Development of Robust and Customizable Zero-Order Release Push-Pull Osmotic Tablets

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Introduction

Push-pull osmotic pump (PPOP) tablets are specialized dosage forms delivering zero-order drug release and patient benefits in safety, efficacy and convenience compared to other solid dosage forms. Drug release from such 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, use of this technology has been limited due to the perceived complexity of these systems and manufacturing challenges.

Corelease OPL™ and Corelease CA™ are fully formulated products that facilitate a simplified approach to manufacturing robust PPOP tablets and tailoring zero-order release profiles to fit the needs of patients. Corelease OPL is a controlled release, box-to-hopper, direct compression osmotic push layer comprising a polyethylene oxide (PEO) swelling agent and a sodium chloride (NaCl) osmogen. Corelease CA is a one-step semipermeable membrane coating system comprising cellulose acetate (CA) polymer and a polyethylene glycol (PEG) pore former.

Objectives

This study evaluates the effects on zero-order release profiles from PPOP tablets when varying:

- The molecular weight of PEO used in the push layer.
- Osmogen levels in push layer formulations.
- Coating weight gain and pore former levels of Corelease CA.

Methods

Push layer formulations containing varying levels of high viscosity grades of PEO (43.5 – 88.5% w/w), sodium chloride (10 – 55% w/w), iron oxide (0.5 – 1.0% w/w) and magnesium stearate (0.5% w/w) were used to manufacture glipizide 11.2 mg PPOP tablets. The push layer formulations were based on the Corelease OPL direct compression (box-to-hopper) concept, which does not require granulation or other preprocessing or handling steps by the user prior to tablet manufacturing. In conjunction with a glipizide drug layer formulation comprising a low molecular weight grade of PEO, bilayer tablets were produced by direct compression into 330 mg, 9.5 mm round standard concave tablets using a Piccola rotary bilayer tablet press to an approximate breaking force of 10 kp. These tablets were coated with Corelease CA formulations of varying pore former concentrations (10 – 30% w/w). Film thickness was varied by applying a range of theoretical coating weight gains (5.5 – 14% w/w) for formulations prepared in a co-solvent mixture of acetone and water (94:6). Coated PPOP tablets were laser drilled with a 0.5 mm drug delivery orifice and dissolution was conducted using USP apparatus II at 50 rpm in pH 7.5 simulated intestinal fluid.

Results

When varying the grades of PEO used in the push layer across a molecular weight range of 2,000,000 – 7,000,000, little to no change was observed in the release rate of glipizide or the duration of lag time needed for osmotic pump activation (Figure 1). This provides evidence that drug release may not be as sensitive to the inherent viscosity decrease of PEO over time. This also suggests that modulating PPOP drug release from tablets using Corelease OPL could be better pursued through formulation factors other than altering molecular weight of PEO in the push layer.

Varying the push layer formulation ratios of PEO to osmogen was observed to have a similarly low impact in modulating the release rate from glipizide PPOP tablets (Figure 2). Only at the extremes of the ratios evaluated (i.e., 10% and 55% NaCl) were there notable changes in the release profiles of glipizide.

Altering the composition and thickness of the semipermeable membrane coating was found to be a more controllable and tailorable approach to modulating release profiles from PPOP tablets. Varying the pore former concentration of Corelease CA across inclusion levels of 10% to 30% provided a wide range of release rates (7.1 – 21.0%/hr) (Figure 3). Increasing the semipermeable membrane thickness proved similarly effective in modifying glipizide release rates (5.4 – 14.2%/hr) (Figure 4). A combination of these film coating approaches can provide formulators with the ability to widely customize release profiles for their PPOP dosage form. It further suggests that core formulation variables should be considered first for aspects such as robustness and tabletability rather than modulating release profiles.

Figure 1. Effect of Push Layer PEO Grade on Glipizide Dissolution

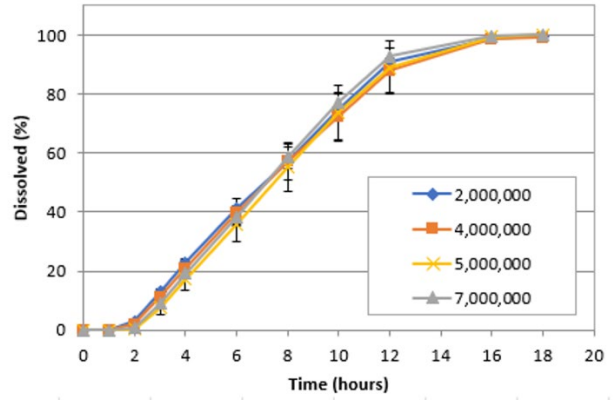


Figure 2. Effect of Osmogen Level on Glipizide Dissolution

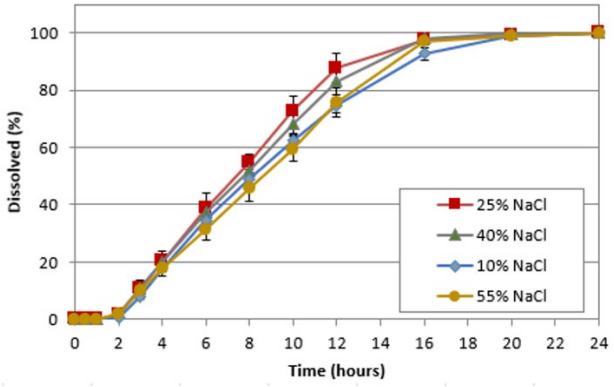


Figure 3. Effect of Pore Former Level on Drug Release Rates for Glipizide PPOP Tablets.

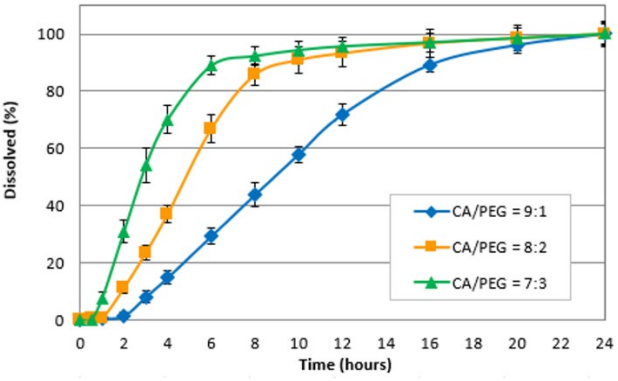
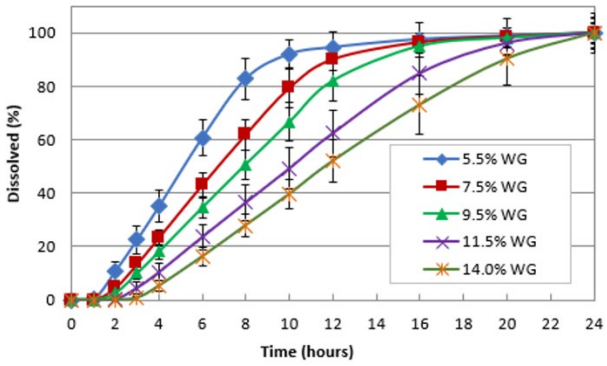


Figure 4. Effect of Coating Weight Gain on Drug Release Rates for Glipizide PPOP Tablets.



Conclusions

The use of Corelease OPL and Corelease CA provided robust and customizable release profiles for PPOP tablets. The bilayer core remained functional through a wide range of push layer polymer viscosities and osmogen levels, while the coating was optimized through weight gain and pore former level to provide a range of release rates.