Effect of Different Processing Conditions on the Performance of Push-Pull Osmotic Pump Tablets of 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. The effects of tablet mechanical strength, drying method of granules and methods of tablet manufacture (manual vs. rotary tablet press) on performance of PPOP tablets were evaluated. Results revealed that, irrespective of the process used, drug release from the PPOP tablets was not significantly affected. The findings of this study showed a robust osmotic system which could 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 drugs can be delivered in a sustained pattern (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] The objective of this study was to evaluate the effect of various processing conditions on performance of PPOP tablets of a slightly water soluble model drug (drug X). This involves investigating the effect of (i) tablet core hardness; (ii) drying method for granules (tray drying vs. fluid bed drying); and (iii) manual compression vs. bilayer rotary press on tablet manufacture. This investigation could lead to better understanding of the robustness of the PPOP tablets and designing studies to assess process variable impact.

Experimental Methods

Evaluation of the Effect of Tablet Core Hardness

Individual pull and push layer ingredients (**Table 1**), except for magnesium stearate, were added to a high shear granulator (Diosna P/VAC 10) 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 200 and 2000 rpm, respectively. The granules were dried in a vacuum drying oven at 40ºC for 16 hours to achieve initial 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. Bilayer tablets were prepared on a manual press (GlobePharma Inc.) using standard round concave tooling (11 mm) at the target weight of 500 mg (pull:push layer, ~2:1 w/w). A tamping force (pressure) of 0.1kN (1MPa) was used to compress the pull layer, followed by addition of push layer to the die and final compression to achieve bilayer tablets of different hardness. Tablets were coated to 8% w/w weight gain (WG) using an organic coating solution of cellulose acetate, CA-398-10 (Eastman Chemical Company), and PEG 3350 (Dow Chemical Company) (9:1 w/w) in a solvent mixture of acetone-deionized water (96:4 w/w) at 7% w/w solids content. Coating process was performed in a Vector Hi-Coater LDCS using a product temperature of 28ºC. Coated tablets were dried in a vacuum oven at 40ºC 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). Tablets were evaluated for physical properties and in vitro drug release based on the USP monograph for this model drug. Drug release profiles were compared using similarity factors (f_2).[3]

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)	The Dow Chemical Company, USA	96.2
Magnesium stearate (MgSt)	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 (MgSt)	Mallinckrodt, USA	0.5
Total		**100**

Evaluation of Method of Drying Granules

After granulation, granules were dried using either tray drying method (TD) or fluid bed drying method (FBD). For tray drying, the granules were dried in a vacuum oven at 40ºC for 16 hours. For fluid bed drying, granules were dried using a Glatt GPCG-2 drier at a product temperature of 25ºC. In both methods, the granules were dried to achieve initial moisture content of dry blends (~0.5 %w/w). After milling and lubrication, the granules were evaluated for physical properties and compressed into bilayer tablets.

Evaluation of Tablet Manufacturing Method

Tablets were compressed using either a manual press or a bilayer rotary press (Piccola, Riva) to achieve similar mechanical strength. For manual compression, a tamping force (pressure) of 0.1kN (1MPa) was used to compress the pull layer, followed by compression force (pressure) of 5kN (52MPa). For the bilayer press, a tamping force (pressure) of 0.5kN (5MPa) was used followed by compression force (pressure) of 8kN (83MPa). Coating and drilling processes were conducted as noted above. Tablets were evaluated for physical properties and in vitro drug release.

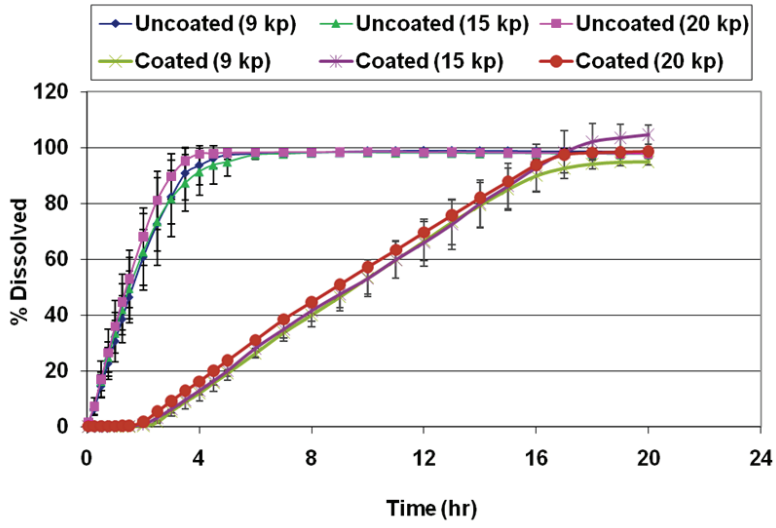
Results and Discussion

Evaluation of tablet core hardness showed that an increase in compression force resulted in subsequent increase in tablet hardness and decrease in tablet thickness (**Table 2**). Drug release from uncoated and coated tablets was not significantly affected by tablet hardness (**Figure 1**), with f_2 values ranging from 68 to 89.

Table 2. Physical Properties of Uncoated Bilayer Tablets of Different Core Hardness

Compression force (kN) (Compression pressure (MPa))	**Tablet hardness (kp) (Tensile strength (MPa))**	**Weight (mg)**	**Thickness (mm)**
2.2 (23)	9 (0.9)	500 ± 2.3	5.9 ± 0.1
3.8 (39)	15 (1.6)	500 ± 0.9	5.7 ± 0.0
7.4 (76)	20 (2.4)	501 ± 1.6	5.4 ± 0.0

Figure 1. Release Profiles of Drug X Tablets of Varying Core Hardness

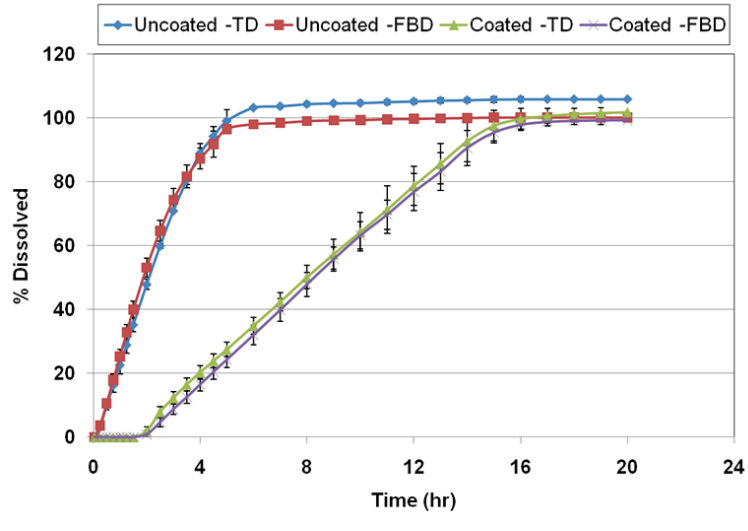


Evaluation of different drying methods revealed similar physical properties (particle size distribution, bulk and tapped density, compressibility index) for the granules of both processes (data are not shown). In addition, the properties of tablets were similar (**Table 3** and **Figure 2**).

Table 3. Physical Properties of Uncoated Bilayer Tablets using Different Processes

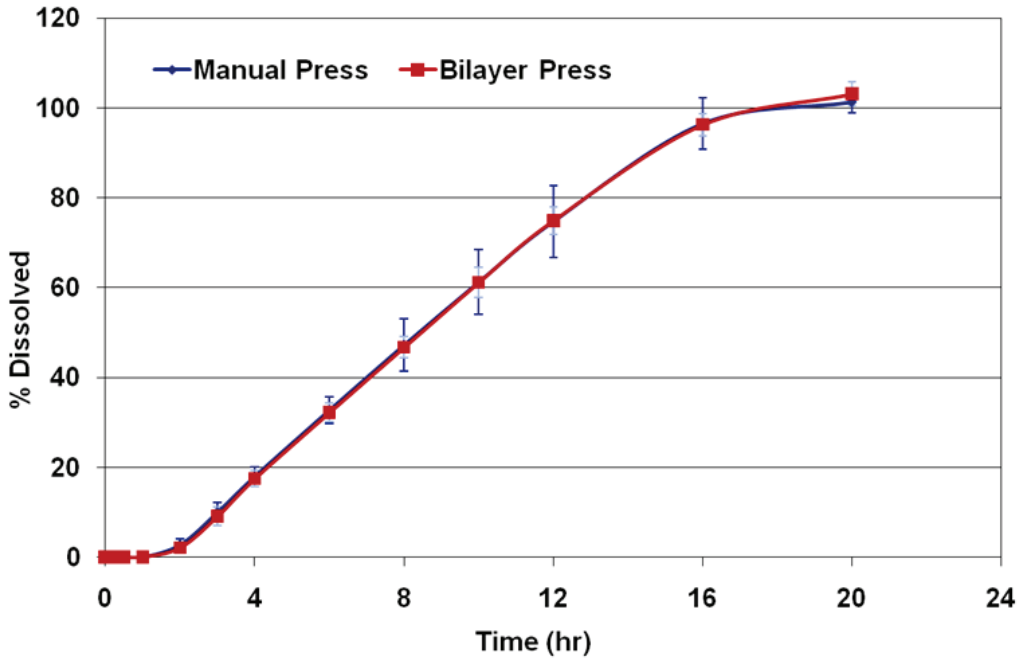
Process	Weight (mg)	Thickness (mm)	Tablet hardness (kp) (Tensile strength (MPa))
Tray drying	500 ± 0.8	5.6 ± 0.0	14.5 ± 0.7 (1.6)
Fluid bed drying	501 ± 1.3	5.6 ± 0.1	14.7 ± 0.5 (1.6)
Manual Press	502 ± 3.3	5.7 ± 0.0	14.6 ± 0.9 (1.6)
Bilayer Press	503 ± 6.2	5.6 ± 0.0	16.9 ± 2.9 (1.9)

Figure 2. Release Profiles of Drug X Tablets using Different Methods to Dry the Granules, Tray Drying (TD); Fluid Bed Drying (FBD) (f_2 values > 71)



Comparison of manual vs. bilayer press in compression of tablet cores yielded similar results as well (**Table 3** and **Figure 3**).

Figure 3. Release Profiles of Drug X Tablets using Different Methods of Tablet Compression (f_2 = 98)



Conclusions

Results demonstrated that varying tablet core hardness, method of drying granules (tray drying vs. fluid bed drying), and method of tablet manufacture (manual compression vs. bilayer rotary press) did not significantly affect the drug release from the PPOP tablets of this slightly water soluble model drug. Results showed a robust osmotic system which could yield satisfactory results for similar dose and solubility drug candidates. These studies illustrate the viability of osmotic systems whose complexity can be readily managed by satisfactory development and manufacturing controls.

Acknowledgement

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