Effect of Granulation Processing Parameters on Performance of Push-Pull Osmotic Pump Tablets of a Practically Water Insoluble Model Drug

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ABSTRACT SUMMARY

Push-Pull Osmotic Pump (PPOP) tablets of a practically insoluble model drug were manufactured using different granulating parameters for the pull and push layers. The results showed that while differences were observed in physical properties of the resulting granules, drug release from the PPOPs was not significantly affected ($f_2 > 61$). This study confirmed that PPOPs are robust drug delivery systems, which could yield satisfactory results for similar drug candidates.

INTRODUCTION

Push-Pull osmotic pumps typically consist of a bilayer tablet core coated with a semipermeable membrane and a laser-drilled orifice to facilitate the drug release.[1] The bilayer tablet core contains pull (drug) layer and push layer which are generally prepared using a hydro-alcoholic granulation process. In this study, PPOPs of a practically insoluble model drug (Drug Y) were developed using the formulation strategy as described previously.[2] The objective was to evaluate the effect of different granulating process parameters on physical properties of the granules and tablets as well as on drug release from the PPOP tablets. This involved: (i) inclusion/ exclusion of the chopper during granulation; and (ii) inclusion/ exclusion of a milling step for dried granules in this small-scale study.

EXPERIMENTAL METHODS

Effect of Inclusion/ Exclusion of Chopper during Granulation

The formulation of Drug Y PPOPs is displayed in Table 1. Individual pull and push layer ingredients were prepared using a high shear granulation process (Diosna P/VAC 10, Germany) (batch size, 1 kg). The first process (P1), regarded as control, involved dry blending of the ingredients for 3 minutes using an impeller and chopper speeds of 100 and 1000 rpm, respectively. The granulating liquid, ethanol: deionized water (85:15 w/w), was applied onto the blends using a spray application. The impeller and chopper were operated at 150 and 2000 rpm, respectively. To evaluate the effect of the chopper, the second process (P2) involved preparation of pull and push layer granules using only the impeller at the above-mentioned speeds, for both dry blending and wet granulation steps. The resulting granules of P1 and P2 were dried in a vacuum drying oven at 40 ºC for 16 hours to achieve an initial moisture content of ~0.5 % w/w. The dried granules were milled (Quadro® Comil®, 1.18 mm grated screen), then lubricated for one minute. Bilayer tablets were prepared on a 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). A tamping force of ~0.7 kN (9.8 MPa) was used to compress the pull layer, followed by main compression force of 7 kN (98 MPa) to compress the bilayer tablets.

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Tablets were coated in a Vector Hi-Coater LDCS to 8-12% weight gain (WG) using an organic coating solution of cellulose acetate, CA-398-10 (Eastman Chemical Company, USA), and PEG 3350 (International Flavors and Fragrances Inc., USA) (9:1 w/w) in a solvent mixture of acetone-deionized water (96:4 w/w). Coated tablets were dried in a vacuum oven at 40ºC for 24 hours to remove residual solvent and moisture. A delivery orifice was laser-drilled on the drug layer side (Cobalt 250, InkCupsNow, USA).

Dried granules and bilayer tablet cores were evaluated for physical properties. Drug release from the PPOP tablets was evaluated based on the relevant USP method. Drug release profiles were compared to the control process using similarity factors (f_2).

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)	International Flavors and Fragrances Inc., USA	93.9
Magnesium stearate	Peter Greven, Germany	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	Peter Greven, Germany	0.5
Total		**100**

Effect of Inclusion/ Exclusion of Milling of Dried Granules

The pull and push layer granules were prepared as described earlier for P1. To evaluate the effect of milling, for P3, the milling step was excluded, and the dried granules were simply passed through a coarse screen (mesh #16; 1.18 mm).

RESULTS AND DISCUSSION

The physical properties of dried granules are shown in Table 2 and Figure 1. Higher bulk and tapped density for the pull layer granules were obtained when chopper was not utilized. As for the push layer, the unmilled granules had the lowest density compared to other processes. The particle size distribution of drug layer granules showed comparable results for all processes; whereas, for the push layer, inclusion of the milling step (P1) produced more fines.

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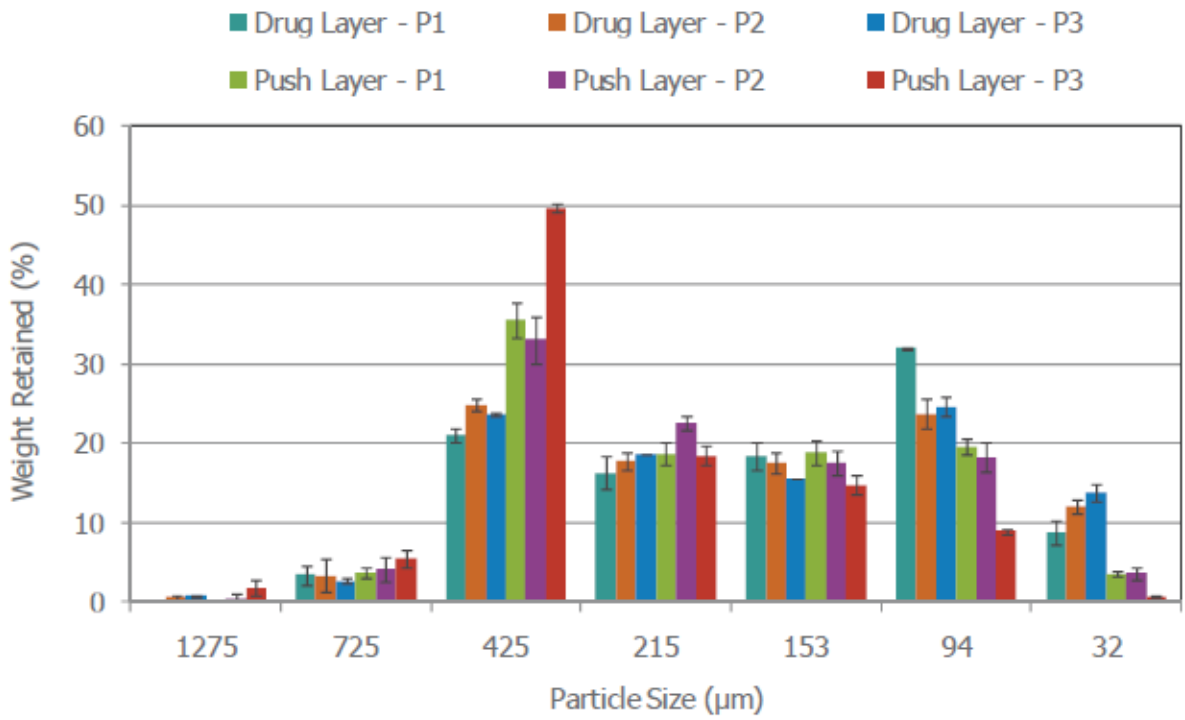
Table 2. Physical Properties of Dried Granules

Formulation		Bulk Density (g/cm3)	Tapped Density (g/cm3)	Carr's Compressibility Index (%)
Drug Layer	P1 (control)	0.43	0.52	18.3
	P2 (no chopper)	0.48	0.57	15.7
	P3 (no mill)	0.43	0.53	19.3
Push Layer	P1 (control)	0.48	0.60	19.3
	P2 (no chopper)	0.44	0.54	18.6
	P3 (no mill)	0.38	0.48	20.9

Figure 1. Particle Size Distribution of Granules (n=3)



The physical properties of uncoated bilayer tablets were generally similar for all processes (Table 3). Results showed that varying the granulating process parameters does not significantly affect the drug release from the PPOP tablets ($f_2 > 61$) (Figure 2).

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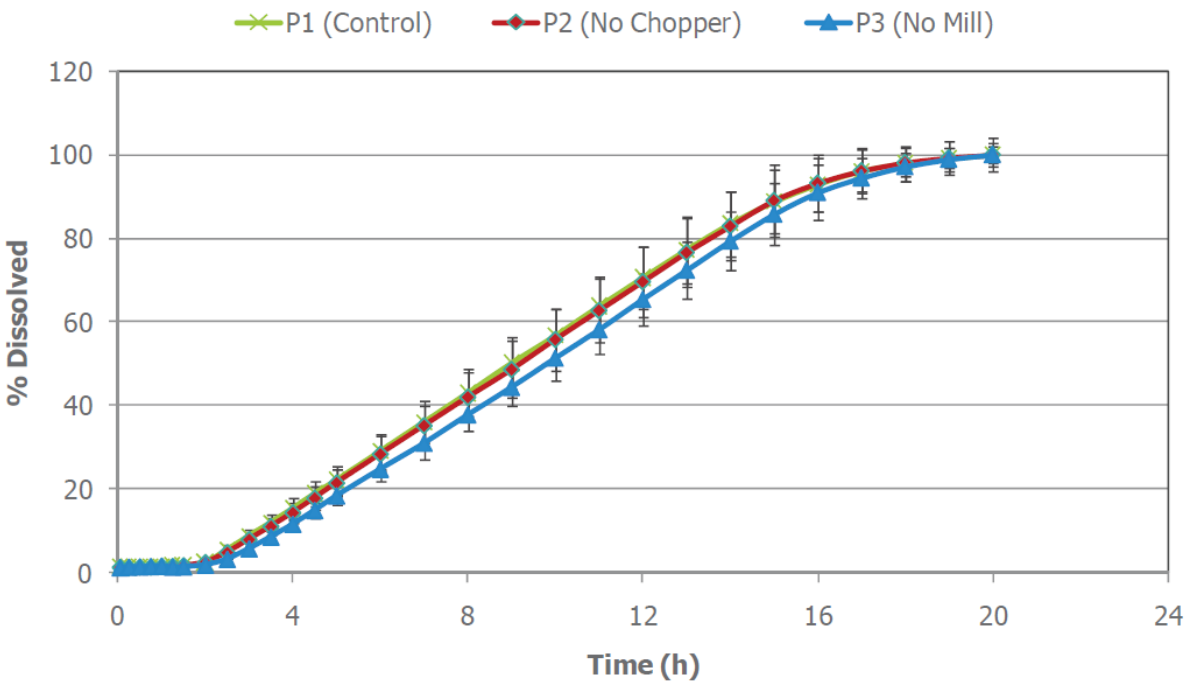
Table 3. Physical Properties of Uncoated Bilayer Tablets (n=10)

Tablets	Weight (mg)	Thickness (mm)	Tablet hardness (kp) (Tensile strength (MPa))
P1 (control)	332.0 ± 4.1	5.03 ± 0.05	9.4 ± 1.2 (1.36)
P2 (no chopper)	331.4 ± 3.1	5.03 ± 0.07	8.1 ± 0.5 (1.18)
P3 (no mill)	330.7 ± 1.5	5.06 ± 0.05	9.1 ± 0.5 (1.31)

Figure 2. Release Profiles of Drug Y PPOP Tablets, Coated to 12% WG (n=6)



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CONCLUSIONS

Osmotic PPOP systems are very robust, providing consistent drug release. Good formulation practice allows sensitivities to potential manufacturing processes to be mitigated. In this study, pull and push layer granules of a practically insoluble model drug were prepared in a high shear granulator. Evaluation of the effect of chopper use and/or a milling step, as different granulation parameters, resulted in slight differences in the physical properties of the granules. However, tablet properties and the drug release from the PPOPs were not significantly affected by the process variation. The results of this study demonstrate a robust, yet flexible, PPOP system and enable a more fundamental understanding of the relationship between process variables and PPOP performance, which may be helpful in meeting the requirements prescribed in ICH Q8, Pharmaceutical Development.

REFERENCES

1. Shamblin SL, In: Wen H, Park K, Oral controlled release formulation design and drug delivery: Theory to practice. 2010; John Wiley & Sons, Inc., 129-153.
2. Patel P et al, AAPS 2011, Washington DC, Poster No: W5113.

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