Investigation of Direct Compression Processing of Push Layer System for Osmotic Pump Tablets

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PURPOSE

Push-pull osmotic pump (PPOP) tablets can deliver drugs at a constant rate.[1-2] Push and pull layers are generally manufactured via a solvent granulation process. The purpose of this study was to investigate the direct compression (DC) method for manufacture of a ready-mix push layer system, as a direct-to-hopper approach, compared to the solvent-based high shear wet granulation (WG) process. The stability of the ready-mix push layer was also evaluated.

METHODS

Push layer blend was prepared using POLYOX™ WSR Coagulant NF LEO (swelling polymer) (73.5 %w/w), sodium chloride (osmogen) (25.0 %w/w), iron oxide (colorant) (1.0 %w/w) and magnesium stearate (lubricant) (0.5 %w/w), using a dry blending technique (batch size of 5 kg). For comparison, a push layer blend was also prepared using a high shear granulation process with similar components and ratios (Figure 1). The blends were evaluated for uniformity, particle size distribution and loss on drying (LOD). Both push layer blends were further used to prepare bilayer tablet cores using a pull layer formulation consisting of glipizide (10 mg) and POLYOX WSR N-80 NF LEO. Tablets were coated with Opadry® CA fully formulated osmotic coating system and laser drilled (Figure 2). The resulting PPOP tablets were evaluated for drug release. The DC-push layer blend (ready-mix) was packaged in polybags (with and without desiccant), stored in accelerated condition (40oC/75% RH) and evaluated for stability at pre-determined time intervals for 3 months.

Figure 1. Comparison of Push Layer Manufacturing Process (Direct Compression vs. Wet Granulation)

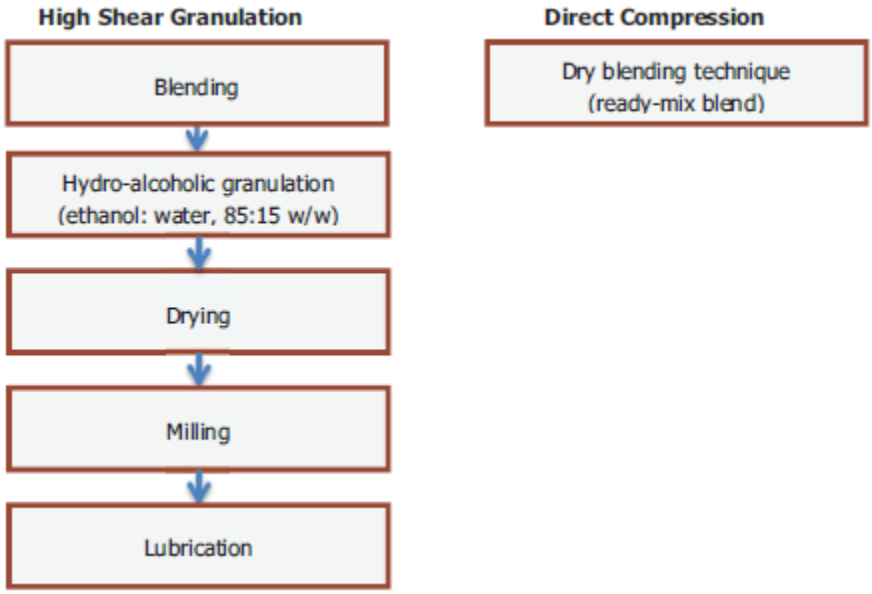
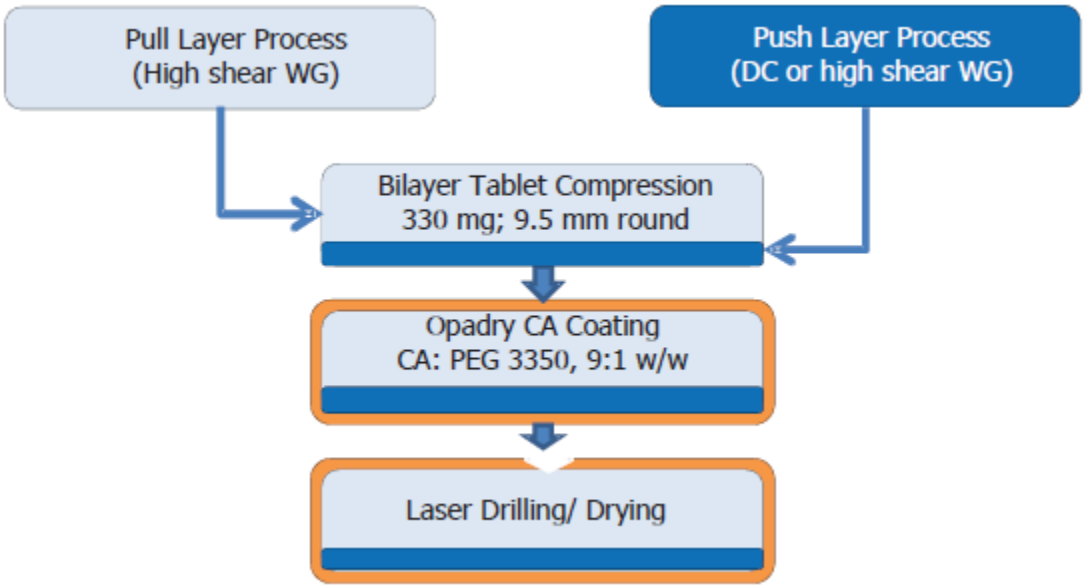


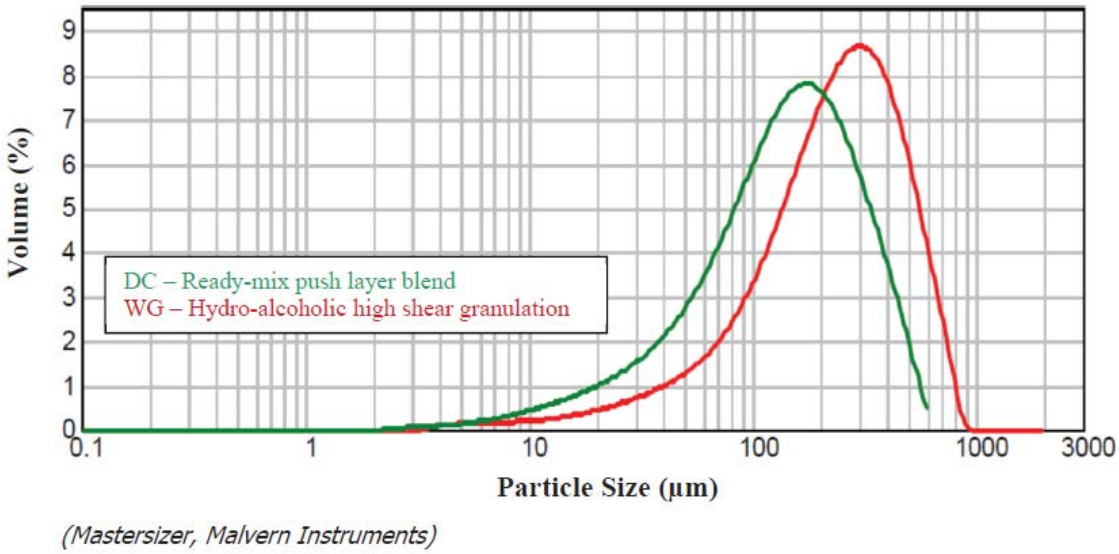
Figure 2. Manufacturing Process for Push-Pull Osmotic Pump Tablets



RESULTS

Figure 3 shows that the wet granulation process produced larger particles compared to the dry blending process (median particle size of 240 and 143 µm, respectively). The LOD values for both blends were similar (equal or below 0.5 %w/w). The ready-mix push layer demonstrated excellent content uniformity of the osmogen (RSD<2.5%), an indication of blend homogeneity. The glipizide bilayer tablet cores showed desirable properties (tablet weight variation RSD<2.0%; tablet hardness of ~12 kp/1.8 MPa), irrespective of the process used to manufacture the push layer (DC vs. WG method). Moreover, drug release profiles were similar for the resulting PPOP tablets, confirming that the performance of the push layer is comparable for both manufacture processes (Figure 4).

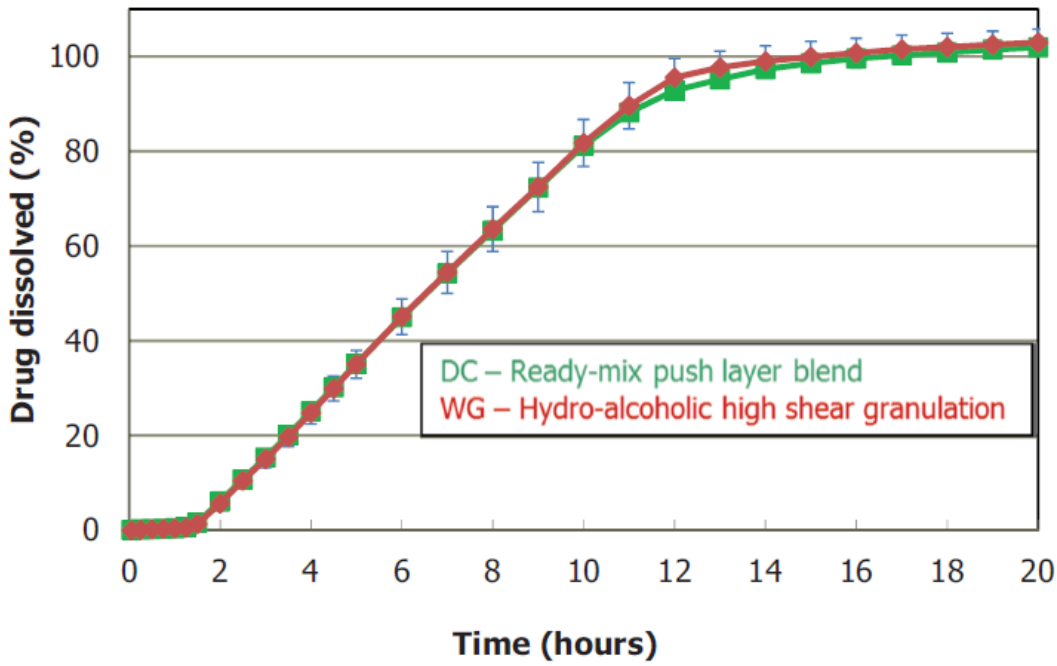
Figure 3. Particle Size Distribution Profiles for Push Layer Blend – DC (Ready-Mix) and WG-High Shear Granulation Process (Mastersizer, Malvern Instruments)



(Mastersizer, Malvern Instruments)

Figure 4. Drug Release Profiles for Glipizide PPOP Tablets: Ready-Mix vs. WG-Push Layer; Opadry CA Coating at 10 %w/w weight gain (n = 6, f2 = 98.7)

Dissolution method: USP Apparatus II, at 50 rpm with sinkers in 900 ml of simulated intestinal fluid (SIF, pH 7.5) without enzyme, 37 ± 0.5°C



To assess the stability of the ready-mix push layer, the powder samples at different time points were evaluated for LOD, sodium chloride uniformity, particle size distribution; and the PPOP tablets for drug release (Figures 5-7).

Figure 5. Loss on Drying for Ready-Mix Push Layer under Accelerated Storage Condition
(IR moisture balance, Denver Instrument, Model: IR-200, USA)

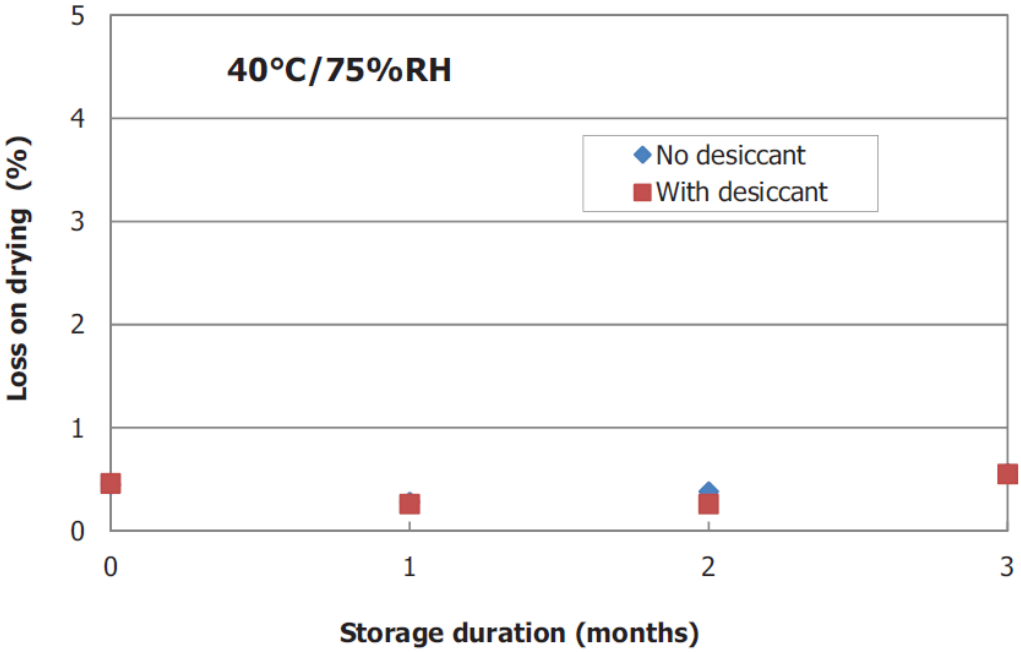


Figure 6. Sodium Chloride Content of Ready-Mix Push Layer under Accelerated Storage Condition

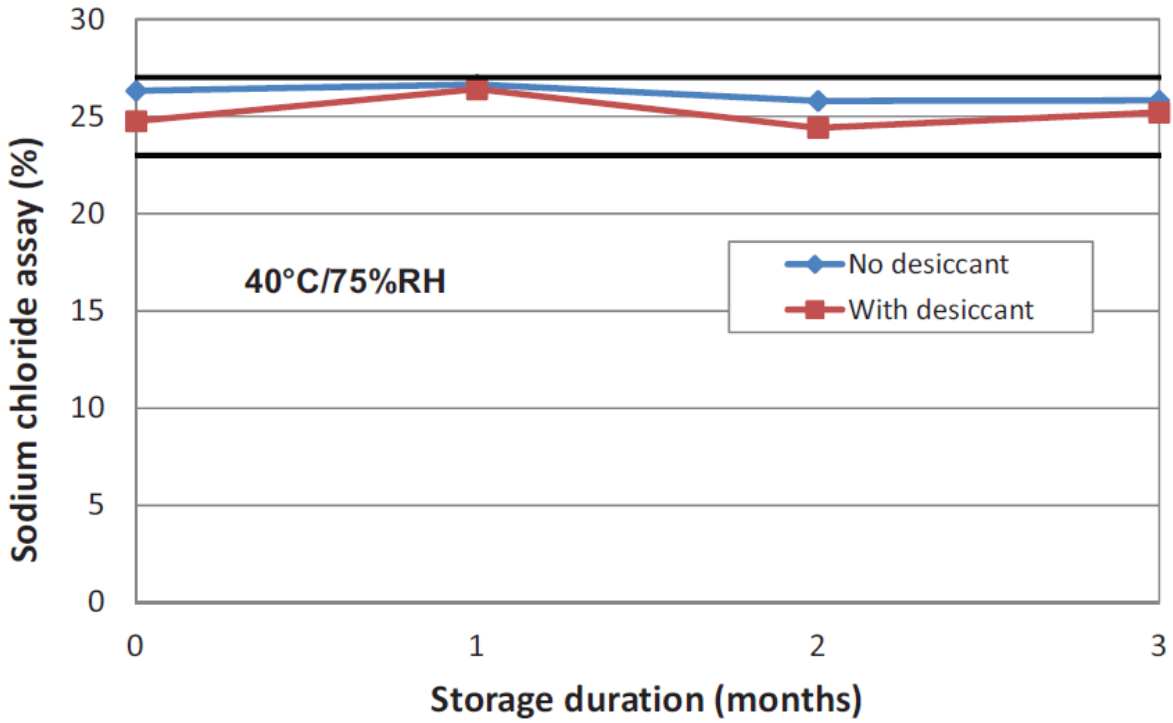
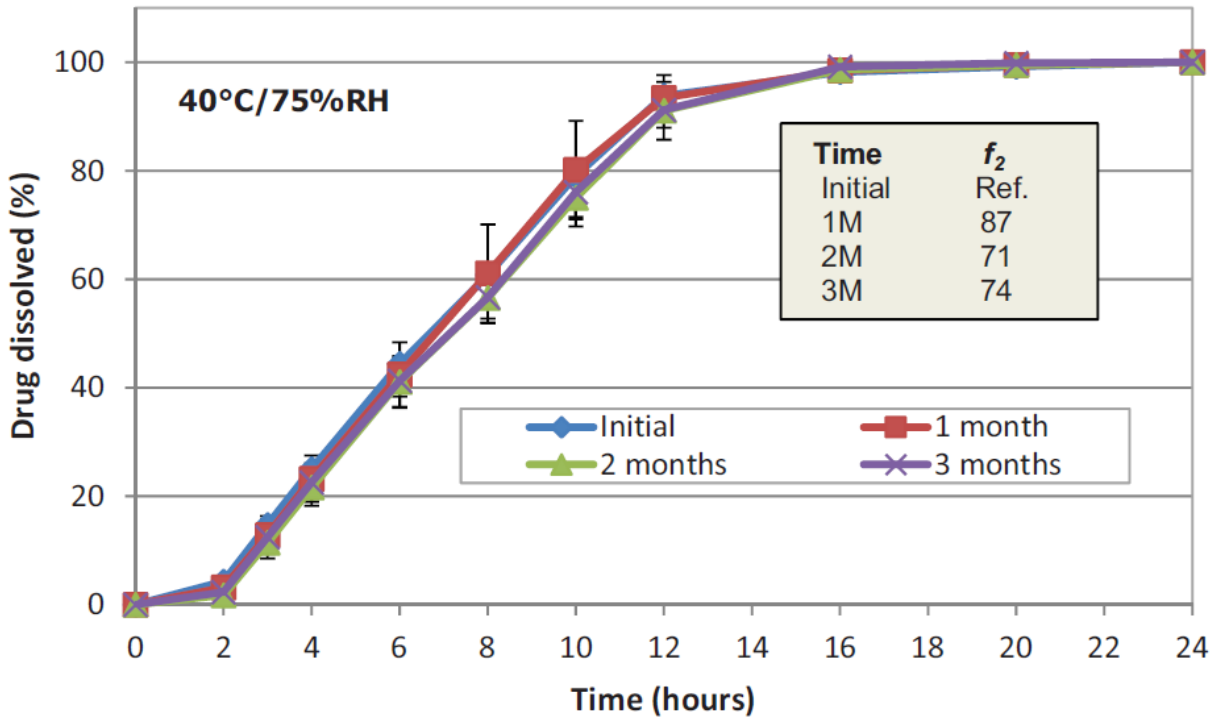


Figure 7. Drug Release Profiles for Glipizide PPOP Tablets Developed using Ready-Mix Push Layer as Stored in Accelerated Condition (n = 6)



Results showed the LOD values for the ready-mix push layer were consistently low (0.26-0.59 %w/w) during the 3-month storage at accelerated condition. All powder samples exhibited desirable content uniformity for sodium chloride (24.4-26.6 %w/w compared to the target value of 25.0 %w/w). The particle size distribution profiles remained unchanged over time (median particle size range of 127-135 µm). The use of desiccant did not appear to enhance the stability of the ready-mix push layer system. In addition, the use of ready-mix push layer system in formulation of glipizide PPOP tablets provided similar drug release profiles ($f2 \geq 71$) during the stability study. The results of this study were consistent with our previous data where the performance and robustness of ready-mix push layer blends were evaluated and confirmed for varying ratios of POLYOX and sodium chloride within the formulation.[3]

CONCLUSIONS

The ready-mix push layer demonstrated desirable and consistent powder characteristics and exhibited similar performance to the commonly used wet granulation method with regard to tablet properties and drug release. Moreover, it showed excellent stability under the accelerated condition. Thus, the ready-mix push layer can offer ease-of-use, removal of organic solvent and requires less processing steps in comparison to a wet granulation process. This, in turn, provides safer operation and facilitates a direct-to-hopper approach in manufacture of osmotic tablets.

REFERENCES

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