Zero-Order Drug Release from Push-Pull Osmotic Tablets in Varying Dissolution Media

Jeffrey Gimbel, Lawrence Martin, David Ferrizzi, and Ali Rajabi-Siahboomi

Colorcon, Inc.

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CONTACT INFORMATION: jgimbel@colorcon.com

INTRODUCTION

Push-pull osmotic pump (PPOP) tablets are specialized dosage forms providing zero-order drug release profiles, offering patients enhanced safety, efficacy, and convenience over other solid dosage forms. PPOP tablets have gained notoriety as being generally insensitive to variations in physiological conditions and demonstrating consistent release in varying dissolution media (e.g., pH, hydrodynamics, ionic strength). Marketed PPOP tablets are commonly manufactured using solvent granulation in the manufacture of push and pull layer formulations, which adds processing challenges and safety concerns of solvent handling and reclamation. A direct-to-hopper, direct compression (DC) osmotic push layer was developed to eliminate the issues in processing and safety risks associated with solvent use. This study evaluates the effects of changes in dissolution conditions and media on zero-order release profiles of PPOP tablets utilizing a DC push layer, while evaluating the impact of either a direct compression or granulated pull layer.

METHODS

A direct compression push layer (Corelease® OPL, Colorcon) and either a granulated or direct compression pull layer were used to manufacture glipizide 11.2 mg PPOP tablets. A cellulose acetate-based semipermeable membrane (Corelease® CA, Colorcon) was applied at a coating weight gain of 10%, and tablets were laser drilled with a drug delivery orifice. Dissolution testing was performed using USP apparatus II while varying media pH (6.8-7.5), paddle speed (50-150 rpm), and ionic strength (0-0.19 M/L).

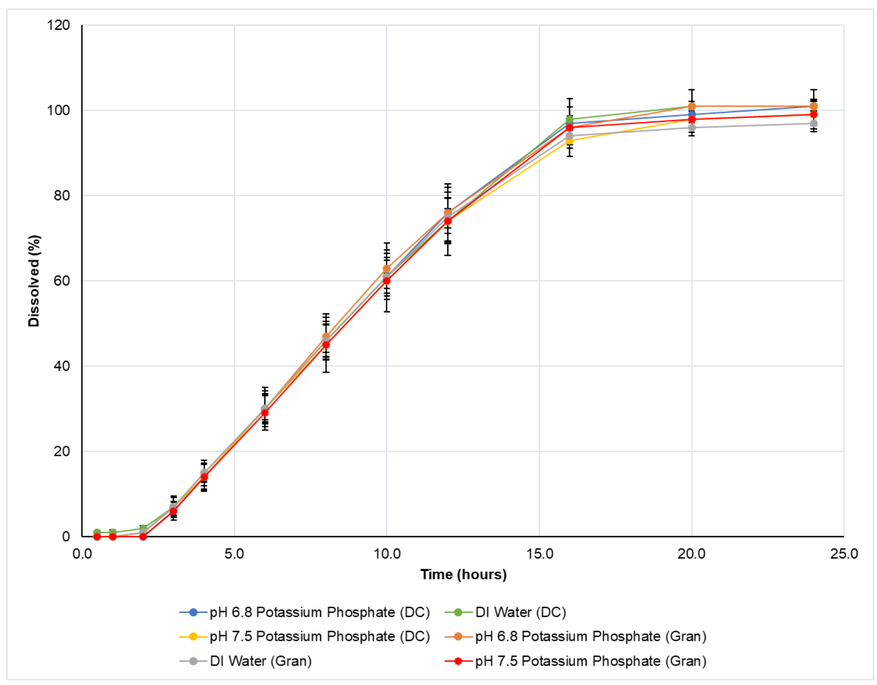

Figure 1. Effect of pH for PPOP Glipizide Tablets

RESULTS

Varying pH across a range of 6.8-7.5 resulted in little to no change in the release rate of glipizide or the duration of the lag time of the PPOP tablets (Figure 1). These profiles were identical to those obtained using deionized water. There was also no impact observed by granulating the pull layer vs. using a direct compression formulation. Similarly, little to no change was observed with a paddle speed range of 50-150 rpm in pH 7.5 phosphate buffer, indicating release profiles were insensitive to hydrodynamic conditions for both tablet types (Figure 2). The high ionic strength medium appeared to slightly decrease the rate of zero-order release but did not impact lag time or final amount released (Figure 3). This decrease was observed with both granulated and direct compression pull layers. Comparison of the fastest and slowest release profiles (Figure 3) using the f_2 similarity factor indicated that all release profiles were similar (f_2 = 63) despite differences in media ionic strength or method of manufacture of the pull layer.

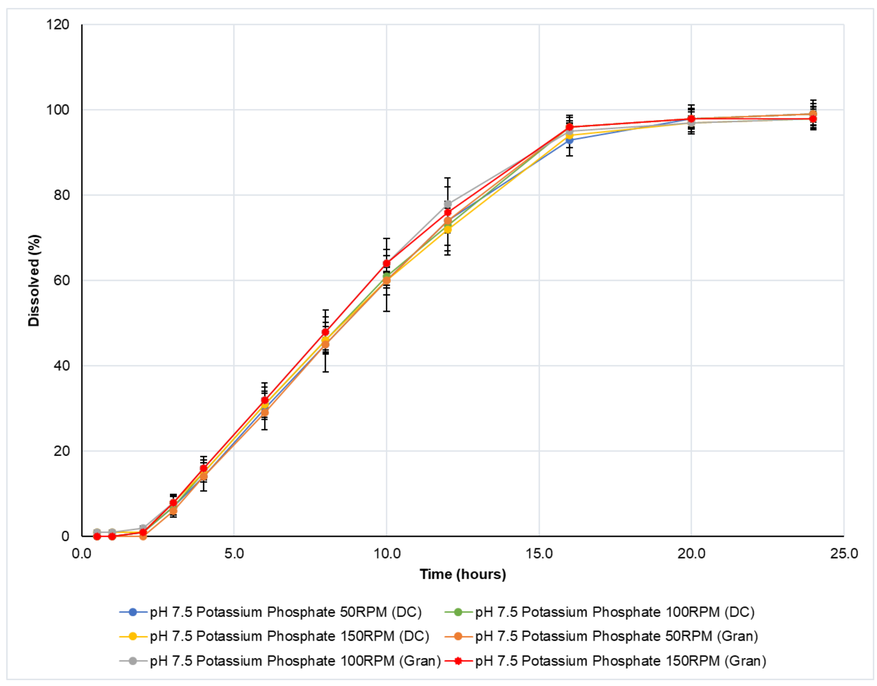

Figure 2. Effect of Paddle Speed for PPOP Glipizide Tablets

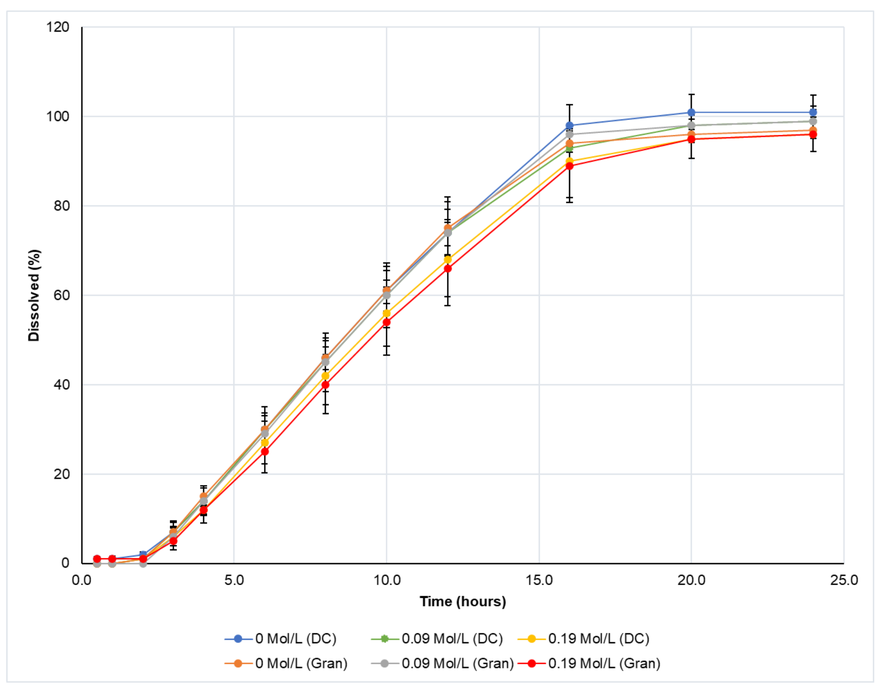

Figure 3. Effect of Ionic Strength on Glipizide Dissolution

CONCLUSIONS

The use of a direct compression push layer provided consistent and robust zero-order release from PPOP tablets over a wide variety of dissolution conditions. Varying dissolution media and hydrodynamic conditions resulted in minimal impact to release rates or lag times and maintained zero-order release profiles. Formulators can choose granulation or direct compression of the pull layer as no difference was seen in release profiles.