Evaluation of Suitability of Push-Pull Osmotic Pump Systems for Drugs with Different Solubilities and Doses

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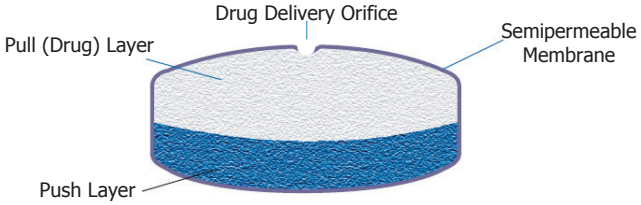
Purpose

There has been an increasing interest in the development of oral osmotic dosage forms in which drugs can be delivered at a constant rate over a long period of time. Drug release from osmotic dosage forms is 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. Nevertheless, access to the osmotic technology has been restricted due to the perceived complexity of these formulations, manufacturing challenges and patent landscape.[1] In this study, the influence of dose and solubility of 4 model drugs on push-pull osmotic pumps[2] (PPOP) (Figure 1) has been investigated.

Figure 1. Components of a PPOP Tablet



Methods

Pull and push layer blends were prepared in a high shear granulator followed by bilayer tablet compression, semipermeable membrane coating and laser drilling of a delivery orifice on the pull layer side (Figure 2). Four model drugs, glipizide, theophylline, acetaminophen (APAP) and verapamil HCl (Table 1), were incorporated in the pull layer of the PPOP systems and evaluated at different dose levels, corresponding to a range of 5.6-60.0% w/w of drug within the pull layer. The higher dose levels were accommodated by reducing the POLYOX™ water-soluble resins N-80 content within the pull layer formulation (Table 2). Push layer composition remained the same (Table 3). Bilayer tablets were compressed at a target tablet weight of 330 mg, except for verapamil HCl where tablets were compressed at 450 mg to accommodate higher dose levels. The ratio of pull-push layers (~2:1 w/w) was constant for all PPOPs. The dissolution profiles of the PPOP tablets were obtained using an Apparatus II (50 rpm) dissolution bath with sinkers. Drug release profiles were compared using similarity factors (f_2).[3]

Figure 2. Manufacturing Steps for PPOP Tablets

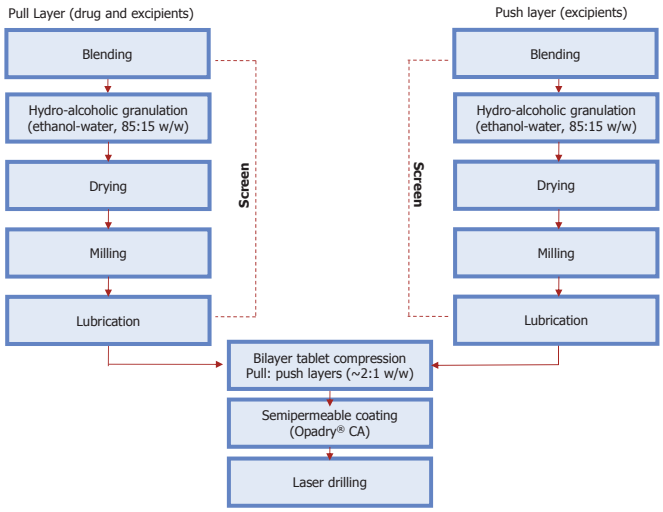


Table 1. Model Drugs of Varying Dose and Solubility

		Dose Level (mg)		
Model Drug	**Solubility**	**Low**	**Medium**	**High**
Glipizide	Practically insoluble (0.02 mg/ml)	11	50	-
Theophylline	Slightly soluble (8 mg/ml)	11	50	100
APAP	Sparingly soluble (14 mg/ml)	11	50	100
Verapamil HCl	Soluble (50 mg/ml)	40	100	180

Table 2. Formulation of Pull Layer used in PPOP Tablets of Various Model Drugs at Different Dose Levels

(A) Pull layer for glipizide, theophylline and APAP

Dose levels: Low, 11 mg, Medium, 50 mg, High, 100 mg

Pull Layer – Ingredients	Quantity (%w/w)
Model drug (glipizide*, theophylline, APAP)	**5.6**, **25.0**, **50.0**
Polyethylene oxide (POLYOX™ WSR N-80 NF)	**93.9**, **74.5**, **49.5**
Magnesium stearate	0.5
Total (200mg)	**100**

* High dose of glipizide was not evaluated due to the lack of sink condition in the dissolution medium.

(B) Pull layer for verapamil HCl

Dose levels: Low, 40 mg, Medium, 100 mg, High, 180 mg

Pull Layer – Ingredients	Quantity (%w/w)
Model drug (verapamil HCl)	**13.3**, **33.0**, **60.0**
Polyethylene oxide (POLYOX™ WSR N-80 NF)	**86.2**, **66.2**, **39.5**
Magnesium stearate	0.5
Total (300mg)	**100**

Table 3. Formulation of Push Layer used in PPOP Tablets of Various Model Drugs

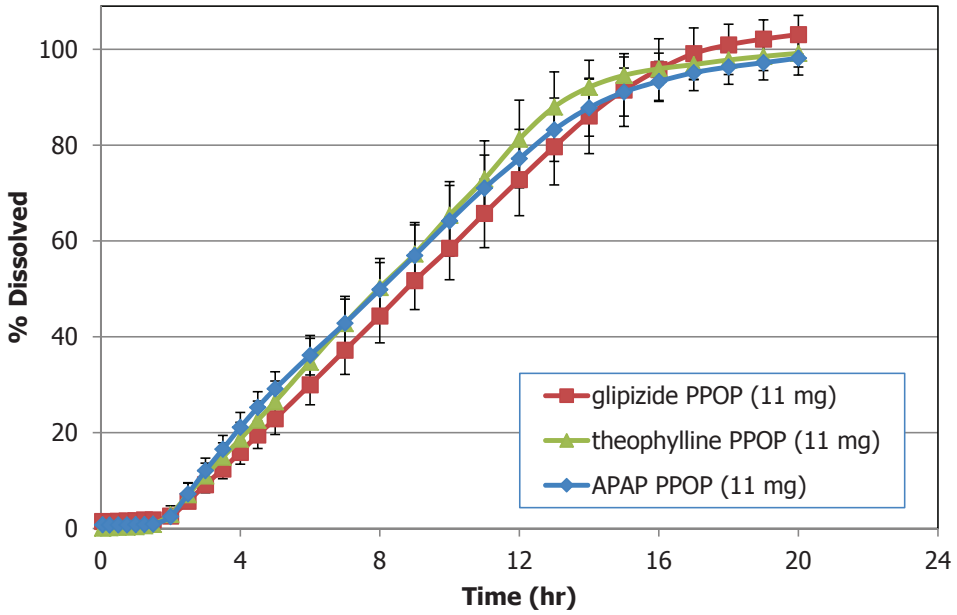
Push Layer – Ingredients	Quantity (%w/w)
Polyethylene oxide (POLYOX™ WSR Coagulant NF)	64.0
Sodium chloride	35.0
Pigment, red iron oxide	0.5
Magnesium stearate	0.5
Total (130 mg) * 150mg for verapamil HCl PPOP	**100**

Results

Evaluation of pull layer granules showed that increase of dose and subsequent decrease of POLYOX™ N-80 resulted in higher Carr's compressibility indices for drug layer granules (18-33%), indicating poor powder flow which led to difficulties in tablet compression.

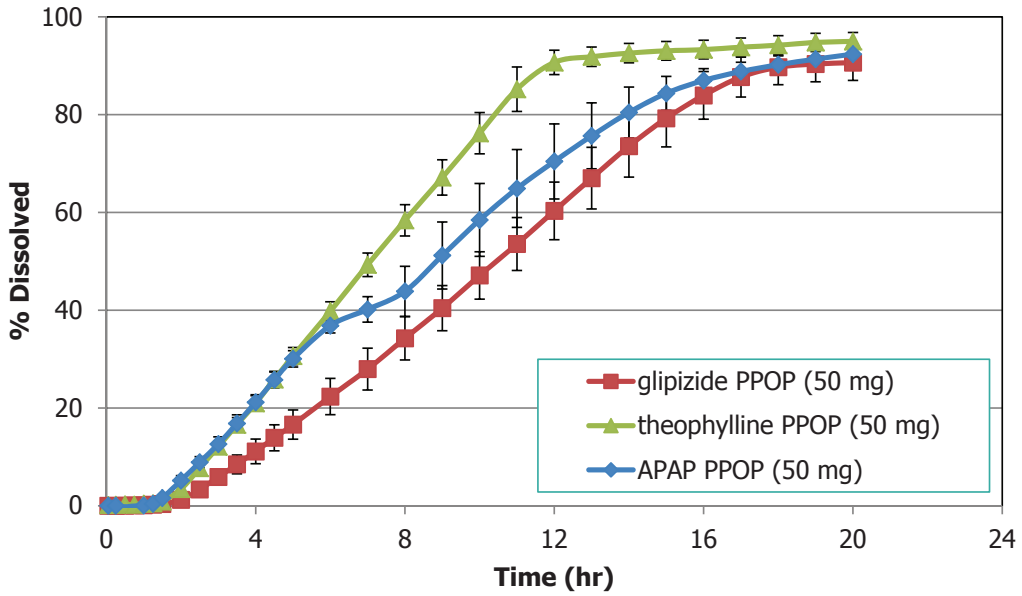
For all drugs, regardless of solubility, low dose PPOP (5.6-13% w/w of the pull layer) were successfully manufactured and resulted in desirable drug release pattern (i.e. presence of lag time followed by zero order kinetics). Using a similar core formulation (bilayer) and Opadry® CA weight gain, resulted in similar drug release profiles for glipizide, theophylline and APAP at a low 11 mg dose (Figure 3).

Figure 3. Comparative Dissolution Profiles for Model Drugs at Low Dose (11 mg) Opadry CA: 12% w/w WG (n=6)



At medium 50 mg dose, manufacture of PPOPs was challenging but although the drug release followed the expected pattern, the release profiles were different amongst the model drugs (Figure 4).

Figure 4. Comparative Dissolution Profiles for Model Drugs at Medium Dose (50 mg) Opadry CA: 12%w/w WG (n=6)



At high 100 mg dose, in addition to compression challenges, drug release profiles deviated from a typical PPOP system which may be due to the imbalance of pull-push layers viscosities. Figures 5 and 6 show the drug release profiles for increasing doses of theophylline and verapamil HCl PPOP, respectively. Drug release form the PPOP of other model drugs showed a similar pattern.

Figure 5. Comparative Dissolution Profiles for Theophylline PPOP, Opadry CA: 12% w/w WG (n=6)

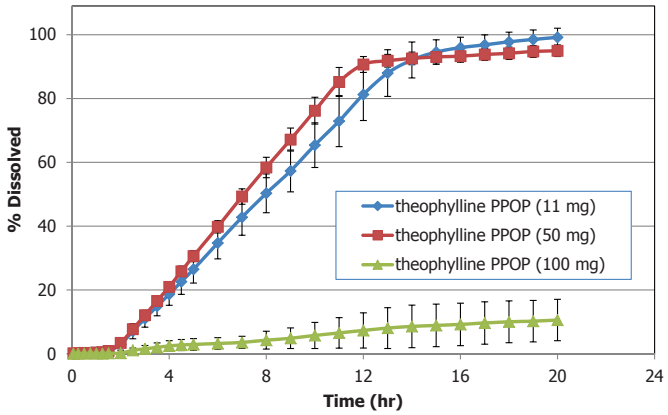
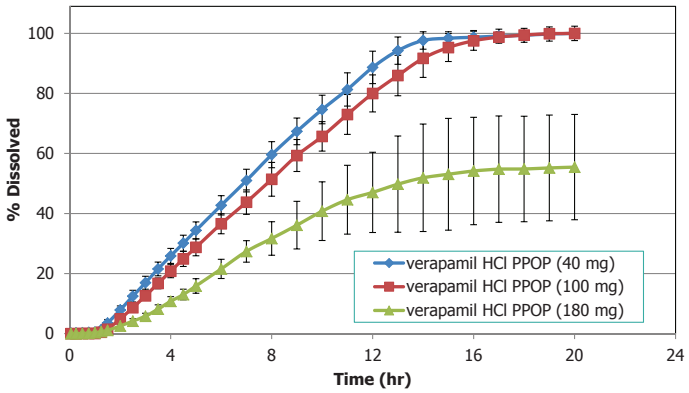


Figure 6. Comparative Dissolution Profiles for Verapamil HCl PPOP Opadry CA: 8%w/w WG (n=6)



Conclusions

The standard PPOP system may be suitable for a wide range of drugs of varying solubility and doses (below 25% w/w of pull layer formulation). This investigation demonstrated the robustness, and yet flexibility, of the PPOP system for various model drugs. To accommodate higher dose levels, the standard formulation, granulation step and size of the tablets need to be modified in order to achieve a zero order release.

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.
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3. Moore JW, Flanner HH. Mathematical comparison of curves with an emphasis on in vitro dissolution profiles. *Pharm. Tech.* 1996; 20(6): 64-74.

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