THE EFFECT OF LOAD VOLUME ON PARTICLE SIZE AND TEMPERATURE RISE OF WET-GRANULATIONS IN A HIGH-SHEAR GRANULATOR

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PURPOSE

High-shear mixers are commonly used in the production of wet granulations. These granulations can be used for both immediate and controlled release dosage forms. Occasionally it is necessary to modify the batch size to meet production requirements. This study was done to determine the effect of product load volume in a high-shear granulation process using both immediate and controlled release formulations.

Table 1 – Formulations

Dry Ingredients	Controlled Release A	Controlled Release B	Immediate Release C
HPMC, K 100 M	30%	--	--
HPMC K 4 M	--	30%	--
Starch 1500	--	--	15%
MCC 50M	--	--	30%
Lactose	70%	70%	55%
Bulk Density (g/cc)	0.423	0.447	0.489

Table 2 – Processing Conditions

Formulation	A			B			C		
Percent Load	50	75	100	50	75	100	50	75	100
Load (kg)	10.47	15.70	20.94	11.06	16.60	22.13	12.23	18.34	24.45
Water Used (kg)	5.8	8.7	11.6	4.33	6.5	8.6	4.0	6.0	8.0
Percent Water	35.7	35.7	35.7	28.1	28.1	28.1	24.7	24.7	24.7
Pre-Mix (min)	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Infusion (min)	6.9	10.0	13.5	5.4	7.5	10.0	6.0	8.0	11.5
Wet Mass (min)	5.0	5.0	5.0	7.0	7.0	7.0	7.0	7.0	7.0

METHODS

Two controlled release formulations (A and B) and one immediate release formulation C were used. Formulations are shown in Table 1.

Based on bulk density, Formulations A, B and C were granulated at 50%, 75% and 100% volumetric loads of working capacity. The wet granulations were performed in a 75-liter vertical top-drive high-shear granulator equipped with a chopper (Vector Corporation GMX-75). Mixer blade speed during pre-mix and water infusion times was 210 rpm, and 330 rpm during the wet-mass (or high shear) time. Processing conditions are shown in Table 2.

The change in product temperature (ΔT) during the wet-mass time was monitored. After granulation, a portion of the batch was oven dried overnight at 90°C. The remaining portion was dried with air at 65°C using a fluid-bed dryer (Vector FL-M-15) until the product LOD was less than 2.5% moisture content. Sieve analyses were performed to determine the arithmetic mean diameters (D_{50}) for oven and fluid bed dried granules.

RESULTS

The results of the sieve analysis and temperature change are presented in Tables 3-5. A comparison of the particle size distributions for each of the formulations (for both oven and fluid bed dried granules) is shown in Figures 1-3. The product temperature curves for the experiments can be seen in Figures 4-6. A profile of product temperature change for each phase of processing (pre-mix, water infusion, and wet mass time) is shown in Figures 7-9.

RESULTS

Table 3 – Formulation A Summary

Parameter	50%	75%	100%
D50 (Oven), µm	1193	1096	1434
D50 (FB), µm	981	1065	1505
ΔT, °C	9.1	10.0	9.9

Table 4 – Formulation B Summary

Parameter	50%	75%	100%
D50 (Oven), µm	819	866	766
D50 (FB), µm	699	809	686
ΔT, °C	12.5	11.9	12.8

Table 5 – Formulation C Summary

Parameter	50%	75%	100%
D50 (Oven), µm	1176	1247	1472
D50 (FB), µm	1216	1474	1478
ΔT, °C	20.4	23.2	34.4

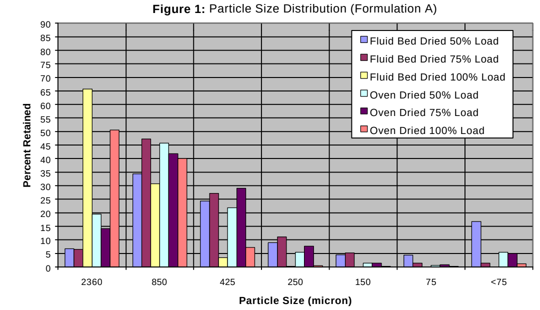

Figure 1: Particle Size Distribution (Formulation A)

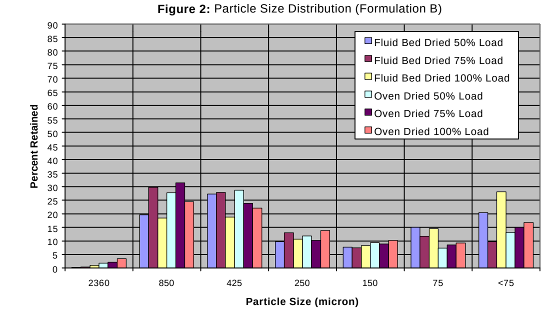

Figure 2: Particle Size Distribution (Formulation B)

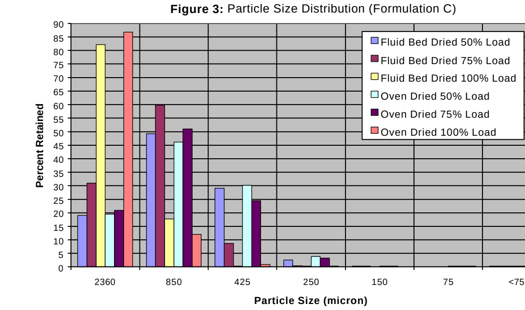

Figure 3: Particle Size Distribution (Formulation C)

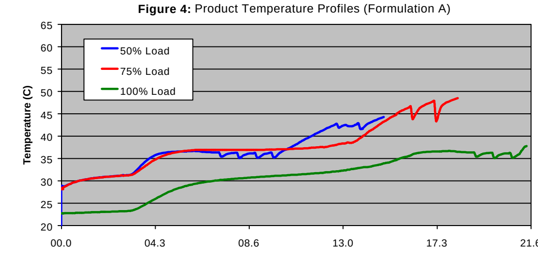

Figure 4: Product Temperature Profiles (Formulation A)

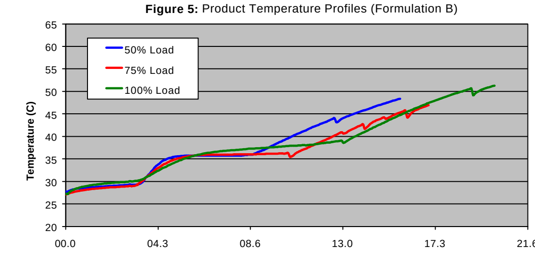

Figure 5: Product Temperature Profiles (Formulation B)

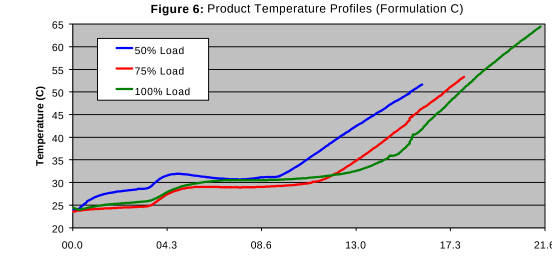

Figure 6: Product Temperature Profiles (Formulation C)

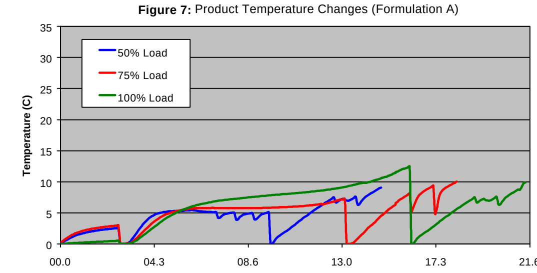

Figure 7: Product Temperature Changes (Formulation A)

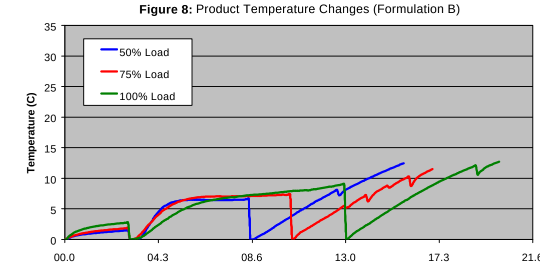

Figure 8: Product Temperature Changes (Formulation B)

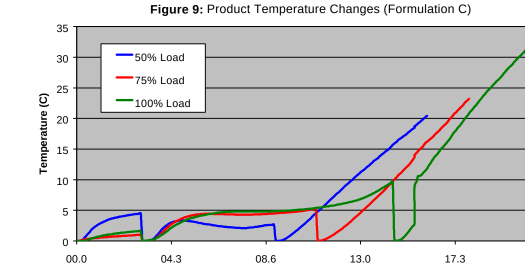

Figure 9: Product Temperature Changes (Formulation C)

CONCLUSIONS

For formulation A and C, which were designed to produce larger granules, a 100% load volume produced a significantly larger particle size than did the smaller loads. However, for formulation B that was designed to produce smaller granules, the load volume had no effect. Formulation C exhibited a trend of increasing particle size with an increased load volume. Formulations A and B displayed constant temperature rises for the loads tested. Formulation C exhibited a substantial increase in temperature rise as the load volume was increased. This is possibly due to non-linear shear-force behavior, gravitational compressional force, or viscosity change during the high shear process.

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