The Influence of Manufacturing Method on Physical Properties and Drug Release from Push-Pull Osmotic Pump (PPOP) Products

CRS Poster Reprint 2014

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Abstract Summary

The objectives of this study were to evaluate manufacturing methods to prepare push-pull osmotic pump (PPOP) tablets via Direct Compression (DC), Fluid Bed (FB), High Shear (HS) and Roller Compaction (RC) granulation methods. Using these processes, understand the challenges of processing POLYOX™ water soluble resin, with different equipment, to understand the impact on the physical and chemical properties of granules and tablets and resulting drug release.

Introduction

PPOP products can be tricky to manufacture. These products contain high levels of polymer responsible for entrainment of drug in the drug layer and high swelling in the push layer to produce controlled extrusion of the drug layer through the delivery port of the osmotic pump. The key polymer utilized in these dosage forms is POLYOX (polyethylene oxide).[1] The polymer is water soluble and has a rapid hydration rate producing a viscous gel. The polymer is plastically deformable, has a fairly low melting point (~68ºC) and is viscoelastic. These factors present issues when trying to utilize typical granulation and compression techniques.[2]

Commonly PPOP products are wet granulated utilizing hydro-alcoholic granulating fluid. The use of alcohol reduces the hydration of the polymer and facilitates uniformity in the granulation process. Because of the low melting point of the polymer, friction and heat in the granulator can lead to the formation of molten chunks of polymer in the blend.

Experimental Methods

The four manufacturing methods were used to prepare both drug and push layers. The formulation is detailed below (Table 1); different pigments were used in the push layer for each process to differentiate the products visually. Fluid Bed granulation utilized red dye, high shear used blue lake, roller compaction used yellow lake and the direct compression batch used a combination of blue and yellow lake to produce green. Granulation properties such as bulk and tapped density, particle size, LOD and flow properties were measured for each layer made by each process. Drug and salt content in each layer were assessed by particle size, dividing each powder blend into three sizes, coarse, medium and fine cuts.

Table 1: Formulation

Ingredient	Percent	mg/ tab
Drug Layer		
Theophylline Anhyd. (Jilin Shulan Synthetic Pharma)	5.00%	10.00
POLYOX WSR N-80 NF LEO (Dow)	92.75%	185.50
Hypromellose 2910 (METHOCEL™ E6 LV, Dow)	2.00%	4.00
Magnesium Stearate (Liga MF2-V, Peter Greven)	0.25%	0.50
Total	**100.00%**	**200.00**
Push Layer		
POLYOX WSR Coagulant NF LEO (Dow)	72.71%	94.52
Sodium Chloride (pin milled) (Advantor)	25.00%	32.50
Hypromellose 2910 (METHOCEL™ E6 LV, Dow)	2.00%	2.60
Pigment (Colorcon)	0.05%	0.06
Magnesium Stearate (Liga MF2-V, Peter Greven)	0.25%	0.320
Total	**100.00%**	**130.00**
Total Tablet	**100.00%**	**330.00**

Bilayer tablets were compressed on a bilayer Piccola tablet press (SMI) by compressing the drug layer as layer 1. Compaction scans were generated for each process. Productions runs were then compressed to produce tablets for coating. Tablet cores were assessed for both drug and salt content uniformity. Tablets from each of the processes were combined to create two coating batches. One combined batch of tablets was coated with Opadry® CA using an 80:20 ratio of CA : PEG while another used a 90:10 ratio. Tablets were laser drilled, dried and then tested for content uniformity, dissolution and residual solvents.

Results and Discussion

Each process produced very different granule characteristics ranging in particle size from 120 - 377 microns; bulk density from 0.321 - 0.526 g/cc and FloDex flow orifice diameter of 4 - 6 mm. In general, drug layers were smaller in particle size than their counterpart push layers, processed by the same technique (Table 2). This may be due to the solubility of the sodium chloride in the push layer or the higher viscosity of the POLYOX polymer. The RC process produced the largest granule sizes. This is due to the high compactibility of POLYOX in the formulations. Typical roll pressures used for standard immediate release roller compacted products, resulted in ribbons of extremely high hardness. Milling these produced very large granules. The push layers also showed higher density compared to the drug layers; primarily due to the dense sodium chloride in this layer.

Assay by sieve cut showed interesting results (Table 3). In each case, both drug and salt assays were low in the coarse sieve cuts and high in the fine sieve cuts. Variation was lowest with the fluid bed granulation process. Segregation of the drug is of major concern for PPOP products as many are low dose products.

Table 2: Granule Properties

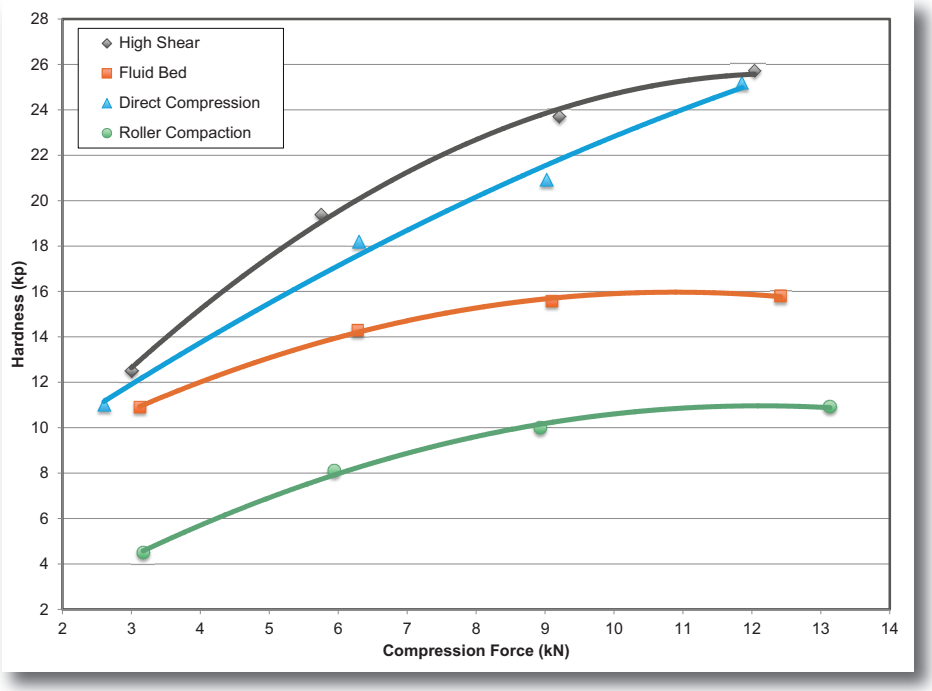
Property	DC	FB	HS	RC
Drug Layer				
Bulk Density (g/ cc)	0.472	0.321	0.427	0.417
Tapped Density (g/ cc)	0.556	0.373	0.500	0.481
Carr's Index (%)	15.09	14.10	14.52	13.33
Flow Category	Good	Good	Good	Good
Geom. Mean Size (micron)	125	219	134	364
Geometric Std Deviation	1.93	1.53	1.91	1.77
Loss on Drying (%)	0.38	0.46	0.41	0.49
FloDex Flow Orifice (mm)	5	6	4	6
Push Layer				
Bulk Density (g/ cc)	0.526	0.376	0.446	0.510
Tapped Density (g/ cc)	0.641	0.446	0.516	0.581
Carr's Index (%)	17.9	15.8	13.4	12.2
Flow Category	Fair	Fair	Good	Good
Geom. Mean Size (micron)	120	187	191	377
Geometric Std Dev	1.90	1.60	1.72	2.06
Loss on Drying (%)	0.43	0.35	0.37	0.52
FloDex Flow Orifice (mm)	4	4	4	6

Table 3: Drug and Sodium Chloride Assay by Sieve Cut

Drug Layer					
Product	**Sieve Cut**	**Mesh Size**	**% Drug**	**Range (max-min)**	**Wt Adj Drug Assay %**
DC	Coarse	35 / 70	48.3	129.5	117.5
	Medium	70 / 230	127.2		
	Fine	230 / pan	177.8		
FB	Coarse	30 / 45	95.8	37.4	99.4
	Medium	45 / 80	86.9		
	Fine	80 / pan	124.3		
HS	Coarse	30 / 80	52.6	90.2	99.2
	Medium	80 / 170	103.8		
	Fine	170 / pan	142.8		
RC	Coarse	14 / 40	59.0	154.3	96.4
	Medium	40 / 80	119.6		
	Fine	80 / pan	213.3		
Push Layer					
Product	**Sieve Cut**	**Mesh Size**	**% NaCl**	**Range (max-min)**	**Wt Adj NaCl Assay %**
DC	Coarse	35 / 60	8.0	135.8	116.2
	Medium	60 / 230	143.8		
	Fine	230 / pan	111.8		
FB	Coarse	40 / 60	57.7	85.6	100.2
	Medium	60 / 100	108.8		
	Fine	100 / pan	143.3		
HS	Coarse	30 / 50	40.7	157.9	96.2
	Medium	50 / 120	72.7		
	Fine	120 / pan	198.6		
RC	Coarse	16 / 40	66.3	150.9	87.0
	Medium	40 / 70	34.9		
	Fine	70 / pan	185.8		

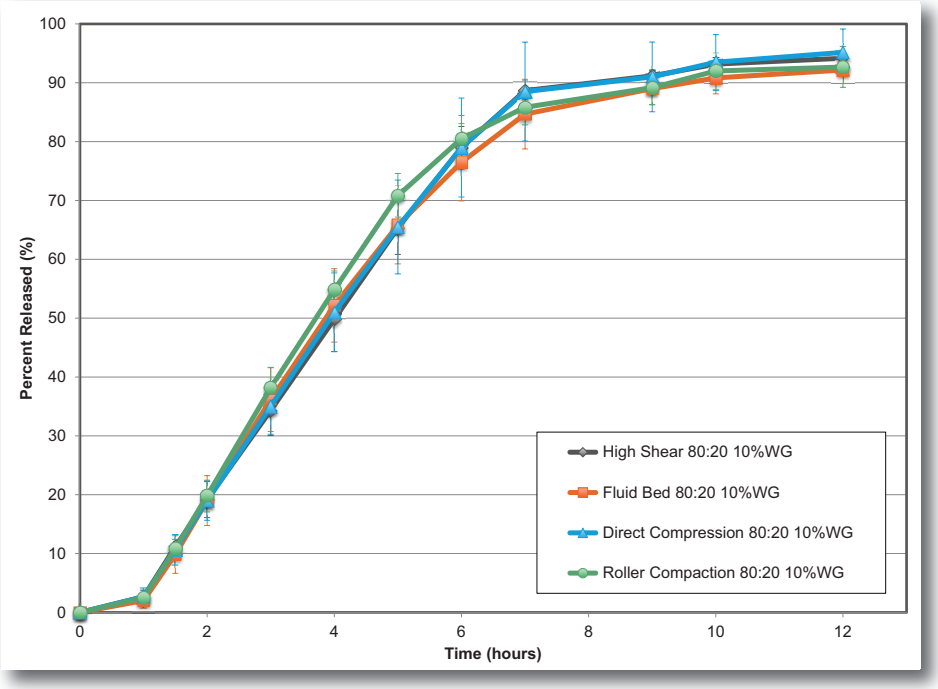
Compaction profiles for each process are shown below (Figure 1). Again, of the four techniques, RC produced the lowest quality (hardness) product. Tablet weight variation was lowest with the DC batch producing an RSD of 1.38% while RC produced the highest RSD of 2.34%. This is most likely attributed to the large particle size of the granules produced by this method. Content uniformity followed the same trend as weight variation, DC = RSD 1.0%, RC = RSD 2.7%.

Figure 1: Compaction Profiles



Dissolution of the Opadry CA 80:20 ratio at a 10% weight gain (WG) is shown below (Figure 2). Similarity (f_2) values were calculated using the HS batch as reference. All profiles were "similar" to the HS batch: DC = 97, FB = 82, RC = 74. Roller compaction produced the lowest f_2 value. This is most likely due to the higher variability in drug content and salt content from tablet to tablet. As expected, higher weight gains of Opadry CA coating produced slower dissolution rates and use of lower PEG level also produced a slower dissolution rate. All residual solvents (alcohol and acetone) were below 20 ppm.

Figure 2: Dissolution Opadry® CA 80:20 Ratio, 10% WG



Conclusions

Regardless of wide variation in granule and tablet properties, drug release remained fairly consistent with passing f_2 values. Operations such as high shear granulation, roller compaction and milling can be challenging for PPOP formulations. Care must be taken to optimize these processes to ensure manufacture of acceptable product. Segregation of drug and salt from the formulations is a concern during tableting. Semipermeable film coating weight gain and CA : PEG ratio can be used to modulate drug release.

References

1. Missaghi S. et al. Investigation of Critical Core Formulation and Process Parameters for Osmotic Pump Oral Drug Delivery. *AAPS Pharm Sci Tch*, 2014, 15 (1): 149-160.
2. Rane M. et al. Applications of Polyethylene Oxide in Hydrophilic Matrix Tablets. *Pharma Times*, 2013, 45 (3): 41 – 48.

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