Investigation of Cellulose Acetate Polymer Viscosity and Coating Solution Concentration on Performance of Push-Pull Osmotic Pump (PPOP) Tablets

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Abstract Summary

This study investigated the effect of cellulose acetate (CA) viscosity and coating solution concentration (solids content) on the properties of Opadry® CA ready formulated osmotic coating system and performance of push-pull osmotic pump (PPOP) tablets. Variations in solids content of the coating solutions significantly impacted solution viscosity and film opacity but did not affect drug release profiles. Variations in cellulose acetate viscosity grade did not affect the viscosity of the coating solutions or the performance of PPOP tablets.

Introduction

Cellulose acetate has been commonly used as the water-insoluble, semipermeable membrane (SPM) in osmotic dosage development. Polyethylene glycol (PEG) 3350 is the most commonly used plasticizer and/or pore-former in SPMs. These two components are typically dissolved in a co-solvent mix of acetone/water and prepared in a range of solution concentrations. Varying the relative amounts of CA and PEG in the film coating influences the permeability of the film, changing the rate of media ingress into the core and potentially altering drug release rate.[1]

This study investigated whether variations in cellulose acetate viscosity or coating solution concentration can influence the performance of PPOP tablets, in terms of drug release profiles and coating quality.

Experimental Methods

Opadry® CA, a ready formulated SPM coating system comprising CA and PEG3350, was used in this study with a co-solvent mixture of acetone (90% w/w) and water (10% w/w) for coating solution preparation. An experimental design with 2 variables, at 3 levels, for a total of 9 coating trials (Table 1) was used. CA grades with low, medium and high range of the product viscosity specification were examined, and coating solutions were prepared at low, medium and high solids content. Coating solutions were applied to bilayer tablets containing a low dose (10 mg) and practically insoluble model drug. Solution viscosity was measured using a rheometer with concentric cylinder geometry (AR-G2, TA Instruments, USA). Pull and push layer formulations (Table 2)[2] were produced using a high-shear, hydro-alcoholic granulation process (P/VAC-10, Diosna, Germany) (1.5 kg batch size). The granules were lubricated and compressed into bilayer tablets using an instrumented rotary press (Piccola, Riva, Argentina) with standard round concave tooling (9.5 mm) at the target weight of 330 mg (pull:push layer, ~2:1 w/w). The Opadry CA solutions were coated onto the bilayer tablets to a theoretical weight gain of 10% w/w using a 2.5 L side-vented coating pan (LDCS, Vector, USA). The coating parameters are listed in Table 3. Coated tablets were dried in a vacuum oven at 40°C for 24 hours. A 0.5 mm delivery orifice was laser-drilled (Cobalt 250, InkCupsNow, USA) through the film coating on the pull layer side of each PPOP tablet.

Opadry CA film coating opacity was determined by measuring the contrast ratio of coatings removed from flat-faced tablets, on black and white backgrounds using a spectrophotometer (Model 600, Datacolor, USA) at the wavelength range of 400 – 700 nm. Dissolution studies were conducted in simulated intestinal fluid (SIF) at pH 7.5 without enzymes, using USP Apparatus II with sinkers at 50 rpm. Drug release profiles were measured spectrophotometrically (Agilent Technologies, USA) using 10 mm path length quartz flow-through cells. The drug release rate constant k, (%/hour) was obtained by calculating the slope of the linear section of the dissolution profiles in the range of 5-80% of drug release. The morphology of the SPM was examined using a Hitachi Field Emission Scanning Electron Microscopy (FE-SEM) (vs4300, Hitachi High-Tech, Japan).

Table 1. Experimental Design

Variables	Level		
	Low	Medium	High
CA viscosity (sec.[a])	8.3	10.5	12.5
Solids content (% w/w)	5.5	7.0	8.5

[a] Specification: 8.0 s to 13.0 s (ASTM-A falling ball viscosity).

Table 2. Formulation of Pull and Push Layers for PPOP Tablets of Model Drug Y

Pull Layer – Ingredients	Supplier	Quantity (%w/w)
Drug Y	-	5.6
Polyethylene oxide (POLYOX™ WSR N-80)	International Flavors and Fragrances Inc., USA	93.9
Magnesium stearate	Mallinckrodt, USA	0.5
Total		**100**
Push Layer – Ingredients	**Supplier**	**Quantity (%w/w)**
Polyethylene oxide (POLYOX™ WSR Coagulant)	International Flavors and Fragrances Inc., USA	64.0
Sodium chloride	Mallinckrodt, USA	35.0
Pigment, red iron oxide	Rockwood Pigments, Italy	0.5
Magnesium stearate	Mallinckrodt, USA	0.5
Total		**100**

Table 3. Coating Process Parameters

Parameters	
Inlet temperature (°C)	41 - 43
Exhaust temperature (°C)	31 - 32
Product temperature (°C)	27 - 28
Airflow (cfm)	80
Fluid delivery rate (g/min)	28 - 30
Atomizing air pressure (psi)	21.0
Pattern air pressure (psi)	7.5
Pan speed (rpm)	18
Batch size (kg)	1.5

Results and Discussion

Solution Viscosity

Samples of CA within viscosity specification (low, medium and high) had no significant impact on coating solution viscosity (Figure 1) in this study. However, increasing the solution concentration from 5.5 to 8.5% w/w resulted in large increases in solution viscosity. Opadry CA coating solutions showed the behavior of Newtonian fluids, where the viscosity was generally independent of shear rate.

Figure 1. Viscosity of Coating Solutions

Drug Release Profiles

Similar zero order drug release profiles (f_2 = 64-98) were obtained for Opadry CA formulations evaluated in this study, and the release constant (k) was in the range of 7.3-8.2 %/hour (R^2 = 1.0) (Figure 2). The linear regression model was applied to examine the relationship between release constant (k) and polymer viscosity/solids content, and the results indicated a statistically insignificant relationship. Therefore, variations in either CA viscosity or coating solution concentration had minimal influence on the rate of drug release from the PPOP tablets.

Figure 2. Dissolution Profiles of PPOP Tablets

Dissolution condition: SIF pH 7.5, Apparatus II, 50 rpm (k, rate constant, %/hr).

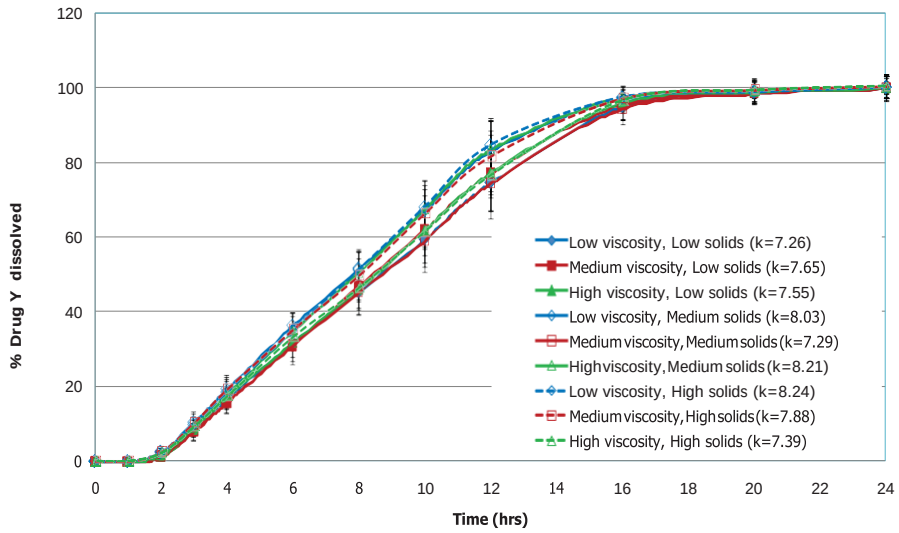
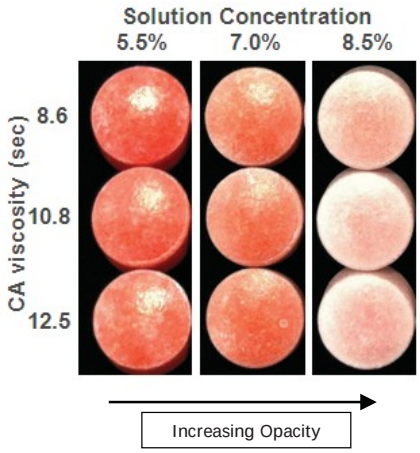


Figure 3. Appearance of PPOP Tablets: Push Layer Side at Varying Polymer Viscosity and Solution Concentration



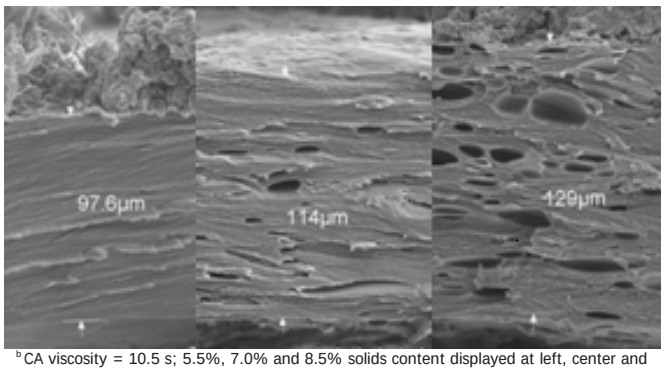
Coating Quality

Opadry CA film coatings became more opaque with increasing solution concentration from 5.5% to 8.5% w/w (Figure 3). A similar trend was observed through spectrophotometric opacity measurement (Figure 4).

SEM images confirmed that increases in film opacity were a result of greater porosity in films formed from the coating solutions of higher concentration (Figure 5). Although all 9 coating trials had similar yields (≥95%), the more porous films were found to be thicker (129 μm vs. 98 μm) and, therefore, could be expected to have longer diffusion paths.

Figure 4. Opacity of Semipermeable Membranes

Figure 5. . SEM Images of SPM Coated onto Bilayer Tablets at Varying Solution Concentrations[b]



[b] CA viscosity = 10.5 s; 5.5%, 7.0% and 8.5% solids content displayed at left, center and right, respectively.

Conclusions

Variations in CA viscosity, or solution concentration, had no significant effect on the drug release profiles from PPOP tablets coated with Opadry CA system, indicating the robustness of PPOP dosage forms. However, the solids content of coating solutions impacted the film opacity, an important quality attribute of PPOP tablets. This evaluation identifies the critical material attributes and process parameters for future consideration on the development of osmotic pumps coated with Opadry CA.

References

1. Malaterrea,V, Ogorka,J, Loggia N, et al. Approach to design push–pull osmotic pumps. *Int J Pharm.* 2009 Jul 6;376(1-2):56-62
2. Patel P, Liu Q, Missaghi S, et al. Effect of Semipermeable Coating Composition and Opadry® Top-Coating Systems on Performance of Push-Pull Osmotic Pump Tablets of a Practically Water Insoluble Model Drug. AAPS annual meeting and exposition, 2011.

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