Preparation of Osmotic Tablets Using a Direct-to-Hopper Formulated Push Layer Based on Polyethylene Oxide

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Introduction

The purpose of this study was to investigate the use of a direct-to-hopper push layer blend for use in the direct compression manufacture of bilayer push-pull osmotic pump (POPP) tablets. These specialized dosage forms are designed to deliver zero-order drug release and valuable patient benefits in terms of safety, efficacy and convenience compared to other solid dosage forms (Figure 1).

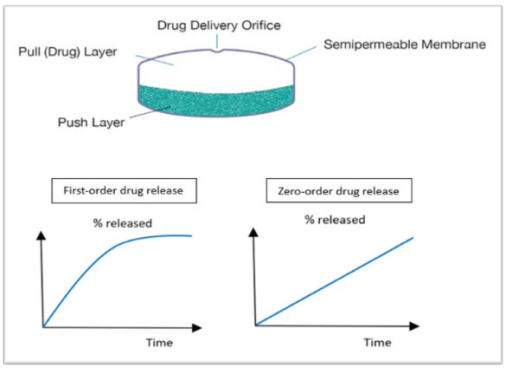
PPOP's often contain polyethylene oxide (PEO) and during manufacture require multiple processing and cleaning steps, which are time-consuming, complex, and can potentially introduce safety hazards. Use of a fully formulated PEO-based push layer blend will eliminate multiple processing steps (e.g., milling and blending operations) and reduce the cleaning burden associated with PEO. This push layer blend consists of a high viscosity PEO as the swelling agent, sodium chloride as the osmogene, an iron oxide pigment for identification of the layer, and magnesium stearate as an optional lubricant.

The PPOP manufacturing process was further simplified by producing the drug layer formulation with an ordered mixing approach, where a uniform blend is created by adhering fine particles to the surface of coarse particles primarily by electrostatic forces. The PPOP manufacturing process was further simplified by producing the drug layer formulation with an ordered mixing approach, where a uniform blend is created by adhering fine particles to the surface of coarse particles primarily by electrostatic forces.

Methods

The push layer blend was prepared using a high viscosity grade of PEO (POLYOX Coagulant, IFF; 73.5-74.0% w/w), sodium chloride (25% w/w), iron oxide (1% w/w), and optionally magnesium stearate (0.5% w/w), using a dry blending process in a twin shell blender. The drug layer blend was prepared using low viscosity grade PEO (POLYOX N80, IFF; 94.4% w/w) and micronized glipizide (5.6% w/w; d90 ~4 µm) using an ordered mixture, dry blending process in a Turbula blender. The drug layer blend was evaluated for content uniformity. Glipizide 11.2 mg bilayer tablets were produced by direct compression into 330 mg, 3/8" (9.5 mm) round standard biconcave tablets using a Piccola rotary bilayer tablet press to an approximate breaking force of 9 kp.

Figure 1. PPOP Tablet Illustration and Example Drug Release Profiles



Tablets were coated with Opadry® CA fully formulated osmotic coating system to a 10% weight gain and then laser drilled to create a 0.5 mm delivery orifice on the drug layer tablet face. Glipizide PPOP release profiles were measured in simulated intestinal fluid pH 7.5 over the course of 24 hours.

Results

The drug layer blend, prepared using the ordered mixture approach, involved sieving of micronized glipizide API and PEO N80, then mixing these materials together in a Turbula blender. The three-dimensional action of this blender type provided a thorough layering of the micronized glipizide particles on the surfaces of the coarser PEO particles. This dispersion and layering process was visualized using scanning electron microscopy (SEM), showing adhesion of the API particles to the surface of the carrier particles (Figure 2). This technique yielded favorable blend uniformity of the pull layer formulation within a short processing time (n=6; 95.3% +/- 3.5% confirmed by HPLC analysis).

The manufacturing steps, equipment, and processing times were considerably reduced by using an ordered mixture approach instead of a solvent wet-granulation approach in the manufacture of the drug layer blend at laboratory/pilot scale (Figure 3). A visual timeline of a placebo PPOP tablet dissolution in water is displayed in Figure 4, showing complete extrusion and dissolution of the white pull layer over the course of 24 hours. Drug release profiles for glipizide 11.2 mg PPOP tablets were similar (f_2=71) for tablets manufactured with and without magnesium stearate in the push layer formulation. Both push layer formulas provided equivalent lag times of 2 hours and showed zero-order release profiles (Figure 5).

Figure 2. Ordered Mixture Process and SEM Images of Drug Layer Blend

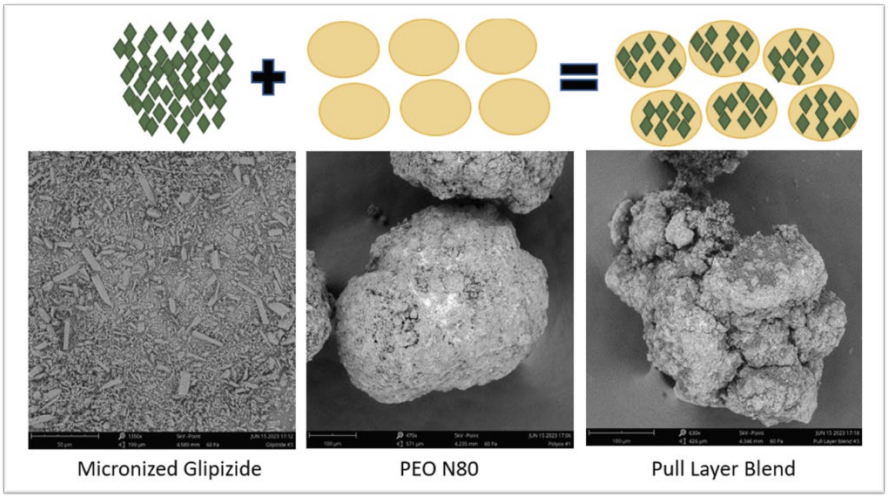


Figure 3. Comparison of Required Time and Steps for Pull Layer Production: Ordered Mixture Process vs. Solvent Granulation Process

Figure 4. Dissolution of Placebo PPOP Tablet Containing Push Layer (Red) and Pull Layer (White)

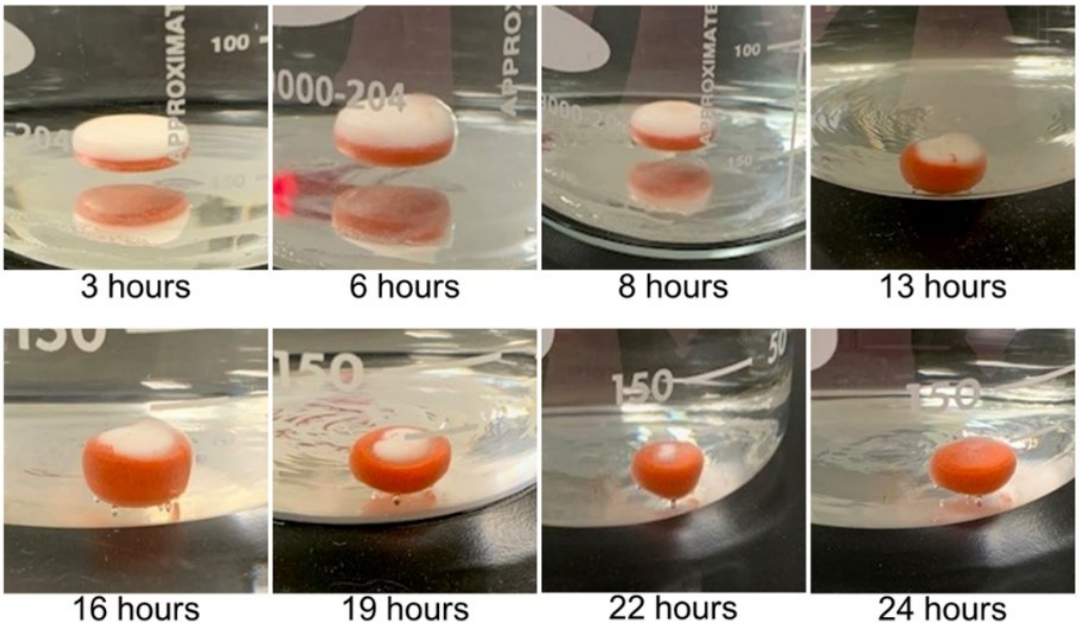
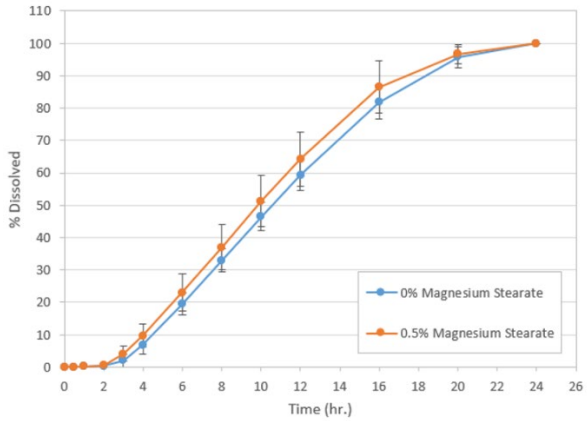


Figure 5. Drug Release Profiles for Glipizide 11.2 mg PPOP Tablets; Opadry CA Coating at 10 % WG



Conclusions

A formulated direct compression push layer blend was prepared, along with the ordered mixture pull layer blend, to manufacture bilayer PPOP tablets which (after Opadry CA coating and laser-drilling) showed favourable zero-order dissolution results. The ready-to-use push layer can offer ease-of-use and reduced cleaning burden associated with PEO. In addition, by having a direct-to-hopper approach, this provides a safer operation environment and efficient manufacturing of osmotic tablets

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