The Influence of Cellulose Acetate Weight Gain and Solvent Ratio on Performance of Push-Pull Osmotic Pump Tablets

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Abstract Summary

This study evaluated the effect of Opadry® CA ready formulated osmotic coating system weight gain and solvent ratio on the properties of push-pull osmotic pump (PPOP) tablets. Opadry CA, a semipermeable membrane (SPM) coating system comprising cellulose acetate (CA) and polyethylene glycol 3350 (PEG) was used in this study. The SPM film coating was applied onto bilayer tablets containing a practically insoluble API at a low dose (10 mg) level. Study results showed that increasing film coating weight gain significantly impacted the film coating thickness and drug release profiles. However, the variation in co-solvent mixture had no significant effect on the overall properties of PPOP tablets.

Introduction

Cellulose acetate (CA-398-10, Eastman Chemical Company, USA) is the water insoluble film former for SPMs in osmotic dosage forms, with PEG 3350 the most commonly used plasticizer and/or pore-former. These two components are dissolved in acetone and water mixtures at various solids contents. The permeability of CA films could influence the ingress of dissolution media into the cores, resulting in different drug release rates.[1]

The purpose of this study was to investigate the effect of preparation and weight gain of Opadry CA, a ready formulated CA based coating system, on the performance of PPOP tablets. The drug release profiles and film properties were discussed in this study.

Experimental Methods

Coating solutions were prepared by directly adding Opadry CA to acetone-water mixtures at ratios of 94:6 or 90:10 w/w, with the clear to hazy solutions ready to use within 45 minutes of preparation. Pull and push layer formulations (Table 1), were produced (1.5 kg batch size) using a high-shear, hydro-alcoholic granulation process[2] (Diosna P/VAC 10, Diosna, Germany). The granules were lubricated and compressed into bilayer tablets on an instrumented rotary press (Piccola, Riva, Argentina) using standard, round, concave tooling (9.5 mm) at the target weight of 330 mg (pull:push layer, ~2:1 w/w). The coating solution (7.0% solids w/w) was applied onto the bilayer tablets, using a 2.5 L side-vented coating pan (Vector Hi-Coater LDCS, Vector, USA), to a target weight gain in the range of 5.5-14.0% w/w; coating parameters are shown in Table 2. Coated tablets were then dried in a vacuum oven at 40°C for 24 hours. A 0.5 mm delivery orifice was laser-drilled (Cobalt 250, InkCupsNow, USA) on the pull layer side of PPOP tablets.

The percent yield was determined using the following equation:

$$\%\text{Yield} = 100 \times (WG_a / WG_t)$$

where WG_a is the actual weight gain and WG_t the theoretical weight gain.

Dissolution studies were conducted using USP apparatus II with sinkers at 50 rpm in simulated intestinal fluid (SIF) at pH 7.5, without enzymes. Drug release was measured using a UV-Visible spectrophotometer (Agilent Technologies, USA) fitted with 10 mm path length quartz flow cells. The similarity factor (f_2) was calculated by comparing two dissolution profiles. 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 coating thickness was measured on the cross-section of semipermeable membranes using a Hitachi Field Emission Scanning Electron Microscopy (FE-SEM) (vs4300, Hitachi High-Tech, Japan).

Table 1. 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)	The Dow Chemical Company, USA	93.9
Magnesium stearate	Mallinckrodt, USA	0.5
Total		**100**
Push Layer – Ingredients	**Supplier**	**Quantity (%w/w)**
Polyethylene oxide (POLYOX™ WSR Coagulant)	The Dow Chemical Company, 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 2. Coating Process Parameters

Parameters	
Inlet temperature (°C)	41 - 43
Exhaust temperature (°C)	30 - 33
Product temperature (°C)	26 - 29
Airflow (cfm / m^3/hr)	80 / 136
Fluid delivery rate (g/min)	29 - 30
Atomizing air pressure (psi / bar)	21.0 / 1.4
Pattern air pressure (psi / bar)	7.5 / 0.5
Pan speed (rpm)	18
Batch size (kg)	1.5

Results and Discussion

Film Coating Yield

Figure 1 shows good coating efficiency (yield > 90%) achieved at an applied weight gain of 7.5% or higher. Applying the coating process parameters in Table 2, the use of an acetone:water ratio of 94:6 w/w gave slightly better yields.

Figure 1. Percent Yield of CA Coatings (n=18)

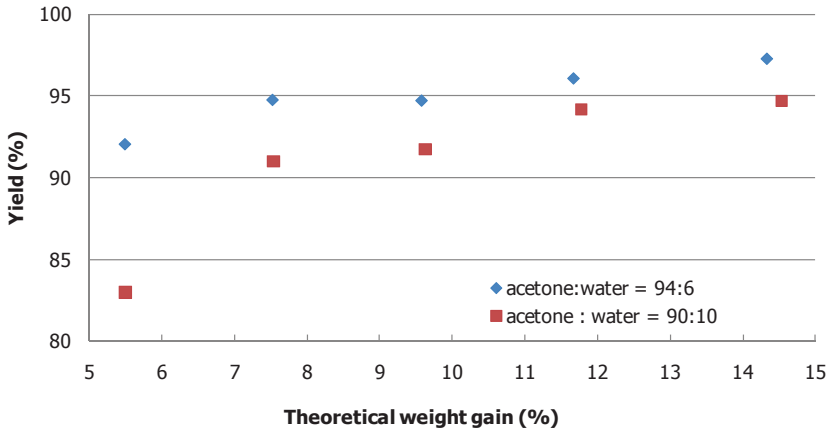
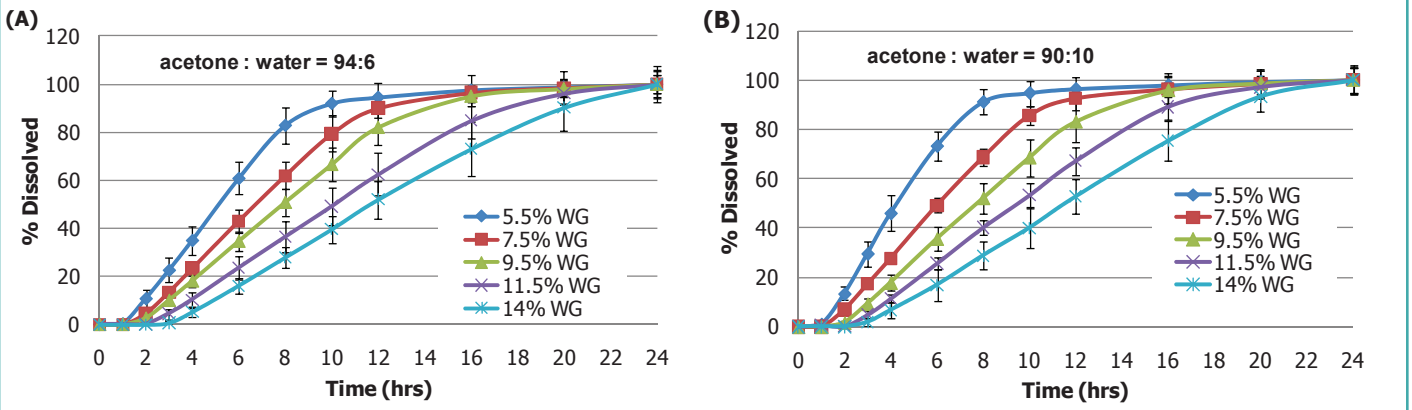


Figure 2. Drug Release Profiles of PPOP Tablets Prepared using Acetone:Water, Ratio of (A) 94:6; (B) 90:10 (n = 6)



Drug Release Profiles

The drug release profiles of the PPOP tablets are shown in Figures 2 (A) & (B). All PPOP tablets demonstrated a period of lag time, followed by zero order release profiles, regardless of variations in film coating weight gain. The drug release became slower, and lag time increased (1-3 hours) with increasing weight gain. At the same weight gain, the acetone : water ratio had no significant impact on the drug release profiles, as indicated by the similarity factor f_2 = 64-85. However, higher f_2 values were obtained with increasing film coating weight gain; possibly explained by the better coating yield at higher weight gain. Figure 3 showed that the release rate constant (k) (R^2 = 1.00) decreased with increasing weight gain. Higher coating weight gains resulted in longer times to release 20% ($t_{20\%}$), 50% ($t_{50\%}$) or 80% ($t_{80\%}$) of the drug content, shown in Figure 4.

Figure 3. Release Rate Constant (k) vs. Weight Gain

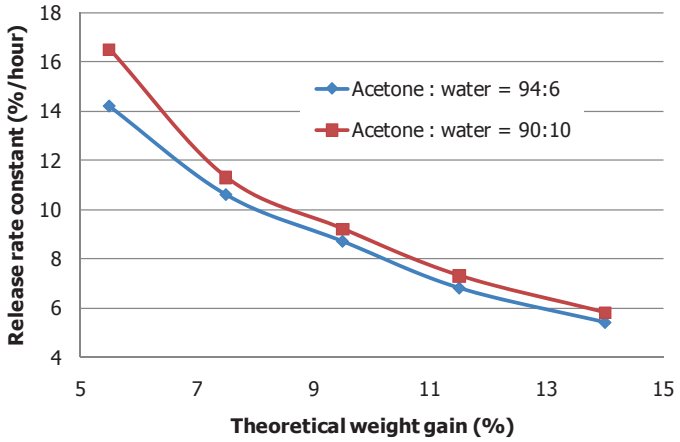
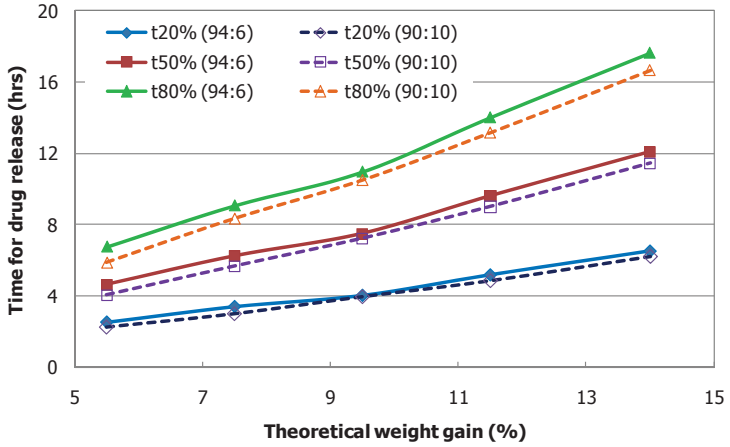


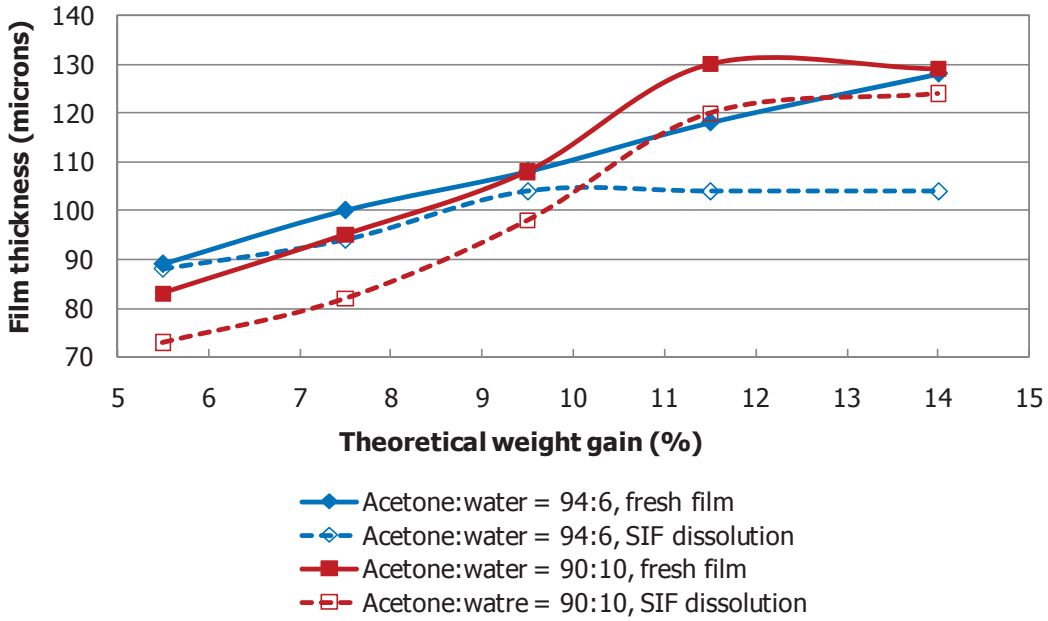
Figure 4. Time for Drug Release $t_{20\%}$, $t_{50\%}$ and $t_{80\%}$



Coating Properties

The Opadry CA film coating became slightly opaque with increasing weight gain, or with higher water concentration. The coating thickness increased with increasing weight gain (Figure 5). After dissolution testing, the coating thickness of dried films (24 hrs at 40oC in a vacuum oven) was slightly lower than the fresh films, which might be explained by PEG dissolving and leaching out of the semipermeable films.

Figure 5. Coating Thickness Before and After Dissolution Testing



Conclusions

Varying the weight gain of Opadry CA film coatings had a major effect on the drug release profiles from PPOP tablets. Therefore, weight gain and coating efficiency should be considered as critical attributes in the osmotic dosage design. Varying the co-solvent ratio had no significant impact on the drug release profiles (f_2 > 50). However, a trend of slightly faster drug release rate was noticed with increasing water content in the co-solvent. The ratio of the co-solvent may also contribute to the overall appearance of the final product when higher weight gain is applied.

References

1. Jinghua Yuan, et al. Formulation Effects on the Thermomechanical Properties and Permeability of Free Films and Coating Films. Pharmaceutical Technology Europe. 2009 June 26;22(6).
2. Patel P, et al. AAPS annual meeting and exposition. 2011.