Investigation of Critical Process Parameters for Coating Push-Pull Osmotic Pump Tablets with Opadry® CA

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Purpose

The semipermeable membrane (SPM) is one of the important components of a Push-Pull Osmotic Pump (PPOP) tablet that controls the osmotic pressure gradient, rate of tablet hydration and drug release rate from osmotic dosage forms. Opadry® CA, a fully formulated coating system, provides a simplified means of preparing and applying semipermeable coatings to PPOP tablets. Optimized film coating processes are key to the film quality and product functionality.[1] The purpose of this study was to investigate the effect of the critical process parameters (CPP) of Opadry CA on the critical quality attributes (CQA) of PPOP tablets.

Methods

Opadry CA powder was dispersed in a co-solvent mixture of acetone-water, 90:10 (w/w) and mixed for 45 min until fully dissolved. Opadry CA was applied onto glipizide bilayer tablets (10 mg dose) using a Labcoat IIX (O'Hara Technologies, Canada) with a 24" fully-perforated pan, two Schlick spray guns and a batch size of 14 kg. From our prior knowledge of Opadry CA film coating applications, atomizing air pressure, fluid delivery rate (FDR) and product temperature were identified as the critical process parameters (CPP), and drug release, semipermeable film opacity and thickness were chosen as the critical quality attributes (CQA) of PPOP tablets.[2] A full factorial design of experiments (DOE) was used in this study to evaluate the impact of the three identified CPP on PPOP tablets (Figure 1).

Figure 1. Design of Experiments (DOE) of Opadry CA Coating Process

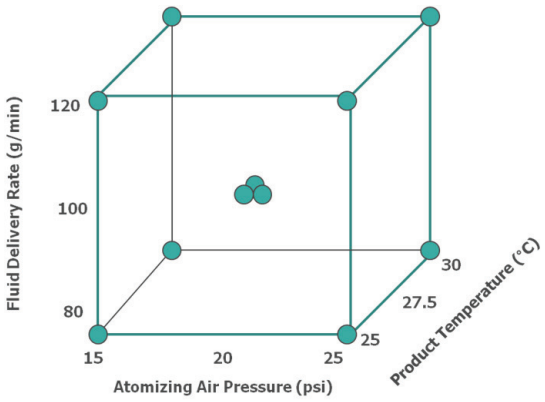


Table 1. Coating Process Parameters

Process parameters	Values
Pan size (inch)	24
Pan charge (kg)	14
Nozzle size (mm)	1.2
Pan speed (rpm)	14
Inlet air temperature (ºC)	31-40
Exhaust air temperature (ºC)	25-30
Pattern air pressure (psi / bar)	20 / 1.4
Air volume [CFM / (m^3/hr)]	250 / 425
Gun-to-bed distance (inch / cm)	3.5 / 8.9
Atomizing air pressure (psi / bar)	**15-25 / 1.0-1.7**
Product temperature (ºC)	**25-30**
Fluid delivery rate (g/min)	**80-120**

Atomizing air pressure (15-25 psi), product temperature (25-30°C) and fluid delivery rate (FDR, 80-120 g/min) were evaluated. The actual experimental process parameters for each trial are shown in Table 2.

Table 2. Experimental Design

Trial #	Atomizing Air Pressure (psi)	Product Temperature (°C)	FDR (g/min)
1	15	25.2	80
2	15	30.2	81
3	15	30.0	120
4	15	25.2	120
5	25	25.4	82
6	25	30.0	80
7	25	30.2	121
8	25	25.2	120
9	20	27.4	100
10	20	27.4	99
11	20	27.2	99

Dissolution studies were conducted in simulated intestinal fluid (SIF, 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 from the slope of the linear section of the dissolution profiles in the range of 5-80% of drug release. Semipermeable film opacity was determined by measuring the contrast ratio of coatings removed from flat-faced tablets, on black and white backgrounds, using a reflectance spectrophotometer[3] (Datacolor, USA). The thickness and morphology of the films were examined with a Hitachi Field Emission Scanning Electron Microscopy (FE-SEM; vs4300, Hitachi High-Tech, Japan). The results were analyzed using Minitab 16 statistical software.

Results

Drug Release

All PPOP tablets showed similar drug release profiles with 2 hr of lag time followed by zero order drug release (Figure 2). Atomizing air pressure did not have a significant relationship with the drug release rate constant *k*, (Figure 3). However, atomizing air pressure had a statistically significant relationship with the amount of drug dissolved at 3, 8, 12 hr time points (*p*-value < 0.1, Figure 3). In general, lower atomizing air pressure is associated with bigger droplets, reducing phase separation and promoting more dense film formation, lower media permeability and hence slower drug release. Statistical analysis indicated that product temperature and fluid delivery rate did not have a significant impact on drug release profiles.

Figure 2. Comparative Drug Release Profiles at Different Coating Parameters (n = 6)

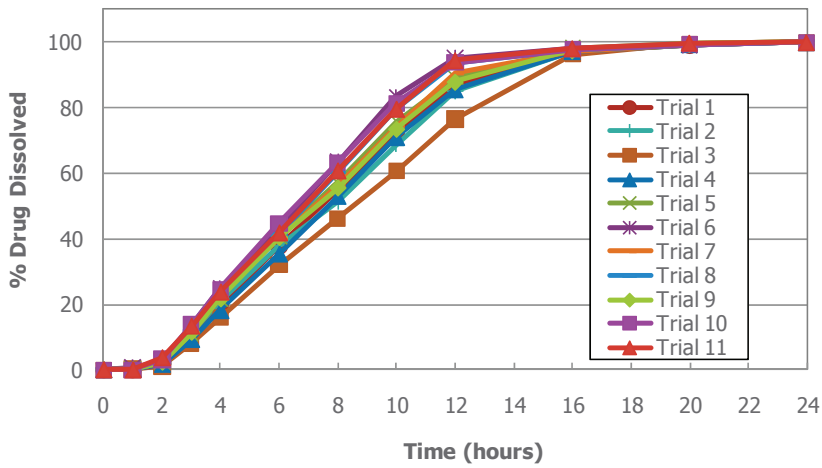
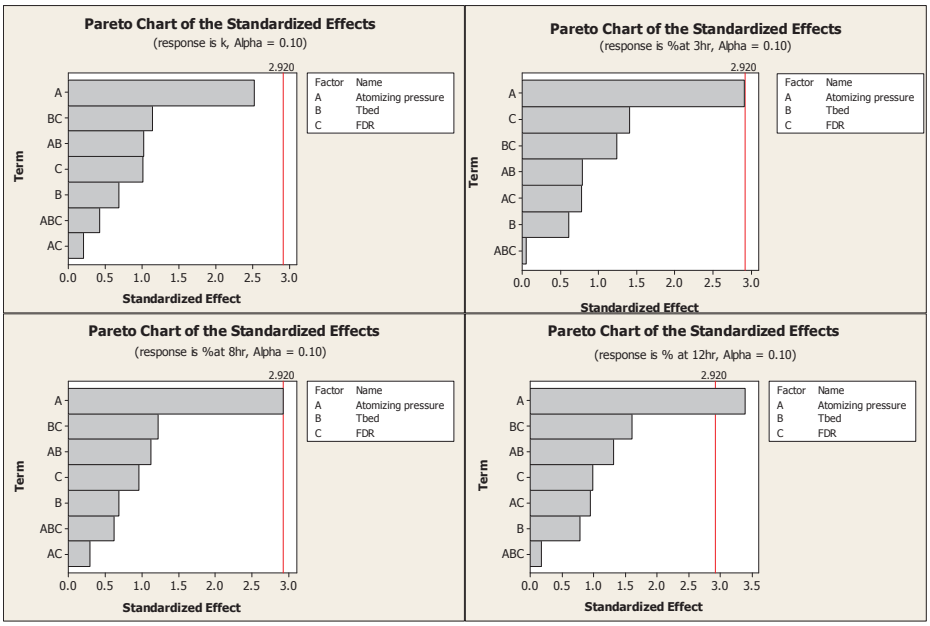


Figure 3. Pareto Charts for Drug Release Rate (k) and % Released at 3, 8 and 12 hr



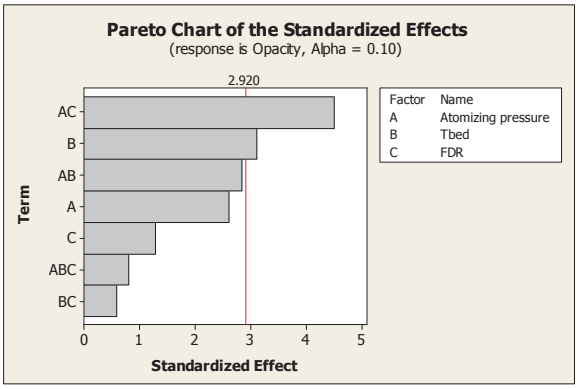
Note: A Pareto chart illustrates the magnitude and the importance of an effect. This chart displays the absolute values of the effects and draws a reference line (2.92), above which a given parameter is considered significant.

SPM Film Opacity

All coated tablets produced in this study had acceptable film clarity (opacity < 40 %) (Figure 4). Statistical analysis indicated that film opacity had significant relationships with product temperature and the interaction of atomizing air pressure and fluid delivery rate (Figure 5). In solvent-based film coating processes, increases in temperature or atomizing air pressure may increase film opacity due to the higher likelihood of spray drying, while higher fluid delivery rates may reduce opacity by providing larger droplets that are more resistant to spray drying.

Figure 4. Example of Clear Acceptable (A, Trial 9) vs. Opaque Unacceptable (B, from a separate study) SPM Opacity

Figure 5. Pareto Chart for SPM Opacity

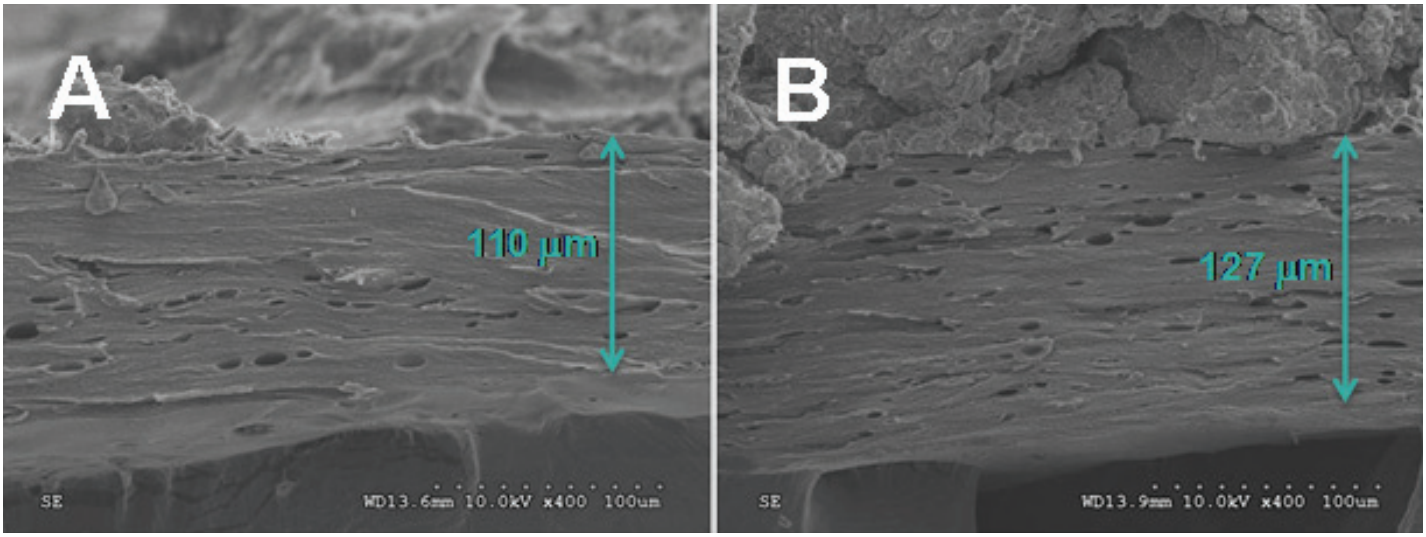


Note: A Pareto chart illustrates the magnitude and the importance of an effect. This chart displays the absolute values of the effects and draws a reference line (2.92), above which a given parameter is considered significant.

SPM Film Thickness

Film thickness is generally correlated with drug release rates as the coating thickness can control the rate of water ingress into the tablet core and hence the rate of hydration and swelling of the push layer. Figure 6 shows the SPM thickness and morphology for the conducted coating trials. All trials showed excellent coating efficiency (yield > 95 %). The observed variation in SPM film thickness (110-127 µm) may be due to the difference in SPM morphology. At equivalent coating weight gains, lower atomizing air pressures resulted in thinner and denser SPM film coatings; whereas at higher pressures, the film was slightly thicker and had more micro-sized pores and voids.

Figure 6. SPM Thickness and Morphology at Low (A, Trial 4) and High (B, Trial 8) Atomizing Air Pressure



Conclusions

The study showed that lower atomizing air pressures resulted in thinner, denser film coatings and consequently relatively slower drug release rates. Higher product temperatures led to faster solvent evaporation and possibly increased spray drying, thereby producing slightly opaque film coatings. The study confirmed that atomizing air pressure and product temperature are the CPP for Opadry CA. Although fluid delivery rate alone was not a main factor impacting CQA of the osmotic tablets, it influenced CQA by its interaction with atomizing air pressure or product temperature. Therefore, the recommended process parameters for Opadry CA coating applications, in the pilot scale coating equipment, are low atomizing pressure and low product temperature, while maximizing fluid delivery rate.

References

1. L. Martin, H. Deng, S. Missaghi, T. Farrell and A. Rajabi-Siahboomi, Investigation of Cellulose Acetate Polymer Viscosity and Coating Solution Concentration on Performance of Push-Pull Osmotic Pump (PPOP) Tablets. 39th CRS Annual Meeting and Exposition, Quebec City, Canada, July 2012.
2. H. Deng, L. Martin, S. Missaghi, T. Farrell and A. Rajabi-Siahboomi, The Influence of Cellulose Acetate Weight Gain and Solvent Ratio on Performance of Push-Pull Osmotic Pump Tablets. 39th CRS Annual Meeting and Exposition, Quebec City, Canada, July 2012.
3. R.C. Rowe, Quantitative opacity measurements on tablet film coatings containing titanium dioxide, *Int. J. Pharm.*, 22 (1984) 17-23.