharmaceutical Research*, 2008:25(4): 781-791.
3. Mehta RY, Teckoe J, Schoener C, Workentine S, Rajabi-Siahboomi A, Investigation of the Effect of Ethylcellulose Viscosity Variation Using QbD Sample, on the Acetaminophen Drug Release from Extended Release Multiparticulate. Controlled Release Society Annual Meeting, Chicago, IL, July 2014.

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