Compositional and Performance Stability of a Fully Formulated Ethylcellulose Barrier Membrane Coating System

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Purpose

The extended release (ER) performance of barrier membrane coated multiparticulates is determined by the concentration of the release controlling components of the coating, such as film forming polymers, pore-formers and plasticizers. Ensuring the compositional stability of coating formulations is a key factor in achieving consistent performance over time from multiparticulate dosage forms. The purpose of this work was to investigate the compositional stability and controlled release performance of Opadry® EC, ethylcellulose organic coating system, under intermediate and accelerated storage conditions for 6 months. The study evaluated the stability of the functional components of the formulation and drug release performance over time for the barrier membrane formulation in powder form, as well as coated multiparticulates comprising chlorpheniramine maleate (CPM) as a model drug.

Methods

Ethylcellulose (EC) barrier membrane coating formulations comprising hypromellose (HPMC) as pore-former, at two concentrations (0% and 40% with respect to EC) with triethyl citrate (TEC) as a plasticizer, were subjected to intermediate and accelerated stability conditions in both powdered form and after application to drug-layered sugar spheres (Suglets® PF011) comprising 30 mg/g CPM. Formulated Opadry EC powders were stored in commercial packaging at 30°C/65% RH and 40°C/75% RH and periodically tested using a gas chromatograph (Model 6890, Hewlett Packard, USA) to investigate whether changes were occurring in the polymer, plasticizer or pore-former concentrations over time. Aged powders were then dispersed in a hydroalcoholic co-solvent system (90% w/w isopropanol, 10% w/w water) and applied to the CPM spheres at 10% weight gain with lab-scale fluidized bed (Wurster) coating equipment using the process parameters shown in Table 1. Another study, conducted concurrently, evaluated the release performance of the finished dosage forms (identically coated CPM spheres) stored for 6 months at 30°C/65% RH and 40°C/75% RH and packaged in induction-sealed HDPE bottles with desiccant.

Table 1. Coating Process Parameters

Drug	CPM
Batch size (kg)	0.75
Suglets grade / size range (micron)	PF011 / 850 - 1000
Coating equipment	Glatt GPCG 2
Inlet temp. (°C)	40 - 43
Exhaust temp. (°C)	28 - 29
Product temp. (°C)	29 - 30
Air velocity (CFM)	45
Atomization pressure (bar)	1.2
Fluid delivery rate (g/min)	6.5 – 8.0

Dissolution Testing

Dissolution testing was conducted on all coated multiparticulates in deionized water using USP Apparatus I (basket) at 100 rpm and release profiles were measured spectrophotometrically at a wavelength of 262 nm. The f_2 similarity factor was used to evaluate the effects of varying coating weight gain and pore-former level on drug release, with values greater than 50 indicating similar release to the initial reference profile.[1]

Results

The concentrations of polymer, plasticizer and pore-former (where applicable) of both barrier membrane formulations in powder form were found to be stable after 6 months of storage at 30°C/65% RH and 40°C/75% RH (Table 2). The values shown are the percentage change of experimentally measured total ethoxyl, methoxyl and TEC contents of the powder formulations compared to the initial measurement conducted at the initial time point. Over time, no trends were observed that would indicate any changes were occurring in the composition of the functional components (EC, HPMC and TEC) through degradation or physical segregation within the blend. Stable values were observed in the data for both storage conditions, and percent change deviations were the result of natural variability in powder sampling and experimental methodology.

The controlled release performance of CPM spheres coated with aged Opadry EC formulations was found to be stable regardless of powder storage condition (Figure 1). Through 6 months of storage, no change was observed in the initial lag times or the overall release profiles for both coating formulations and f_2 values were greater than 85 when compared to the initial reference profile. The consistent performance was likewise observed from the finished coated dosage forms stored under intermediate and accelerated conditions, with no impact of storage condition or duration on initial lag times or overall drug release profiles (Figure 2).

Table 2. Measured Absolute Percent Change (Δ) of Functional Components in Aged Powders Stored for 6M at 30°C/65% RH and 40°C/75% RH

Storage Condition	Pore-former Level (% of EC)	Δ Ethoxyl (%)	Δ Methoxyl (%)	Δ TEC (%)
30°C/65% RH	0	-1.5	N/A	4.0
	40	-0.7	-0.9	0.0
40°C/75% RH	0	-0.8	N/A	5.3
	40	0.3	3.4	2.6

Figure 1. Release Performance of Multiparticulate Dosage Forms Coated with Aged Powders Stored for 6M at 30°C/65% RH and 40°C/75% RH

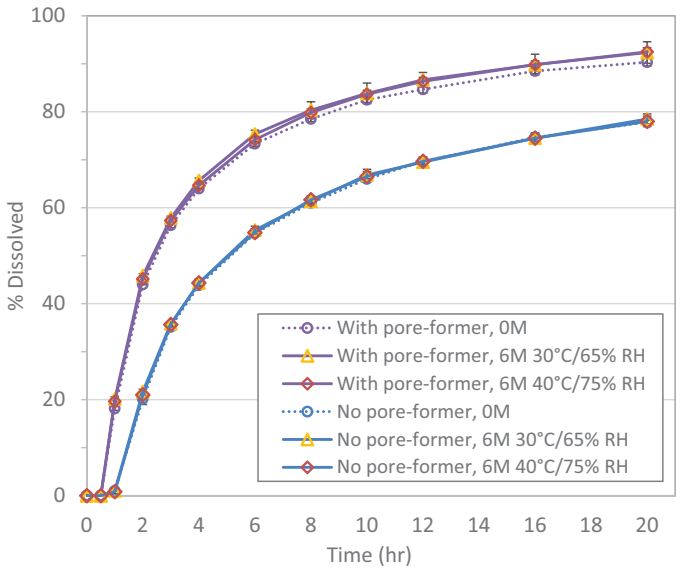

Figure 2. Release Performance of Aged Coated Multiparticulate Dosage Forms Stored for 6M at 30°C/65% RH and 40°C/75% RH

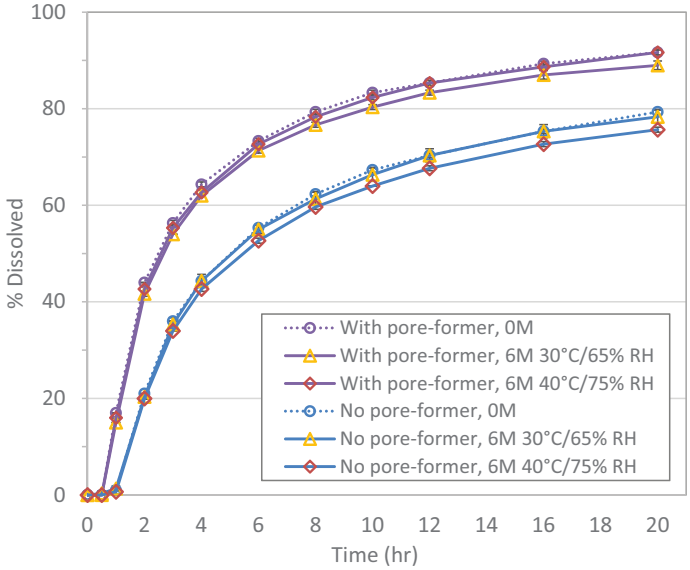

Table 3. Similarity Factor (f_2; 0M reference) Values for Release Profiles of Aged Powders and Coated Spheres Stored for 6M at 30°C/65% RH and 40°C/75% RH

Pore-former Level (as % of EC)	Storage Condition	Sample Type	f_2 Value (6M Release Profile vs. Initial)
0	30°C/65% RH	Powder	96
		Coated spheres	96
	40°C/75% RH	Powder	98
		Coated spheres	80
40	30°C/65% RH	Powder	85
		Coated spheres	81
	40°C/75% RH	Powder	91
		Coated spheres	93

Conclusions

Measurement of polymer, pore-former and plasticizer concentrations over time indicated that the Opadry EC formulations were compositionally stable following 6 months accelerated storage stability testing. In addition, the release profiles of drug-layered multiparticulates coated with the stability study powders were consistent regardless of powder storage condition or storage duration. Finally, consistent drug release was obtained from Opadry EC coated multiparticulates stored under intermediate and accelerated storage conditions for 6 months. These results demonstrate the stability of the Opadry EC coating formulation and the drug release performance it provides over time.

References

1. Moore, J.W. and Flanner, H.H. Mathematical comparison of curves with an emphasis on in vitro dissolution profiles. *Pharm. Tech.* 20(6),1996, 64-74.

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