Investigation of the Effect of Ethylcellulose Viscosity Variation Using QbD Samples on Drug Release from Extended Release Multiparticulate

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Abstract Summary

Extended release multiparticulates (MP) of acetaminophen (APAP) were prepared using ETHOCEL™ Premium Ethylcellulose Polymers (Dow Chemical Company, USA) as a rate controlling barrier membrane coating polymer. Quality by Design (QbD) samples of ETHOCEL Std. 10, 20 and 100 Premium grades were organically coated onto drug layered APAP MP 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 Std. Premium grades, on in vitro drug release from APAP MP.

Introduction

Due to its excellent barrier properties, safety and global regulatory acceptance, ethylcellulose is a commonly used polymer for extended release (ER) MP formulations.[1] The rate of drug release from ER MP is essentially controlled by the properties of the barrier membrane coating.[2,3] The critical material attributes of ethylcellulose that may influence drug release were considered to be viscosity and ethoxyl substitution. The aim of this study was to evaluate the effect of viscosity variation for ETHOCEL Std. 10, 20 and 100 Premium grades on the drug release from APAP ER MP. Samples of ethylcellulose coated APAP MP were tested at 5% and 15% WG to assess drug release variability.

Experimental Methods

Drug Layering

The composition of the drug layered MP is displayed in Table 1. Uncoated sugar spheres (SUGLETS® #18-20 Colorcon Inc., USA) were coated in an Oyster Huttlin Unilab fluid bed (Huttlin GmbH, Germany) using semi-fine grade of APAP (Mallinckrodt, USA) and HPMC based Opadry® (Colorcon Inc., USA) as a binder. Drug to binder ratio of 50:50 w/w was maintained. The drug layered MP 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. These samples cover the viscosity specification range for each ETHOCEL Std. Premium grade. 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. 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 243 nm. Drug release data for all MP were compared using similarity factor (f_2) analysis.

Table 1. Composition of Drug Layer

Ingredients	Supplier	% w/w
Acetaminophen USP Semi-fine Powder	Covidien, USA	7
850/ 1000 Suglets (Sugar Spheres NF 18/20)	Colorcon,USA	86
Opadry	Coloron, USA	7
Total		100

Table 2. ETHOCEL Sample Information

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 3. ETHOCEL 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/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 for MP coated with ETHOCEL Std. 10 Premium QbD samples are shown in Figures 1 and 2 at 5% and 15% WG, respectively. The (f_2) similarity factor values were f_2 >75 at a 5% WG and f_2 >83 at 15% WG. This indicates there is minimal variability of APAP drug release due to variation of viscosity within the ETHOCEL Std. 10cP Premium grade specification.

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

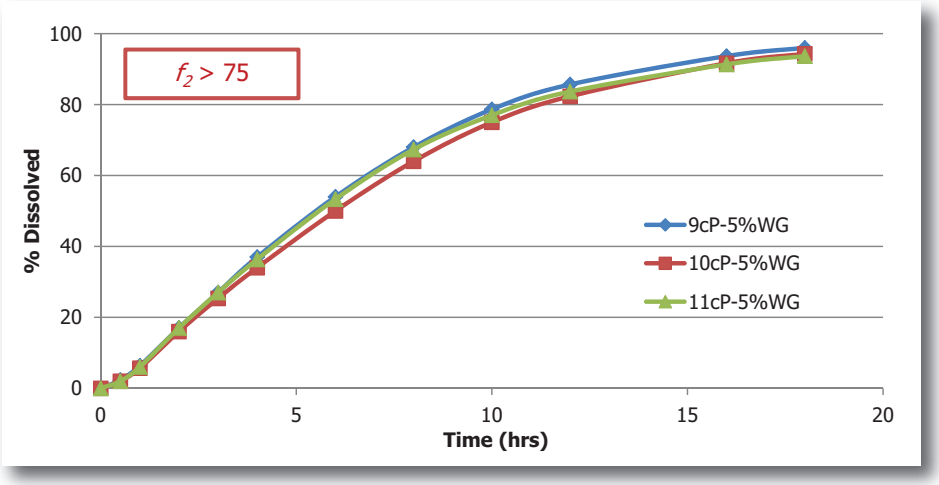
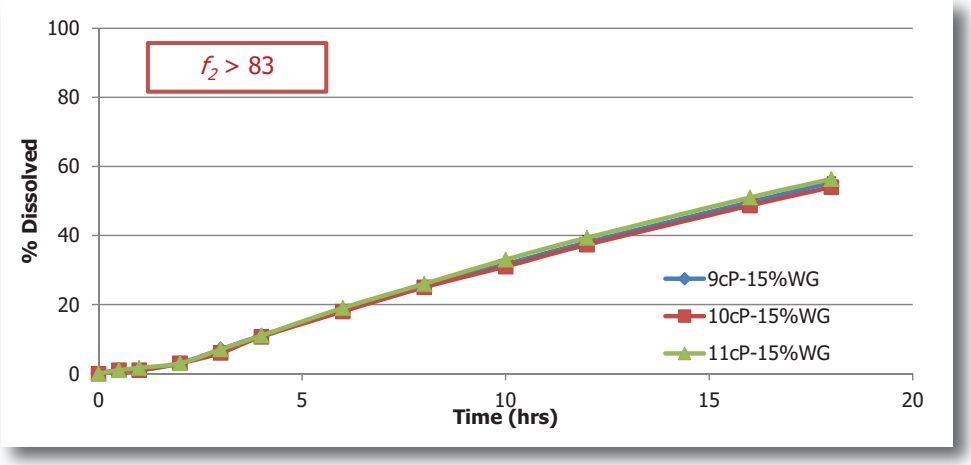


Figure 2: Drug Release from ETHOCEL Std. 10 Premium QbD Samples at 15% WG



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

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

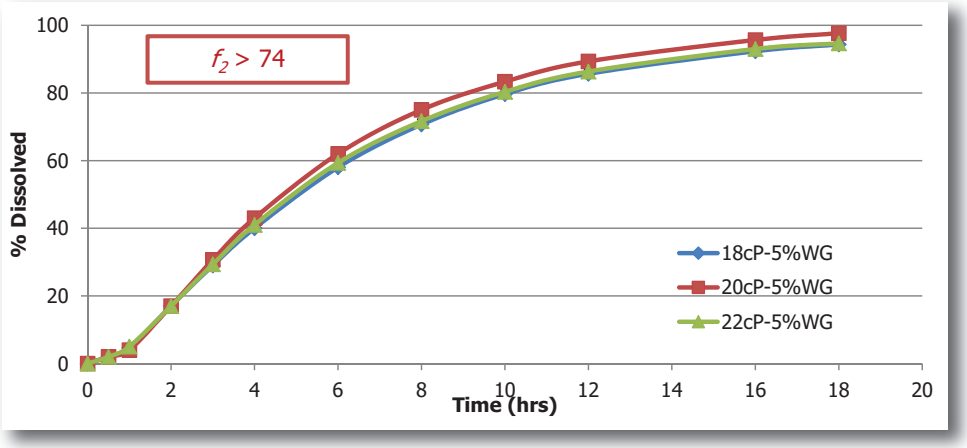
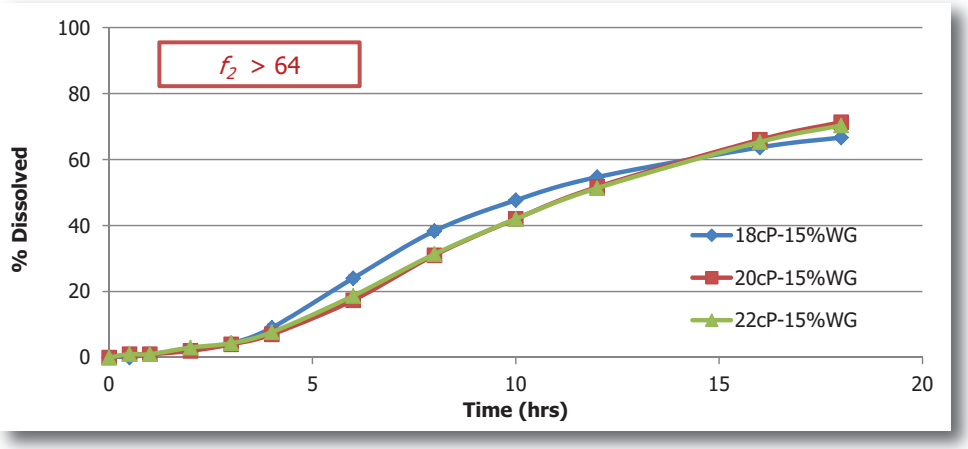


Figure 4: Drug Release from ETHOCEL Std. 20 Premium QbD Samples at 15% WG



The drug release f_2 values for 5% WG and 15% WG ETHOCEL Std. 20 Premium samples were f_2 >74 and f_2 >64 respectively, while the equivalent coating weight gain of the ETHOCEL Std. 100 Premium samples were f_2 >77 and f_2 >70 respectively. This indicates there is minimal variability of APAP drug release due to variation of viscosity within the ETHOCEL grade specifications for both ETHOCEL Std. 20 Premium and ETHOCEL Std. 100 Premium.

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: Drug Release from ETHOCEL Std. 100 Premium QbD Samples at 5% WG

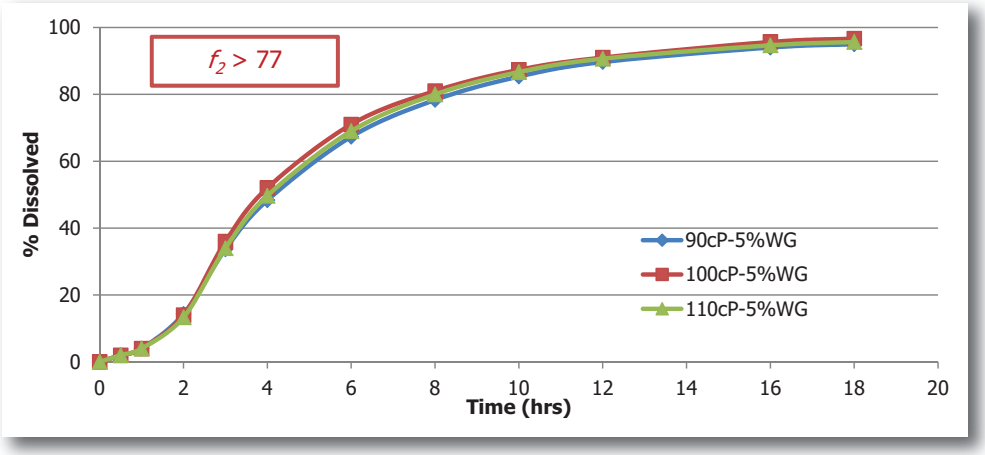
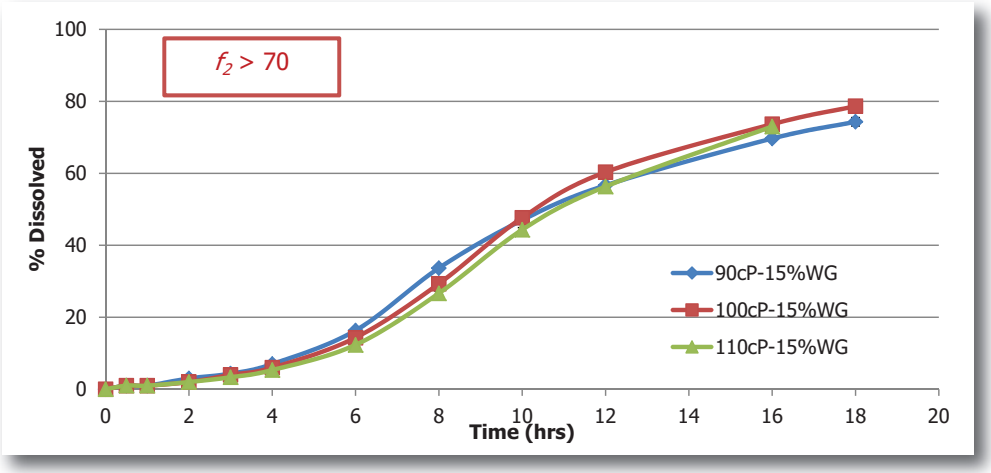


Figure 6: Drug Release from ETHOCEL Std. 100 Premium QbD Samples at 15% WG



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 APAP ER MP 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

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