Evaluation of Various Formulations and Processes on Barrier Membrane Coating of a BCS Class 1 Drug with Aquacoat® ECD-30

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Introduction

Aquacoat® ECD-30 is an aqueous ethyl cellulose pseudolatex dispersion, used for sustained release, taste-masking, and moisture barrier applications. Formulation of the coating dispersion and process parameters used during the coating applications are critical to achieve desired drug release profiles. Selection and levels of pore-former and plasticizer in the formulation, as well as coating weight gain and curing conditions also impact drug release. The purpose of this study was to evaluate the effect of various formulation and process parameters on barrier membrane coated chlorpheniramine maleate (CPM) multiparticulates using Aquacoat® ECD-30.

Methods

Sugar spheres (Suglets® 16/20 mesh size; 841-1190 µm) were used as the base for CPM drug layering, then seal-coated with hypromellose (HPMC) based Opadry® complete film coating system followed by application of Aquacoat® ECD-30 dispersion. Two plasticizers: triethyl citrate (TEC, water-miscible) and dibutyl sebacate (DBS, water-immiscible) were added to the dispersion at 24% w/w concentrations with respect to ethyl cellulose, then mixed for 1 and 24 hours, respectively, using an over-head propeller stirrer at medium speed. Separately, Opadry film coating system (HPMC based) and Opadry QX, quick and flexible film coating system (PVA-PEG graft-copolymer based) were used as pore-former at 15% w/w with respect to the ethylcellulose. The pore-formers were separately mixed with water for 1 hour, added to the pre-plasticized Aquacoat® ECD, and stirred for 20 minutes. The final solids contents of the dispersions, with or without pore-former, were at 15% w/w. The resulting dispersions were screened, through 60 mesh, and applied as barrier membrane coating on seal-coated CPM beads (batch size, 800 g) up to 30% w/w weight gain using a Glatt (GPCG 2) bottom spray fluid bed processor (FBP) fitted with Wurster Column. The processing conditions are shown in Table 1. Samples of coated beads were collected at intermediate weight gains. Beads coated without pore-former at 30% weight gain were cured either in FBP or convection oven (VWR) at 60ºC for a set time range to determine the effect of various curing conditions. Other beads were collected at different weight gains were divided into two groups, one was left uncured, whilst the other group was cured at 60ºC for 2 hours in a convection oven. All samples of coated beads were characterized for particle size distribution and sphericity using Camsizer (Retsch). Assay was tested for all uncured beads at 10, 20 and 30% weight gain. Around 1g (equivalent 32.6 mg of CPM) of coated bead samples were tested for dissolution behavior in 1000 ml DI water at 37ºC using Apparatus I at 100 rpm for 24 h. Samples were collected using an autosampler and analyzed spectrophotometrically at 262 nm.

Table 1: Process Parameters for CPM Bead Coating with Aquacoat® ECD

Coating Process Parameters	Range
Inlet temperature (ºC)	60 - 70
Exhaust temperature (ºC)	37 - 45
Product temperature (ºC)	37 - 45
Air volume (m^3/hr)	65 - 70
Spray rate (g/min)	6 - 15
Average Dew point in (ºC)	10
Atomizing air pressure (bar)	1 - 1.5

Results

The PSD, sphericity, and assay data are presented in Table 2. As expected, higher weight gain resulted in larger size beads. All coated beads showed assay between 99 - 102%, indicating the coating processes were successful. The effect of weight gain on drug release was evaluated for both TEC and DBS containing formulations. As expected, the higher coating weight gain resulted in slower drug release in both formulations (Figure 1). Curing of the coated beads caused a slowdown of drug release for both plasticizers. To evaluate the curing effect, both TEC and DBS formulations were cured using two different conditions (FBP 60°C and convection oven 60°C) (Figure 2). It was clear that oven curing was more effective in reducing drug release, as compared to FBP curing, for both TEC and DBS formulations. For TEC formulations, the oven curing consistently caused slower release than the FBP curing process. For DBS formulations, oven curing caused a slower release during the initial 4 hours. The presence of pore-formers generally increased the rate of drug release; however, the effect was different for TEC and DBS containing formulations (Figure 3). Table 3 shows the amount of drug released at 4 hours dissolution time for uncured and cured samples. The formulation containing TEC as a plasticizer and both pore-formers did not show slowdown of the drug release even at 30% w/w coating weight gain of Aquacoat® ECD-30.

Table 2: PSD, Sphericity and Assay of Uncoated/Coated CPM Beads

	Uncured			Cured		
Formulation	Weight Gain	D50 (µm)	SPHT3*	Assay (%)	D50 (µm)	SPHT3*
Uncoated	0%	949	0.966	101.04	951	0.964
TEC	10%	985	0.971	101.06	994	0.958
	20%	1033	0.971	100.70	1033	0.967
	30%	1078	0.970	100.19	1081	0.968
DBS	10%	988	0.961	100.40	986	0.956
	20%	1040	0.956	100.64	1036	0.943
	30%	1101	0.929	99.57	1097	0.936
TEC-HPMC	10%	987	0.964	101.05	992	0.96
	20%	1033	0.964	101.66	1035	0.964
	30%	1071	0.962	100.88	1077	0.96
TEC-QX	10%	986	0.96	100.52	988	0.956
	20%	1032	0.955	100.25	1030	0.962
	30%	1070	0.964	99.36	1074	0.959
DBS-HPMC	10%	993	0.933	101.20	991	0.947
	20%	1043	0.937	100.94	1046	0.938
	30%	1062	0.948	100.37	1091	0.935
DBS-QX	10%	987	0.943	100.97	994	0.932
	20%	1038	0.918	100.84	1049	0.918
	30%	1090	0.918	100.36	1099	0.924

**SPHT3: Sphericity*

Figure 1: Effect of Weight Gain on CPM Release from BM Coated Beads using Aquacoat® ECD

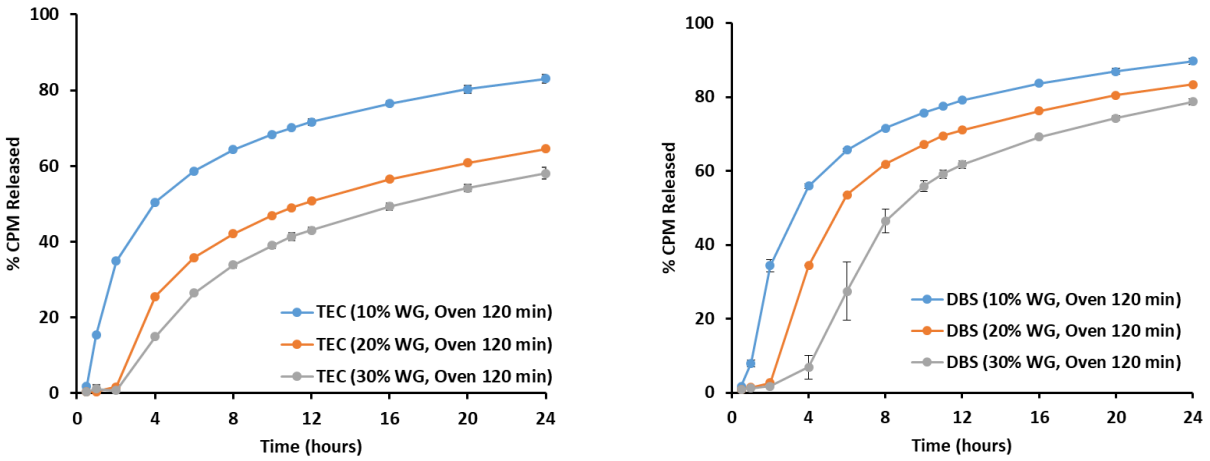

Figure 2: Effect of Curing on CPM Release from BM Coated Beads using Aquacoat® ECD

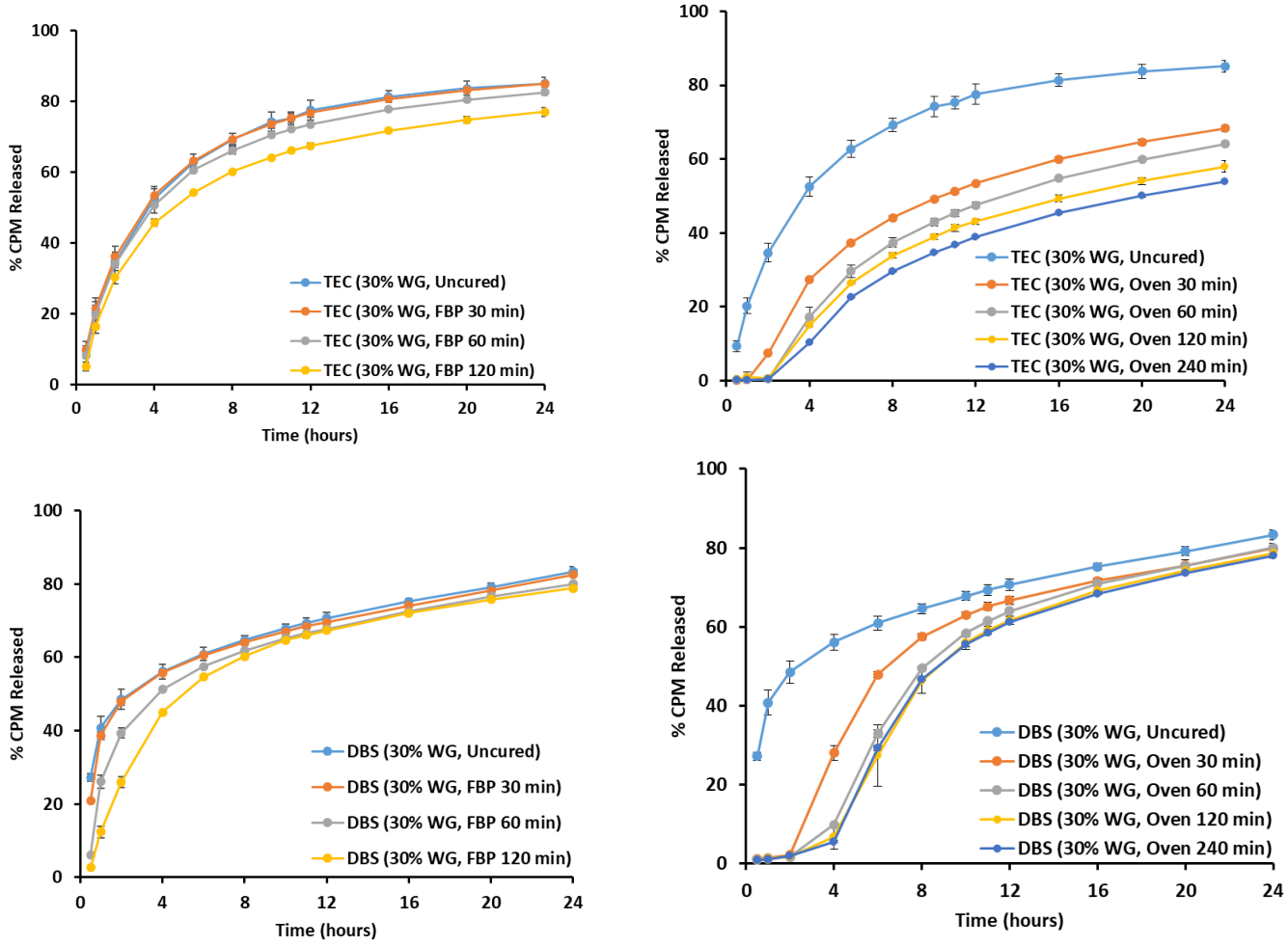

Figure 3: Effect of Type of Plasticizers and Pore-Formers on CPM Release from BM Coated Beads using Aquacoat® ECD

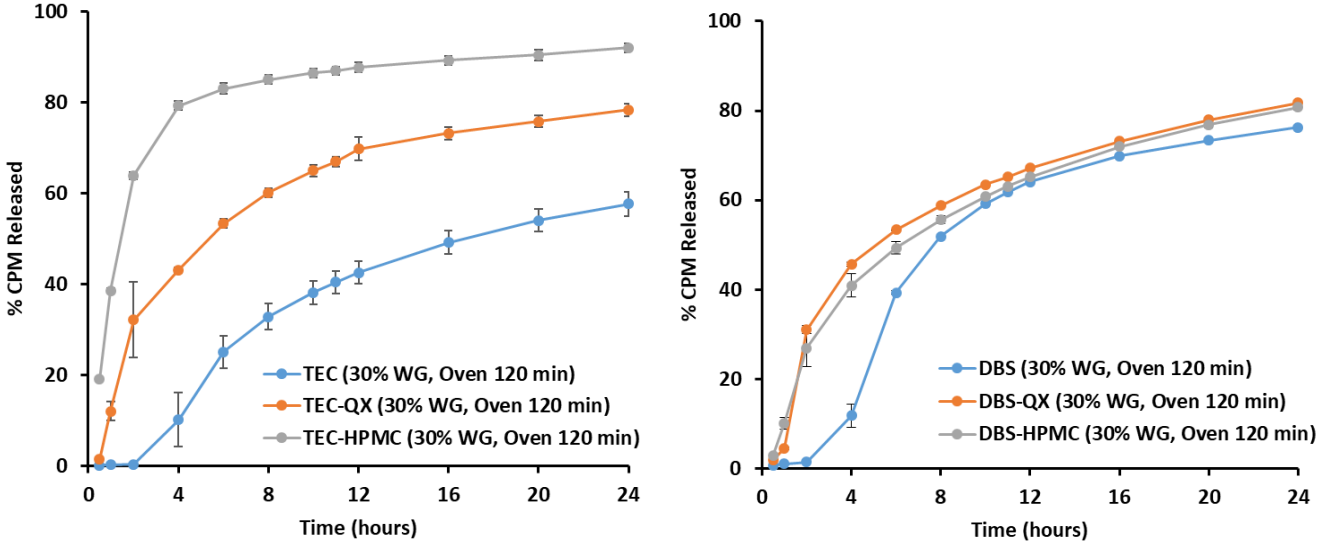

Table 3: Reduction in Drug Release at 4 hours for Uncured and Cured (Oven 120 min) CPM Beads, BM Coated with Aquacoat® ECD

% CPM Released at 4 hours						
Formulation	**10% WG**		**20% WG**		**30% WG**	
	Uncured	**Cured**	**Uncured**	**Cured**	**Uncured**	**Cured**
24% TEC (at 24%) without pore-former	97.14	50.37	79.31	25.56	52.59	14.96
24% DBS (at 24%) without pore-former	70.76	55.89	62.28	34.41	56.11	6.86
24% TEC + 15 % Opadry QX as pore-former	100.02	87.37	92.19	61.65	87.32	43.11
24% DBS + 15 % Opadry QX as pore-former	97.79	66.57	86.81	49.90	77.99	45.62
24% TEC + 15% Opadry (HPMC based) as pore-former	100.13	97.04	94.96	88.50	89.97	79.31
24% DBS + 15% Opadry (HPMC based) as pore-former	98.06	68.88	89.79	33.97	85.31	40.88

Conclusions

Aquacoat® ECD is a flexible aqueous barrier membrane coating used to achieve extended drug release formulations. In this study, the use of water-miscible or water-immiscible plasticizers on CPM (BCS class I drug) did not result in a significant difference in drug release for uncured coated beads. However, when coated beads were cured, slower drug release was found with both plasticizers (more significant with TEC). Curing was required to achieve the required sustained release drug profile. The type of pore-former and plasticizer influenced drug release profiles.