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

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POLYOX

Purpose

There has been increasing interest in the development of oral osmotic dosage forms in which drugs can be delivered at a constant rate (zero order release) over a long period of time. Drug release from osmotic dosage forms is generally independent of pH, ionic strength, agitation and other physiological factors within the gastrointestinal tract. These attributes minimize patient-to-patient variability and allow accurate prediction of in vivo performance from in vitro dissolution profiles. However, access to the technologies has been restricted due to the perceived complexity of these formulations, manufacturing challenges and patent landscape.[1, 2]

In this study, push-pull osmotic pumps (PPOP) of a practically insoluble model drug (Drug Y) were developed using the formulation strategy as described previously.[3] The purpose is to evaluate the effect of tablet formulation and granulation processing on performance of PPOP tablets of this model drug. This involves investigating the effect of using: (i) various viscosity grades of polyethylene oxide (POLYOX™) as the predominant hydrophilic polymer in formulation of pull and push layers; and (ii) different compositions of the hydro-alcoholic granulating liquid. This investigation could lead to better understanding of the robustness of the PPOP tablets and designing studies to assess process variable impact, as prescribed in ICH Q8, Pharmaceutical Development.

Methods

Effect of Viscosity Grades of POLYOX

Polyethylene oxide (PEO) (POLYOX) is the main polymer in the formulation of PPOP tablets due to its hydration kinetics and swelling capacity. POLYOX powder is generally free flowing, compressible and available in different molecular weight/viscosity grades.[1] To evaluate the effect of POLYOX, various grades were examined, i.e. POLYOX WSR N-80 NF or N-750 NF for the pull layer and POLYOX WSR-301 NF, Coagulant NF or 303 NF for the push layer formulations (**Table 1**). A control formulation was developed as shown in **Table 2**. Individual pull and push layer ingredients, except for magnesium stearate, were added to a high shear granulator (Diosna P/VAC 10, Germany) (batch size, 1 kg) and dry blended for 3 minutes. Granulating liquid, ethanol-deionized water (85:15 w/w), was applied using spray application. The impeller and chopper were operated at 150 and 2000 rpm, respectively. The granules were dried in a vacuum drying oven at 40°C for 16 hours to achieve an initial moisture content of ~0.5% w/w and then milled and lubricated for 1 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 (pressure) of ~0.7 kN (9.8 MPa) was used to compress the pull layer, followed by main compression force (pressure) of 7 kN (98 MPa) to compress the bilayer tablets.

Tablets were coated to 8-12% w/w 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) at 7% w/w solids content. The coating process was performed in a Vector Hi-Coater LDCS at a product temperature of 28°C. Coated tablets were dried in a vacuum oven at 40°C for 24 hours to remove residual solvent and moisture. A delivery orifice was drilled on the drug layer side using a laser machine (Cobalt 250, InkCupsNow, USA). Tablets were evaluated for physical properties and in vitro drug release based on the USP methods. Drug release profiles were compared to the control formulation using similarity factors ($f2$).[4]

Table 1. Various Viscosity Grades of POLYOX used in the Study[5]

POLYOX NF Grade	Approx. Molecular Weight	Viscosity at 25°C (cP)
WSR N-80 NF	200,000	55 – 90 *(5% solution)*
WSR N-750 NF	300,000	600 - 1,200 *(5% solution)*
WSR-301 NF	4,000,000	1,650 - 5,500 *(1% solution)*
WSR Coagulant NF	5,000,000	5,500 - 7,500 *(1% solution)*
WSR-303 NF	7,000,000	7,500 - 10,000 *(1% solution)*

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Table 2. Formulation of Pull and Push Layers for PPOP Tablets of Model Drug Y* (Control Formulation)

Pull Layer Ingredients	Supplier	Quantity (% w/w)
Drug Y	-	5.6
Polyethylene oxide (POLYOX WSR N-80)	International Flavors and Fragrances Inc.,	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.,	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**

** To evaluate the effect of POLYOX, different grades were used at the same level as above for both pull and push layers.*

Effect of composition of the granulating liquid (altering ethanol: water ratio)

Blends for pull and push layers were prepared using the formulation as displayed in **Table 2** followed by a high shear granulation process as described earlier. To evaluate the effect of composition of granulating liquid, 3 different ethanol:water ratios were used: 100:0, 85:15 (control) and 70:30 w/w. The resulting granules were evaluated for physical properties and then compressed into bilayer tablets as described above. The physical properties of the resulting PPOP tablets were then assessed.

Results

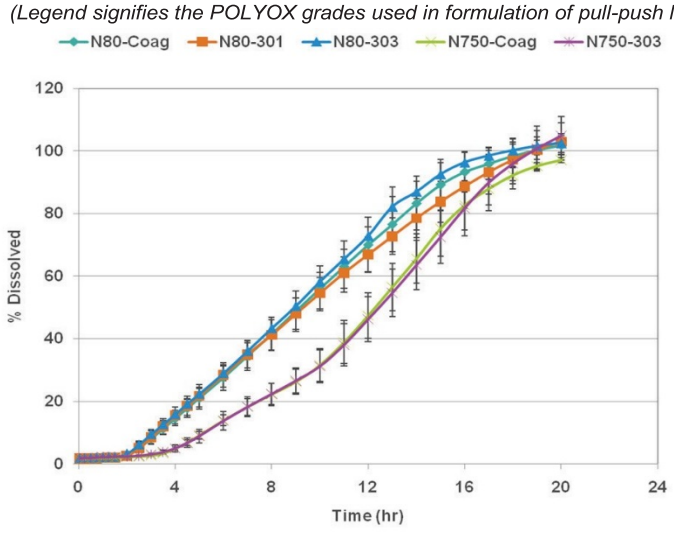
Evaluation of various POLYOX grades in the push layer showed that drug release was not significantly affected by the grade of POLYOX used ($f2$ >70). For the pull layer, using the higher viscosity grade (N-750) prolonged the lag time and slowed down the drug release ($f2$ =32-34) when compared to the control formulation (**Figure 1**). Physical properties of bilayer tablets were generally comparable for all tablets, irrespective of the POLYOX grade used (**Table 3**).

Table 3. Physical Properties of Uncoated Bilayer Tablets using Different POLYOX Grades (n=10)

Tablets	Weight (mg)	Thickness (mm)	Tablet hardness (kp) (Tensile strength (MPa))
N80/Coag (control)	332 ± 4.1	5.03 ± 0.05	9.4 ± 1.2 (1.36)
N80/301	334 ± 2.9	4.99 ± 0.02	10.0 ± 0.8 (1.47)
N80/303	334 ± 2.6	4.92 ± 0.01	11.4 ± 0.6 (1.71)
N750/Coag	331 ± 3.1	4.96 ± 0.01	9.5 ± 1.2 (1.41)
N750/303	335 ± 2.9	4.98 ± 0.02	10.0 ± 0.8 (1.47)

Figure 1. Release Profiles of Drug Y PPOP Tablets, Coated to 12% WG, using Various Grades of POLYOX in Pull and Push Layers (n=6)

(Legend signifies the POLYOX grades used in formulation of pull-push layers)



PPOP Tablets	f_2 value
N80/Coag	Ref.
N80/301	75.1
N80/303	74.8
N750/Coag	33.1
N750/303	32.6

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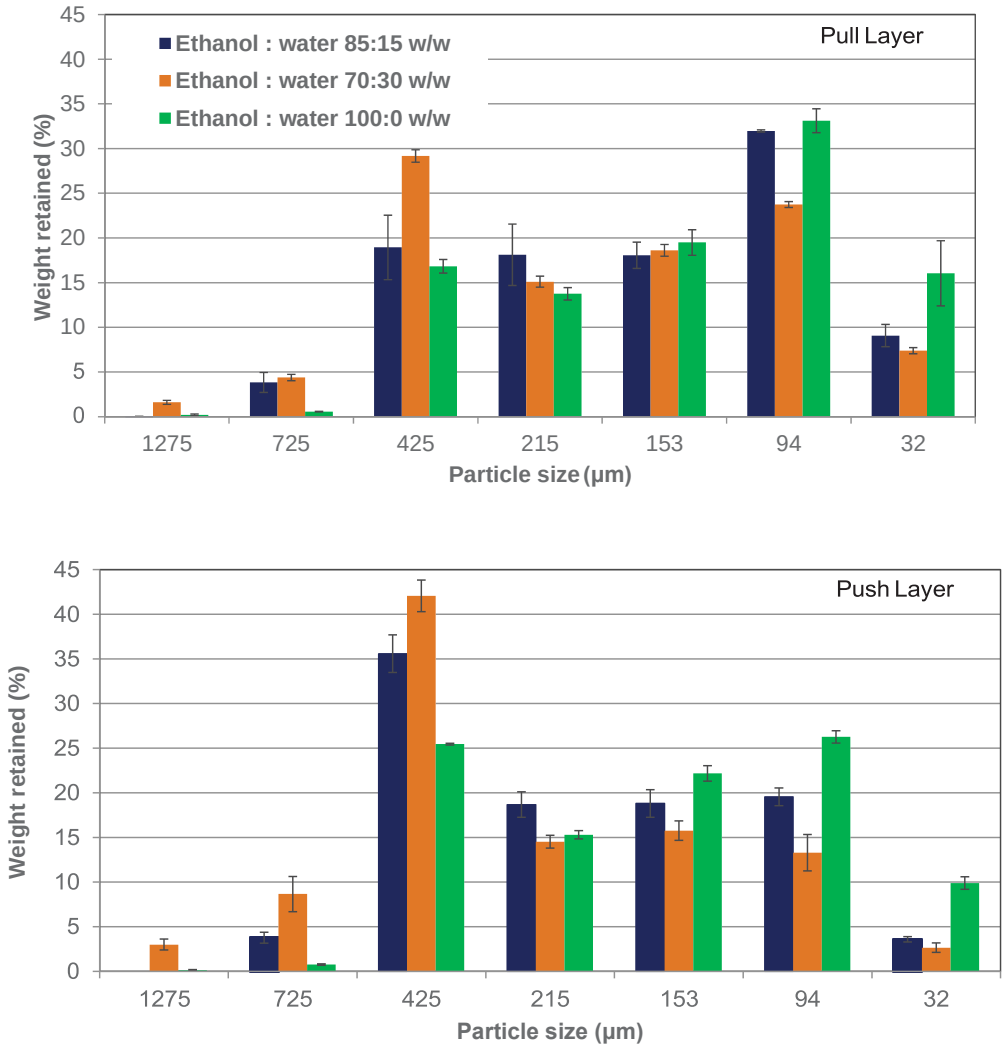
Among different granulating liquids, the use of pure ethanol resulted in slightly higher density for the push layer. Powder flow was good to fair for all granules with Carr's indices in the range of 15.5-18.9% (**Table 4**). Use of ethanol to water ratio at 70:30 w/w resulted in slightly larger particles, while use of pure ethanol led to generation of more fines (**Figure 2**).

Table 4. Physical Properties of Dried Granules

Batches (Ethanol:Water ratio)		Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Compressibility Index (%)
Drug Layer	**70:30 w/w**	0.44	0.52	15.75
	85:15 w/w	0.48	0.60	18.85
	100:0 w/w	0.45	0.55	18.00
Push Layer	**70:30 w/w**	0.43	0.52	17.50
	85:15 w/w	0.47	0.58	18.78
	100:0 w/w	0.56	0.66	15.50

Figure 2. Particle Size Distribution of Different Granules (n=3)



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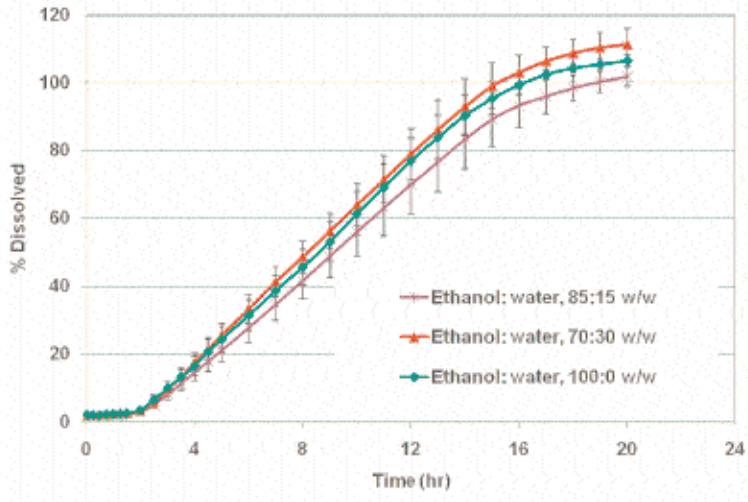
Physical properties of bilayer tablets were generally comparable. Use of pure ethanol resulted in slightly higher tablet hardness (**Table 5**). Drug release was not significantly affected when using different liquid compositions in the granulation process ($f2$ >55) (**Figure 3**).

Table 5. Physical Properties of Dried Granules

Tablets (Ethanol: Water Ratio)	Weight (mg)	Thickness (mm)	Tablet hardness (kp) (Tensile strength (MPa))
85:15 w/w (control)	332 ± 4.1	5.03 ± 0.05	9.4 ± 1.2 (1.36)
70:30 w/w	333 ± 6.5	5.04 ± 0.01	7.9 ± 1.0 (1.14)
100: 0 w/w	333 ± 6.2	4.99 ± 0.01	10.7 ± 1.9 (1.57)

Figure 3. Release Profiles of Drug Y PPOP Tablets, Coated to 12% WG, using Different Granulating Liquid Compositions (n=6)



Ethanol: water (w/w)	f_2 value
85:15	Ref.
100:0	61.4
70:30	55.2

Conclusions

PPOP tablets of a practically insoluble model drug were successfully manufactured and evaluated using various POLYOX grades and different compositions of granulating liquid. The results demonstrated that, unlike the pull layer, a change of polymer grade in the push layer did not impact drug release. Moreover, different granulating liquids yielded similar drug release profiles. These studies illustrated the robustness of osmotic systems, the complexity of which can be readily managed by satisfactory development and manufacturing controls.

References

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