Development of Push-Pull Osmotic Pump Tablets for a Slightly Water Soluble Drug

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ABSTRACT SUMMARY

Push-Pull Osmotic Pump (PPOP) tablets of a slightly water soluble model drug were developed and compared to a commercial product. Results showed that irrespective of the multiple steps involved in manufacture of such dosage forms, developed tablets demonstrated equivalent performance to commercial tablets with respect to physical properties, drug release and push-pull pattern. The developed system could provide a platform to yield satisfactory results for similar drug candidates.

INTRODUCTION

Over the last decade, there has been increasing interest in the development of oral osmotic devices in which the active pharmaceutical ingredient can be delivered in a sustained pattern over a long period of time governed by osmotic pressure. Osmotic dosage forms provide zero order drug release that is generally independent of pH, ionic strength, agitation and other physiological factors within the gastrointestinal tract (GIT). These attributes minimize patient-to-patient variability and allow accurate prediction of in vivo performance from in vitro dissolution profiles. The main clinical benefits of these systems are improving treatment tolerability and patient compliance. However, access to the technologies has been restricted due to perceived and real manufacturing constraints and the patent landscape.[1, 2] The objective of this study was to develop PPOP tablets for a slightly water soluble model drug (drug X), with matching performance to the commercial PPOP tablets.

EXPERIMENTAL METHODS

Manufacture of PPOP tablets involves various processing steps including preparation of respective formulation blends for pull layer and push layer (Table 1) using a hydro-alcoholic wet granulation process, drying of granules, compression of bilayer tablets, preparation and application of semipermeable membrane, drying of coated tablets followed by laser drilling a delivery orifice on the drug layer side.

Hydro-Alcoholic Wet Granulation and Drying

The granulation process was carried out separately for pull layer and push layer using a high shear granulator (Diosna P/VAC 10) (batch size, 1 kg). For each layer, all ingredients except magnesium stearate were added to the granulator and dry blended for 3 minutes using an impeller and chopper speed of 200 and 1000 rpm, respectively. The moisture content of the dry blends was determined and recorded. The granulating liquid, ethanol-deionized water (85:15 w/w), was applied onto the blends at a spray rate of 30 g/min for pull layer and 20 g/min for push layer. The impeller and chopper were operated at 200 and 2000 rpm, respectively. After addition of liquid, the batch was mixed for one minute. The granulation end point was determined manually (conventional snow ball test). The resulting granules were dried in a vacuum drying oven at 40ºC for 16 hours to achieve initial equilibrium moisture content of dry blends (~0.5 %w/w). The dried granules were

milled (Quadro® Comil®, 1.18 mm grated screen), followed by lubrication with magnesium stearate for one minute.

Table 1. Formulation of Pull and Push Layers for PPOP Tablets of Model Drug X

Pull Layer - Ingredients	**Supplier**	**Quantity (%w/w)**
Model drug X	-	3.3
Polyethylene oxide (POLYOX™ WSR N-80)	International Flavors and Fragrances Inc., USA	96.2
Magnesium stearate (MgSt)	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 (MgSt)	Mallinckrodt, USA	0.5
Total		**100**

Compression of Bilayer Tablets

Tablets were manufactured on an instrumented bilayer rotary press (Piccola, Riva) using standard round concave tooling (11 mm) at the target weight of 500 mg. The weight ratio of pull layer to push layer was approximately 2:1. A tamping force (pressure) of 0.5 kN (5 MPa) was used to compress the pull layer, followed by compression force (pressure) of 8 kN (83 MPa) to compress the bilayer tablets.

Semipermeable Coating and Drilling of Delivery Orifice

Table 2 summarizes the composition of the organic coating solution. Coating solution was prepared by dissolving PEG in water followed by addition of this solution to acetone. Cellulose acetate was then added to the above mixture and stirred to achieve a clear solution. Coating process was performed in a Vector Hi-Coater LDCS (batch size, 1.5 kg, with inclusion of placebo tablets) using a product temperature of 28ºC and gun to bed distance of 6 cm. Coated tablets were pulled at different weight gains (WG), 5, 8 and 10% w/w, for evaluation. Coated tablets were dried in a vacuum drying oven at 40ºC for 24 hours to remove residual solvent and moisture. A delivery orifice was drilled on the drug layer side of the coated tablets using a laser machine (Cobalt 250, InkCupsNow).

Table 2. Semipermeable Coating Composition

Ingredients	Supplier	Quantity (%w/w)
Cellulose acetate, CA-398-10	Eastman Chemical Company, USA	6.3
Polyethylene glycol, PEG 3350	International Flavors and Fragrances Inc., USA	0.7
Acetone	Spectrum Chemical, USA	89
Deionized water	-	4
Total		**100**

Evaluation of Tablets

Tablets were evaluated for drug assay and content uniformity, weight variation, thickness, mechanical strength and in vitro drug release based on the compendial monograph for this drug. Drug release profiles were compared using the similarity factor (f_2).3 In addition, the push-pull pattern of the tablets was examined over time by hydrating the tablets in the dissolution media followed by physical and gravimetrical evaluation at different time points. This examination was done to assure that the push layer provided consistent push pattern to the drug layer.

RESULTS AND DISCUSSION

Results showed a drug assay value of 100.7% ± 1.8% for the PPOP tablets, indicating good content uniformity. Table 3 displays the physical properties of the tablets. The PPOP tablets coated to 8% WG showed similar properties to the commercial product.

Table 3. Physical Properties of the PPOP Tablets

Parameters	Uncoated Tablets	Coated Tablets (8% WG)
Tablet weight (mg)	502 ± 3.3	540 ± 3.1
Tablet thickness (mm)	5.7 ± 0.0	6.0 ± 0.0
Tablet hardness (kp) (Tensile strength (MPa))	14.6 ± 0.9 (1.6)	43.4 ± 2.5 (4.4)
Tablet friability (%)	0.0	-

Drug release profiles at various weight gains are shown in Figure 1, indicating that increasing the coating weight gain of the semipermeable membrane resulted in slower drug release. Figure 2 shows comparative dissolution profiles as well as percent tablet weight change upon hydration in the media (including media

uptake and drug/ excipient loss) for PPOP tablets of drug X coated to 8% WG and commercial tablets. Figure 3 illustrates the pro- gressive swelling and pushing pattern of the push layer against the drug layer. Results demonstrate similar behavior for drug X and commercial PPOP tablets with respect to drug release (f^2 = 79), media uptake and push-pull pattern.

Figure 1. Drug Release Profiles of Uncoated and Coated Tablets of Drug X (n=6)

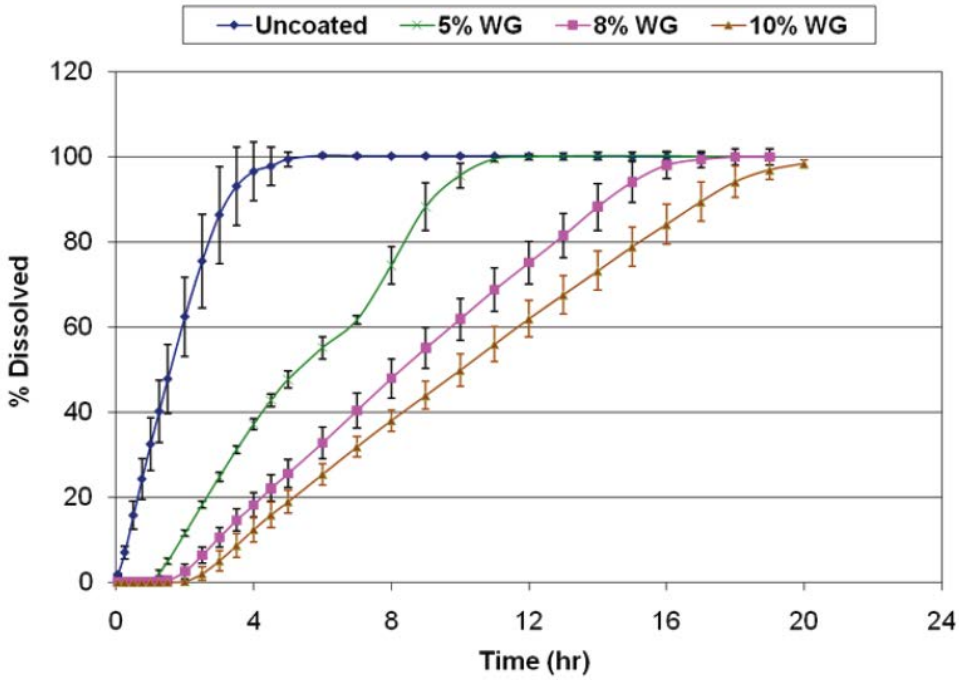


Figure 2. Drug Release Profiles and Percent Weight Change for PPOP Tablets of Drug X and Commercial Tablets

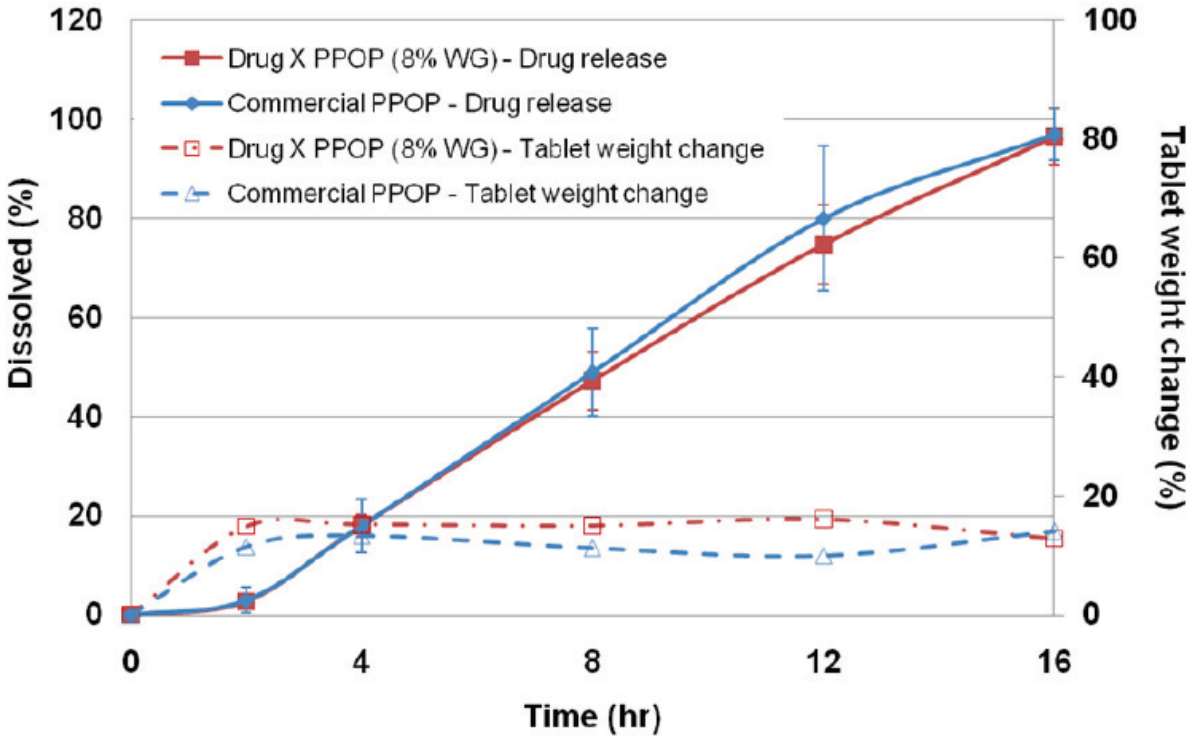
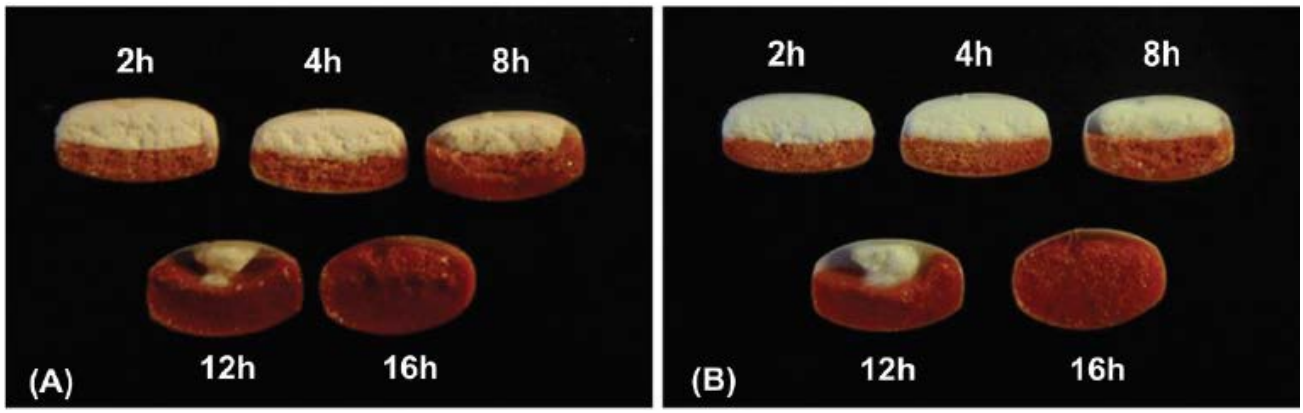


Figure 3. Push-Pull Pattern of PPOP Tablets upon Hydration in Dissolution Media over Time, (A) Commercial PPOP; (B) Drug X PPOP



CONCLUSIONS

PPOP tablets of a slightly water soluble model drug were successfully developed and evaluated. Tablets coated to 8% w/w weight gain of the semipermeable membrane coating showed equivalent performance to the commercial product with respect to physical properties, drug release profiles, media uptake and push-pull pattern. The higher coating weight gain led to slower drug release rate. Results showed a promising osmotic system that could provide a platform to yield satisfactory results for similar dose solubility drug candidates.

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