Effect of Polyethylene Oxide Molecular Weight and Osmogen Content on the Performance of Push-Pull Osmotic Pump Tablets

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Abstract Summary

In this study, the influence of push layer formulation was evaluated using a Design of Experiment (DOE) approach to determine the impact of polyethylene oxide (POLYOX™ Water-Soluble Resins) molecular weight grade and osmogen (sodium chloride) content on the performance of push-pull osmotic pump tablets. Study results revealed that osmogen level and its interaction with POLYOX molecular weight impacted the drug release from osmotic tablets.

Introduction

Push-pull osmotic pumps (PPOP) have been successfully developed and marketed to extend the release of various drugs in a controlled manner (zero order kinetics). PPOP typically consist of a bilayer tablet core surrounded by a semipermeable membrane with a laser-drilled drug delivery orifice. Water diffuses through the membrane, hydrates the polymers in both the drug and push layers, leading to the formation of drug dispersion in the drug layer (also known as pull layer) and the swelling of the push layer. The hydrodynamic pressure generated by the swelling of the push layer forces the drug dispersion through the orifice. Researchers have reported that the drug layer formulation and semipermeable coating are the key factors influencing the release kinetics of these system.[1-4] The aim of this study was to examine the effect of push layer formulation on the drug release profiles of osmotic tablets through a DOE approach, using theophylline as a model drug.

Experimental Methods

The main components of the push layer formulation are POLYOX MW 4,000,000 and 7,000,000 (POLYOX NF LEO 301 and 303 grades) and sodium chloride (10-40% w/w).[5] The formulations of theophylline bilayer tablets are shown in **Table 1**. The drug layer formulation was held constant in this study, while the push layer was varied in PEO MW 2,000,000 to 7,000,000 (POLYOX N60K to 303 grades) and salt concentration of 10-55% w/w. A response surface DOE was performed in the experimental design and a total of 16 formulations were evaluated.

The bilayer tablets were produced by direct compression on an instrumented rotary press (Piccola, Riva, Argentina) using standard round, concave tooling (9.5 mm) at a target weight of 330 mg (11.2 mg dose, pull:push layer ratio of ~2:1 w/w). Opadry® CA, a fully formulated semipermeable coating system in 94:6 w/w acetone:water at 7% solids was applied onto the bilayer tablets, using a 15" fully-perforated coating pan (O'Hara IIX, O'Hara, Canada) to a theoretical weight gain of 10.0% w/w. Coated tablets were then dried in a vacuum oven at 40°C for 24 hours. A 0.5 mm delivery orifice was laser-drilled (Cobalt 250, InkCupsNow, USA) on the pull layer side of the osmotic tablets. Dissolution studies were conducted in DI water using USP apparatus II with sinkers at 50 rpm and drug release was measured using a UV-Visible spectrophotometer (Agilent Technologies, USA). The similarity factor (f_2) was calculated to compare the dissolution profiles. The drug release rate (% per hour) was obtained from the slope of the linear section of the dissolution profiles in the range of 5-80% of drug release. The three-point dissolution data ($t_{10\%}$, $t_{50\%}$, $t_{80\%}$, time needed to deliver 10, 50 or 80% of the drug) were plotted and further analyzed using Minitab 16.

Table 1. Quantitative Formulation of Theophylline Bilayer Tablets

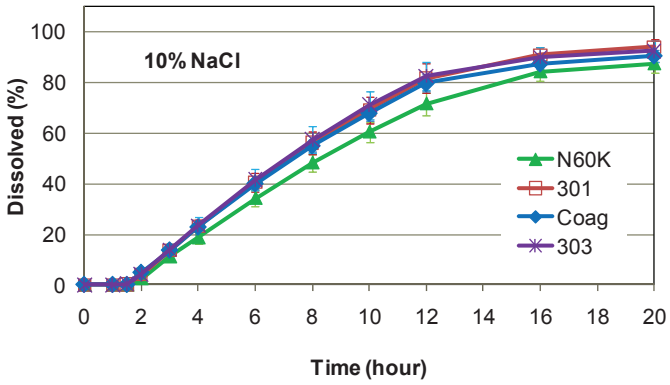
Pull Layer - Ingredients	Quantity (% w/w)
Theophylline	5.6
Polyethylene oxide (POLYOX WSR N-80)	93.9
Magnesium stearate	0.5
Total	**100**
Push Layer - Ingredients	**Quantity (% w/w)**
Polyethylene oxide (POLYOX N60K, 301, Coagulant, 303)	88.5, 73.5, 58.5, 43.5
Sodium chloride	10, 25, 40, 55
Pigment, red iron oxide	1.0
Magnesium stearate	0.5
Total	**100**

Results and Discussion

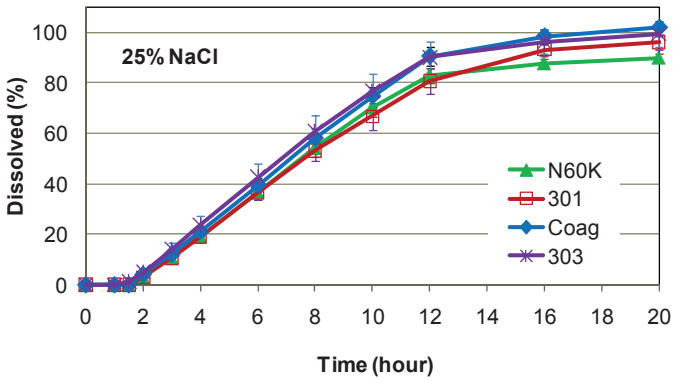
The drug release profiles of theophylline osmotic tablets are shown in **Figures 1(A - D)**. All profiles showed similar drug release (f_2 > 50) with a lag time of ~2.0 hours followed by zero order release (up to 12 hours). Regardless of the difference in the push layer formulation, complete drug release was not achieved; this was related to possible drug entrapment. At either low (10%) or high (55%) salt content, approximately 5-10% drug was retained inside the osmotic tablets after 24hr dissolution testing. The drug release rate was in the range of 6.9-8.8 % per hr for all 16 samples (**Figure 2**). The $t_{10\%}$, $t_{50\%}$, values were in the range of 2.4-2.9, 7.0-8.8, 10.5-13.2 hours, respectively. **Figure 3** illustrated that salt content had bigger impact on $t_{80\%}$ (3.0 hours difference near terminal release) than $t_{10\%}$ (0.5 hour difference in lag time).

Figure 1. Drug Release Profiles of Theophylline Osmotic Tablets (n = 6)

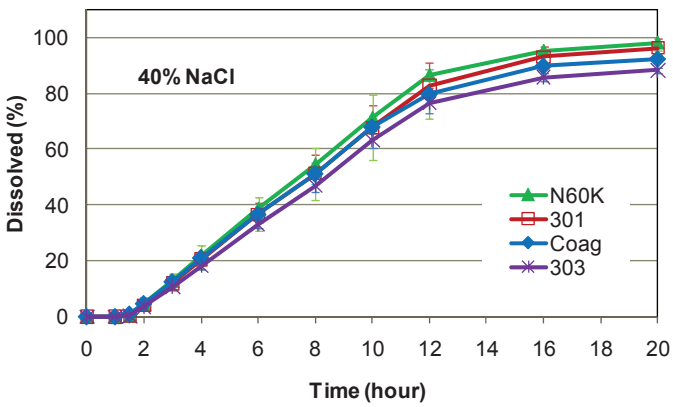
(A) 10% NaCl



(B) 25% NaCl



(C) 40% NaCl



(D) 55% NaCl in the Push Layer

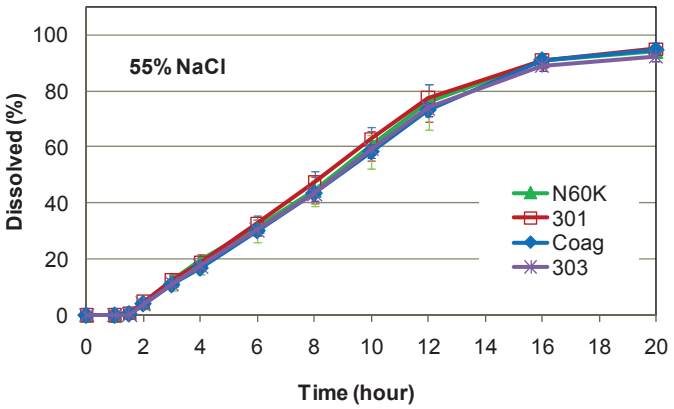


Figure 2. Effect of Salt Content and POLYOX MW on Drug Release Rate from Theophylline Osmotic Tablets

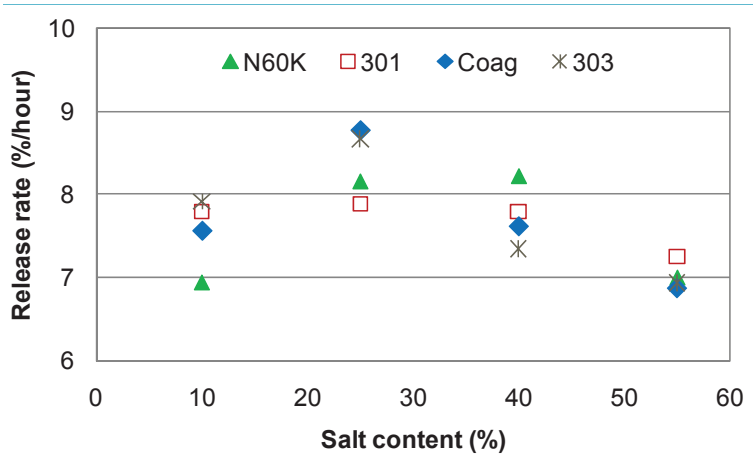


Figure 3. Dissolution Performance of Theophylline Osmotic Tablets: $t_{10\%}$ and $t_{80\%}$

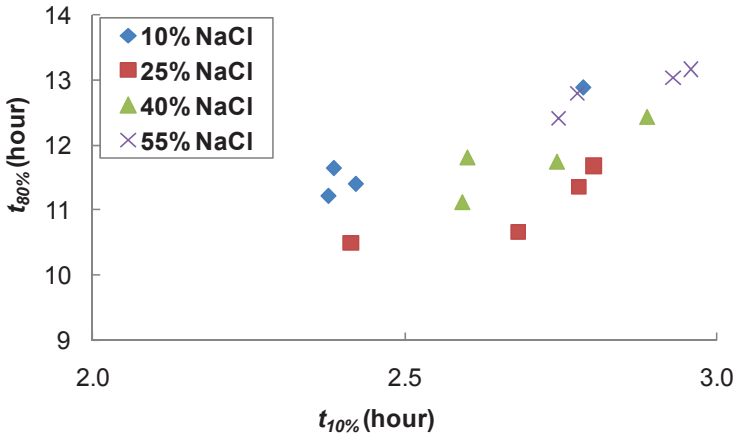
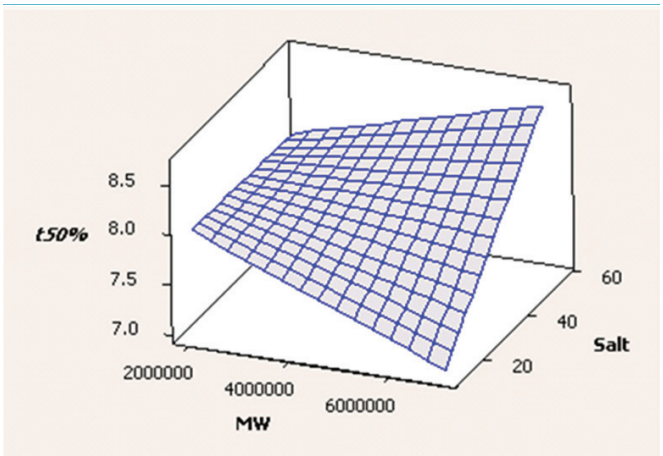


Figure 4. Surface Plot of $t_{50\%}$ as Function of POLYOX MW and Salt Content



Figures 2 to **4** indicate that salt content affects the drug release rate (k) and $t_{10\%}$, $t_{50\%}$ and $t_{80\%}$ values. Further statistical analysis shows significant relationships between the responses (release rate, $t_{10\%}$, $t_{50\%}$, $t_{80\%}$) and the variables (POLYOX MW, salt content) ($p < 0.05$), and as an example, **Figure 4** shows that salt content and its combination with POLYOX MW impacted $t_{50\%}$.

Conclusions

Theophylline PPOP tablets were successfully manufactured using various POLYOX grades and salt content in the push layer formulation. The study results demonstrated that salt content, and the interaction between POLYOX grade and salt content, may impact the drug release; while the change of the polymer MW (viscosity grades) studied here, had no significant effect on drug release. The optimization of the push layer formulation may be a useful approach to fine tune the drug release behavior from PPOP tablets and further enhance the robustness.

References

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