Effect of Coating Weight Gain and Pore-Former Level on Drug Release with a Fully Formulated Ethylcellulose Barrier Membrane Coating System

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Purpose

Ethylcellulose is commonly used in the barrier membrane coating of extended release (ER) multiparticulates and taste-masking applications, which can be applied as a pseudolatex dispersion in aqueous media or as a solution in organic solvents. Drug release profiles from ethylcellulose coated multiparticulates can be modified by altering the membrane permeability through the inclusion of soluble pore-formers. A new fully formulated ethylcellulose barrier membrane coating system has been developed that incorporates a soluble pore-former and allows formulators to tailor drug release profiles.

Modifying the pore-former type and level in an aqueous coating system utilizing ethylcellulose as the rate controlling polymer was previously shown to modulate release of a poorly water-soluble drug.[1] The purpose of this work was to investigate the effects of coating weight gain (% WG) and level of pore-former in Opadry EC on drug release from multiparticulates comprising a freely soluble (250 mg/ml) or slightly soluble (8.3 mg/ml) model drug (chlorpheniramine maleate [CPM] or theophylline, respectively).

Methods

Preparation of Extended Release Multiparticulates

Drug layered sugar spheres (Suglets®, Colorcon Inc, USA) comprising either CPM (30 mg/g dose) or theophylline (70 mg/g dose) were used as the multiparticulate coating substrates. Using an overhead laboratory mixer, Opadry EC powders were dispersed into hydro-alcoholic co-solvent mixtures composed of either 90% w/w isopropanol with 10% w/w water for CPM, or 90% w/w ethanol with 10% w/w water for theophylline. After stirring for 45 minutes, the soluble components of the coating dispersions were fully dissolved. The dispersions were applied to the drug loaded spheres using lab-scale fluidized bed (Wurster) spray coating equipment and appropriate process parameters, as listed in Table 1. CPM spheres were coated with Opadry EC formulations prepared at 6% solids concentration with either a high (21% w/w) level of hypromellose (HPMC, 2910, 6 mPa·s) as a pore-former, or none. The CPM batches were coated to a theoretical weight gain of 14%, with in-process samples also taken at 6% and 10% WG. The theophylline batches were coated to 12% WG with formulations prepared at 8% solids concentration and having either an intermediate (18% w/w) or high (21% w/w) level of HPMC (2910, 6 mPa·s) as a pore-former.

Table 1. Coating Process Parameters

Drug	CPM	Theophylline
Batch size (kg)	0.75	0.80
Suglets grade / size range (micron)	PF011 / 850 - 1000	PF010 / 710 - 850
Coating Equipment	Glatt GPCG 2	Freund-Vector VFC LAB-1
Inlet Temp. (°C)	43	48
Exhaust Temp. (°C)	28	33
Product Temp. (°C)	30	33
Air velocity (CFM)	45	75
Atomization pressure (bar)	1.2	2.0
Fluid delivery rate (g/min)	8.0	9.0

Dissolution Testing

Dissolution testing of the CPM coated spheres was conducted (n=3) in deionized (DI) water using USP Apparatus I at 100 rpm with drug release measured spectrophotometrically at a wavelength of 262 nm. Drug release from the theophylline coated spheres was measured (n=4) at 272 nm in DI water using USP Apparatus I at 50 rpm. The f_2 similarity factor, a mathematical parameter used to quantify the similarity or difference of release profiles, was used to evaluate the effects of varying % WG and pore-former level on drug release.[2]

Results

Chlorpheniramine Maleate (CPM)

The release profiles from the coated CPM spheres were highly influenced by coating % WG (Figures 1 and 2). Increasing the applied % WG of barrier membrane, with and without HPMC pore-former, resulted in large reductions in CPM release rates and delayed the onset of initial release (lag time). CPM release rates were also influenced by the presence of HPMC pore-former in the barrier membrane. Release profiles from the formulations with high levels or no pore-former were determined to be dissimilar (f_2 < 46) when applied at equivalent %WG, and for each sequential 4% increase in weight gain. The time to reach 20%, 50% and 80% CPM release (T20, T50, T80) increased significantly for both barrier membrane formulations (Table 2).

Figure 1. CPM Release Profiles at 6%, 10% and 14% WG, with High Pore-Former Level

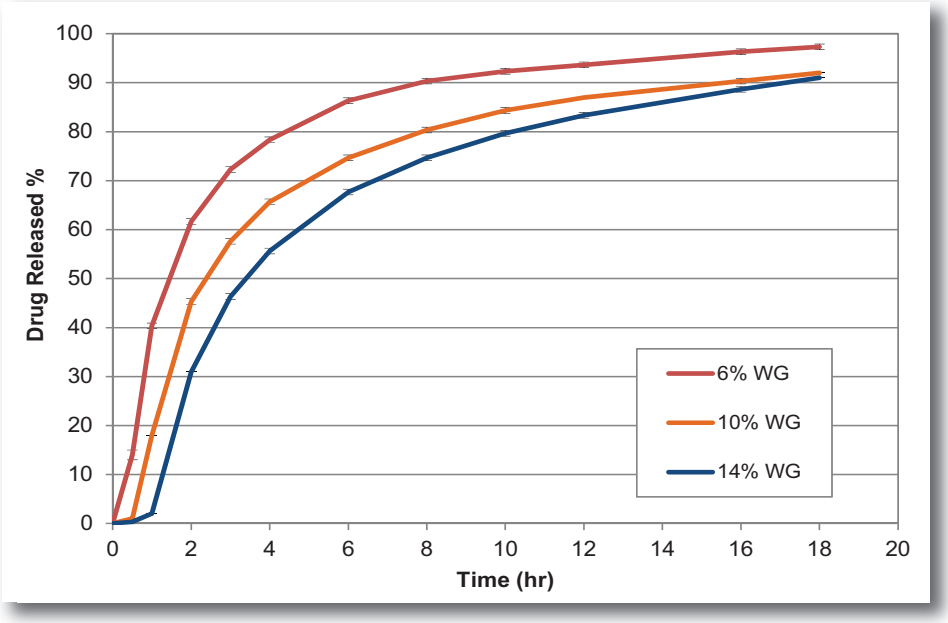

Figure 2. CPM Release Profiles at 6%, 10% and 14% WG, without Pore-Former

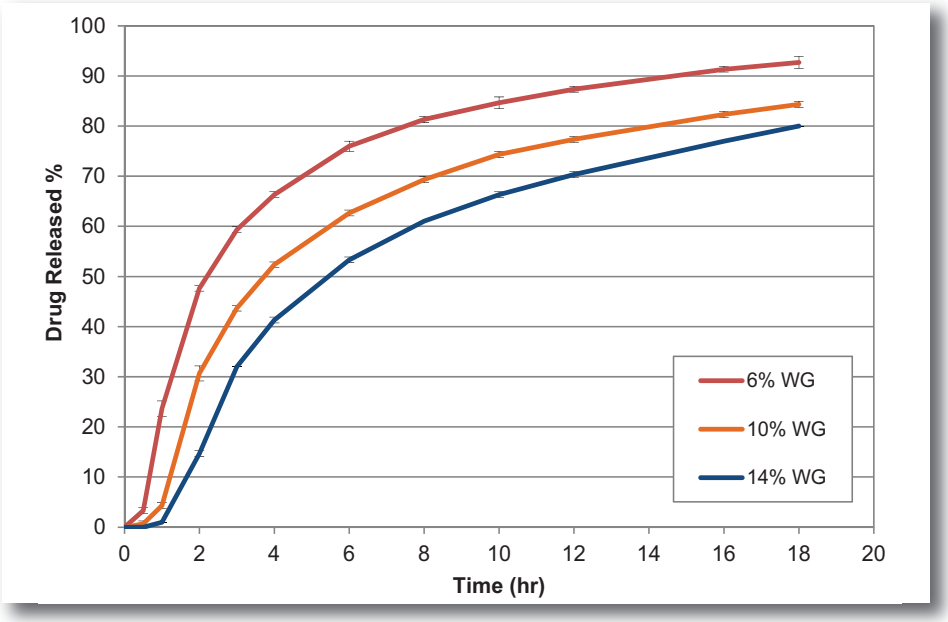

Table 2. Time to Reach 20%, 50% and 80% Dissolved for CPM Spheres at Various Levels of WG and Pore-Former Content

Time (hr) to reach:	CPM					
	No Pore-Former			High Pore-Former		
	6% WG	10% WG	14% WG	6% WG	10% WG	14% WG
T20	0.9	1.6	2.3	0.6	1.1	1.6
T50	2.2	3.7	5.4	1.5	2.4	3.4
T80	7.5	14.1	18.0	4.4	7.9	10.2

Theophylline

The influence of barrier membrane pore-former level on drug release profiles was also observed with the coated theophylline spheres (Figure 3). The intermediate pore-former formulation provided 170% - 195% greater T20 and T50 values compared to the high pore-former level (Table 3). In addition to the slower overall release profiles, the intermediate pore-former formulation had a linear (R^2=0.993) zero order release profile, providing a constant rate of drug release from 1-12 hours.

Figure 3. Effect of Pore-Former Level on Theophylline Release Profiles

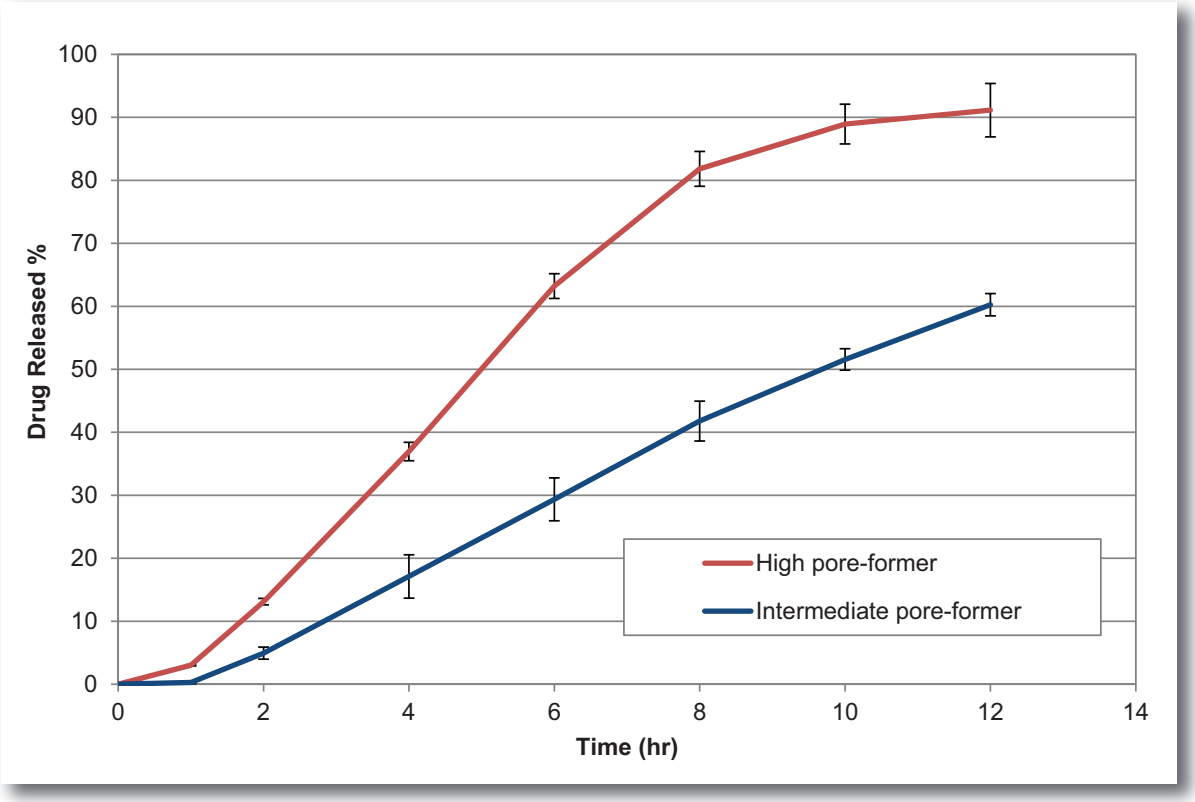

Table 3. Time to Reach 20%, 50% and 80% Dissolved for Theophylline Spheres with Intermediate and High Pore-Former Levels

Time (hr) to reach:	Theophylline	
	Intermediate Pore-Former	High Pore-Former
T20	4.5	2.6
T50	9.7	5.0
T80	15.4 (extrapolated)	7.8

Conclusions

A fully formulated ethylcellulose system, Opadry EC enabled a range of release profiles to be obtained for multiparticulates comprising either a freely soluble or a slightly soluble model drug. Adjusting the pore-former content and the applied coating weight gain modified the barrier membrane porosity and thickness and allowed a range of release profiles to be achieved. These results indicated that Opadry EC could offer fast formulation screening during development and enable flexibility to tailor release profiles for drugs with different aqueous solubility.

References

1. The Influence of Hydrophilic Pore-Formers on Dipyridamole Release from Aqueous Ethylcellulose Film-Coated Pellets. Dasha Palmer, Hue Vuong, Marina Levina and Ali R. Rajabi-Siahboomi, AAPS Annual Meeting 2007, San Diego, CA USA.
2. Moore JW and Flanner HH. Mathematical comparison of curves with an emphasis on in vitro dissolution profiles. Pharm. Tech. 1996;20(6): 64-74.

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