The Influence of Level and Location of NaCl on Performance of Push-Pull Osmotic Pump Tablets of a Practically Water Insoluble Model Drug

Shahrzad Missaghi, Piyush Patel, Thomas P. Farrell and Ali R. Rajabi-Siahboomi

Poster Reprint
CRS 2012

Abstract Summary

Push-Pull Osmotic Pump (PPOP) tablets of a practically insoluble model drug were developed using sodium chloride as an osmogen. Both concentration and location (push and pull layers) of the osmogen were evaluated. Drug release profiles were not significantly affected by osmogen concentration in the push layer, in the range of 10-35% w/w. Presence of osmogen in pull layer resulted in shorter lag time and greater drug release rate. The findings of this study illustrated robustness of osmotic technology for zero order drug release and approaches to modulate drug release using the osmogen concentration and location.

Introduction

Interest has increased 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. 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 more accurate prediction of in vivo performance from in vitro dissolution profiles. However, utilization of the technology has been restricted due to the perceived complexity of these systems, manufacturing challenges and patent landscape.[1]

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.[2] This study evaluates the effect of osmogen (sodium chloride) concentration and location within the bilayer tablet core on drug release from PPOP tablets.

Experimental Methods

Drug release from osmotic pumps is governed by the osmotic potential generated between the water-soluble ingredients, within the tablet core and the surrounding medium. Sodium chloride (NaCl) is a commonly used osmogen, since it is widely available, non-reactive and provides high osmotic pressure across the semipermeable membrane.[1] To further evaluate the role of NaCl, different quantities and locations within the bilayer tablet cores were examined. A formulation, containing 35% w/w salt in push layer was developed as described previously[2], shown in Table 1. Individual pull and push layer blends were prepared in a high shear granulator (Diosna P/VAC 10, Germany) (batch size, 1 kg) using ethanol-deionized water (85:15 w/w) as the granulating liquid. Granules were dried in a vacuum drying oven, milled and lubricated. Bilayer tablets were manufactured 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).

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**

Tablets were coated in a Vector Hi-Coater LDCS 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). 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). To evaluate the effect of NaCl content within push layer, varying levels of 0-35% w/w were evaluated. This was achieved by adjusting the level of POLYOX™ water-soluble resins, Coagulant grade, accordingly. The effect of NaCl location was evaluated in push layer only (0-35%), in pull (drug) layer only (22.8%) and in both pull and push layers (11.4 and 17.5%, respectively). In all instances, NaCl level was kept constant (45 mg) in the bilayer tablet. Incorporation of NaCl in the pull layer was achieved by lowering the level of POLYOX™ N-80 in the formulation. Tablets were evaluated for physical properties and in vitro drug release based on the USP methods. Drug release rate was obtained from the slope of the linear portion of the release profiles. The correlation coefficient (R^2) was calculated accordingly. Moreover, the release profiles were compared using similarity factors (f_2).

Results and Discussion

Table 2 shows the physical properties of uncoated bilayer tablets. In general, an increase in salt level and subsequent decrease in POLYOX™ Coagulant led to lower mechanical strength of the bilayer tablets. Figure 1 shows the drug release profiles for the PPOPs containing different levels of osmogen in the push layer. Drug release was linear (R^2 >0.99) and similar for PPOPs containing 10-35% w/w of NaCl (f_2 >55). The linearity was compromised for the system without NaCl where the drug release is generally slower, compared to other evaluated systems, since the osmotic potential is reduced due to lack of osmogen in the system. Figure 2 shows the release profiles for PPOPs when the location of the osmogen is changed. Presence of NaCl in drug layer for both systems (drug layer only and drug layer + push layer) resulted in shorter lag time (~1.8 vs. 2.6 hours for push layer only) and greater release rate (11 vs. 9%/hr for push layer only). The presence of NaCl and subsequently lower level of POLYOX™ N-80 within the pull layer may have led to quicker water ingress, followed by overall lower viscosity of this layer. This could result in initial drug release from the system. Table 3 shows comparative measures of drug release for all evaluated PPOPs of this study.

Table 2. Physical Properties of Uncoated Bilayer Tablets Containing Varying Salt Content and Locations (PL: push layer; DL: drug layer) (n=10)

Tablets	Weight (mg)	Thickness (mm)	Tablet hardness (kp) (Tensile strength (MPa))
No NaCl	328 ± 2.2	5.1 ± 0.0	11.3 ± 0.9 (1.61)
PL only 10%	331 ± 3.8	5.1 ± 0.0	12.6 ± 0.6 (1.81)
PL only 20%	331 ± 2.7	5.0 ± 0.0	10.1 ± 1.4 (1.49)
PL only 35%	332 ± 4.1	5.0 ± 0.1	9.4 ± 1.2 (1.37)
DL only 22.8%	329 ± 3.0	5.0 ± 0.0	8.6 ± 1.2 (1.25)
DL and PL 11.4 and 17.5%	329 ± 3.4	4.9 ± 0.0	10.1 ± 0.7 (1.51)

Figure 1. Release Profiles of PPOPs of Drug Y with Varying Levels of Osmogen in Push Layer (PL) (semipermeable coating WG: 8% w/w) (n=6)

Figure 2. Release Profiles of PPOPs of Drug Y with Constant Level of Osmogen at Different Locations (semipermeable coating WG: 8% w/w) (n=6)

PPOPs	$t_{10\%}$ (hr)*	$t_{50\%}$ (hr)	$t_{90\%}$ (hr)	Release rate (%/hr)	R^2	f_2 value
No NaCl	2.5	7.4	16.5	5.9**	0.9736	55
PL only-10%	2.2	6.4	12.7	8.2	0.9927	66
PL only-20%	2.3	6.5	11.5	8.8	0.9984	69
PL only-35%	2.6	6.9	11.8	8.8	0.9985	Ref.
DL only-22.8%	1.7	5.3	9.6	10.5	0.9983	39
DL and PL-11.4 and 17.5%	1.8	5.3	9.2	11.2	0.9996	37

Conclusions

PPOP tablets of a practically insoluble model drug were manufactured and evaluated using varying levels and locations of sodium chloride (NaCl) as the osmogen. Results demonstrated the least sensitivity of the developed PPOPs to the osmogen level in the push layer at inclusion levels of 10-35% w/w. Presence of osmogen in pull layer led to shorter lag time and greater drug release rate. The results of this study demonstrated a robust, yet flexible, PPOP system towards 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 annual meeting and exposition, Washington, DC, 2011.
3. Malaterre V et al, *Int. J. Pharm*. 2009; 376, 56-62.

Table 3. Comparative Values for Drug Release Profiles of Drug Y PPOPs with Varying Osmogen Content and Location