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Using Continuous Granulation to Make Robust and High Drug Load APAP Granules

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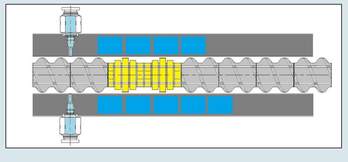
PURPOSE

Since most pharmaceutical ingredients (API) have low density and poor flowability, wet granulation is practiced extensively for ease of handling. Wet granulation can be achieved by means of high shear mixers, fluid beds and twin-screw granulators. The former two methods are commonly used batch processes with long processing times. In addition, scale-up trials can be expensive, time consuming, and complicated. Twin-screw granulation offers the advantages of being easily adaptable into a continuous manufacturing system and elimination of scale up studies. This study explored the advantages of continuous granulation by twin screw technology on Freund-Vector's Granuformer® (Gf-215) to make high load acetaminophen (APAP) granules and studied the effect of polymer choice and process parameters on making robust granules and tablets.

METHODS

Three formulations (see Table 1) of APAP with Klucel™ EXF HPC, or Plasdone™ K-29/32 povidone (PVP) or Plasdone™ S-630 copovidone (Ashland), microcrystalline cellulose (Avicel® PH-102, FMC), and Aerosil® 200 (Evonik) were screened through an oscillatory mill (Colton Granulator, Model No. 542) with 600 µm opening. A continuous granulation method was set up on the Gf-215. The effect of water addition, barrel temperature and screw speed on granular properties was studied. The screw shaft was assembled with various conveying and kneading elements. The kneading elements were at 60° angles. Coperion's K-Tron powder feeder was utilized to gravimetrically feed various powder blends (95.4% APAP content) into a jacketed twin-screw granulator, and water was injected prior to the kneading elements to form granules. Granules were milled at 300 rpm through a 4 mm aperture screen and dried in a Spiral Dryer tube. Resulting granules were tested for residual moisture content and particle size. Tablets of 400 mg were made from the various granulations with a compaction force of 25 kN utilizing 11.28 mm flat-faced punches (Manesty Betapress equipped with 16 punches at 72 rpm which is equivalent to 69120 tablets/hour). Tablets were analyzed for hardness, dissolution profile (USP method, 900 ml pH 5.8 phosphate buffer, 50 RPM paddle), and disintegration time.

Figure 1: Screw Design



METHODS

Table 1: Formulations

Ingredients	Percentage by Mass	Comment
Acetaminophen	90%	Intragranular
Various binders*	4%	
Avicel® PH-102	1.55%	
Aerosil® 200	0.20%	
Polyplasdone XL-10	4%	Extragranular
Magnesium Stearate	0.25%	
TOTAL	100%	

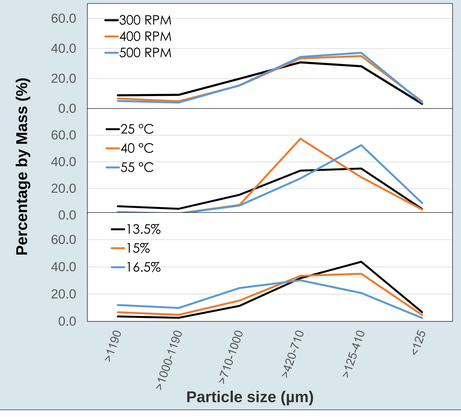
* Klucel™ EXF, Plasdone™ K-29/32, or Plasdone™ S-630

Table 2: Experimental Design

Effect of Water Addition					
Temperature (°C)	Screw Speed (rpm)	Feed Rate (kg/hr)	Water Addition (%)*		
			Klucel™ EXF	Plasdone™ K29/32	Plasdone™ S630
25	400	8	13.5	10	13
25	400	8	15	11.5	14.5
25	400	8	16.5	13	16
Effect of Temperature					
Temperature (°C)	Screw Speed (rpm)	Feed Rate (kg/hr)	Water Addition (%)		
			Klucel™ EXF	Plasdone™ K29/32	Plasdone™ S630
25	400	8	15	11.5	14.5
40	400	8	15	11.5	14.5
55	400	8	15	11.5	14.5
Effect of Screw Speed					
Temperature (°C)	Screw Speed (rpm)	Feed Rate (kg/hr)	Water Addition (%)		
			Klucel™ EXF	Plasdone™ K29/32	Plasdone™ S630
25	300	8	15	11.5	14.5
25	400	8	15	11.5	14.5
25	500	8	15	11.5	14.5

RESULTS

Figure 2: Effect of Screw Speed, Temperature, and Water Addition on Particle Size Distribution: Klucel™ EXF



RESULTS

Figure 3: Effect of Screw Speed, Temperature, and Water Addition on Particle Size Distribution: Plasdone™ K-29/32

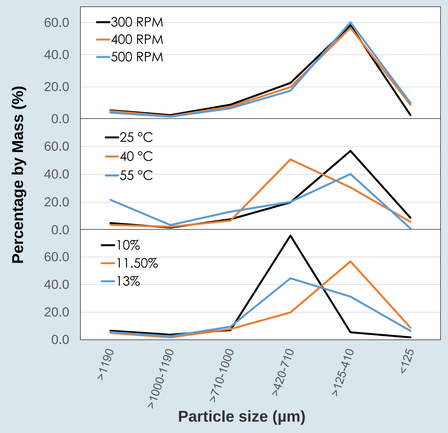
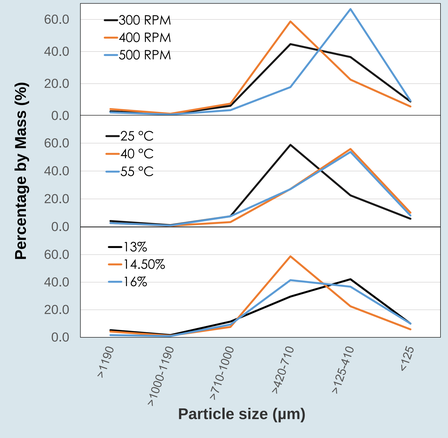


Figure 4: Effect of Screw Speed, Temperature, and Water Addition on Particle Size Distribution: Plasdone™ S-630



RESULTS

Figure 5: Effect of Process Variables on Tablet Hardness

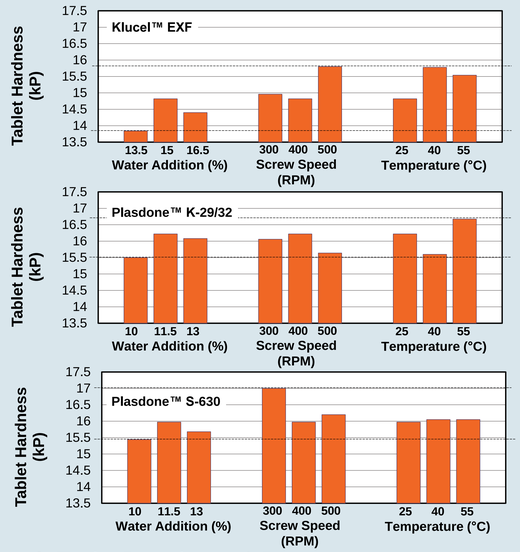
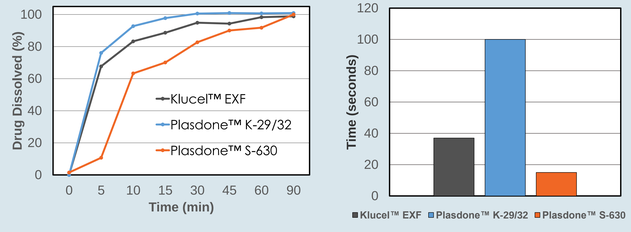


Figure 6: Tablet Dissolution & Disintegration



CONCLUSIONS

- Continuous granulation is capable of making stronger, yet fast-dissolving tablets.
- All polymers yielded robust formulations and there was minimum effect of process variables on tablet hardness.
- Gf-215 provides high mixing intensity, improved tablet strength and robustness.

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