THE EFFECT OF CONSECUTIVE BATCH PROCESSING ON PARTICLE SIZE AND THERMAL BEHAVIOR IN A HIGH-SHEAR GRANULATOR

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PURPOSE

To determine the effect of consecutive multi-batch high-shear granulation processing on:

1) particle size and
2) thermal processing characteristics.

METHODS

Two controlled release formulations (A & B) and one immediate release formulation C were used in this study. Formulations and process parameters are shown in Tables 1 and 2. Formulations A and C were designed to produce large granules and formulation B was designed for small granules. Three batches of approximately 37.5 liters of each formulation were granulated one after the other in a 75-liter high-shear granulator (Vector 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. 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 65°C air using a fluid-bed dryer (Vector FL-M-15) until the product 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.

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%
Total Weight (Kg)	15.70	16.59	18.34
Bulk Density (g/cc)	0.423	0.447	0.489

Table 2 – Processing Parameters

Process Parameters	Controlled Release A	Controlled Release B	Immediate Release C
Pre-Mix Time	3 minutes	3 minutes	3 minutes
Water Infusion Time	10 minutes	8 minutes	8 minutes
Water Added (%, Kg)	35.7% , 8.7 Kg	28.1% , 6.5 Kg	24.7% , 6.0 Kg
Wet Mass Time	5 minutes	7 minutes	7 minutes
Time Between Consecutive Batches	6 to 9 minutes	8 to 9 minutes	6 to 8 minutes

RESULTS

CR Formulation A Summary

Parameter	1st Batch	2nd Batch	3rd Batch
D50 (Oven), µm	1182	1056	1054
D50 (FB), µm	1148	1040	1064
ΔT, °C	13.3	12.3	12.3

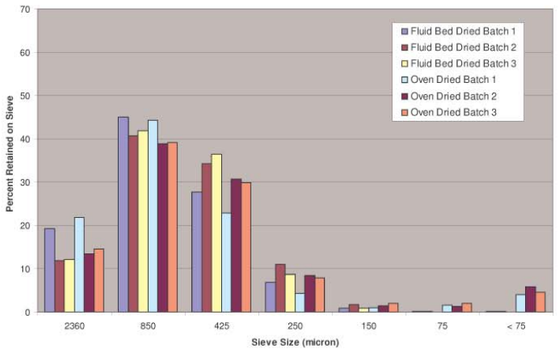
CR Formulation B Summary

Parameter	1st Batch	2nd Batch	3rd Batch
D50 (Oven), µm	761	794	721
D50 (FB), µm	826	790	767
ΔT, °C	13.3	13.0	13.4

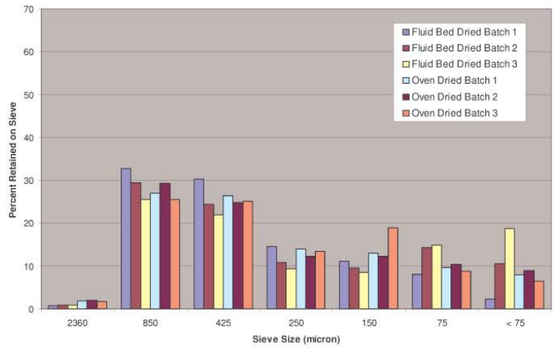
IR Formulation C Summary

Parameter	1st Batch	2nd Batch	3rd Batch
D50 (Oven), µm	1147	1377	1545
D50 (FB), µm	1157	1444	1525
ΔT, °C	21.8	22.9	24.0

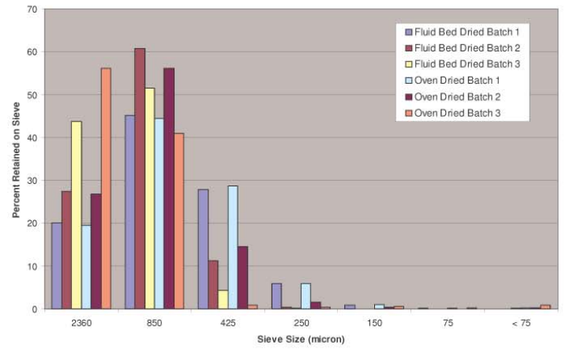
Particle Size Distribution - CR Formulation A



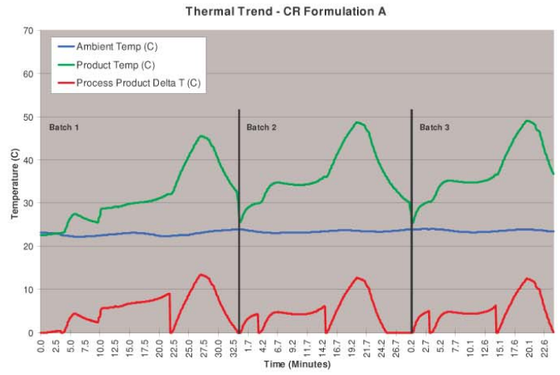
Particle Size Distribution - CR Formulation B



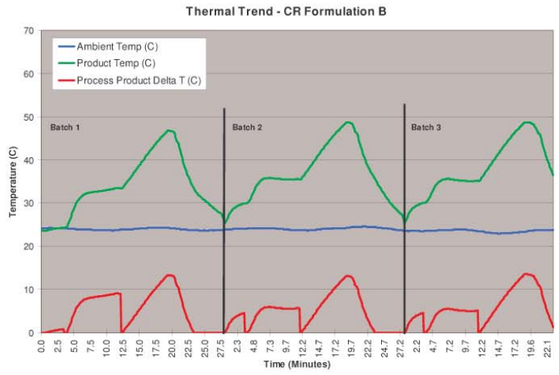
Particle Size Distribution - IR Formulation C



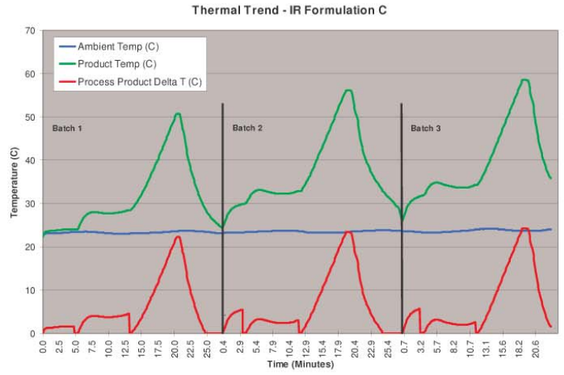
Thermal Trend - CR Formulation A



Thermal Trend - CR Formulation B



Thermal Trend - IR Formulation C



CONCLUSIONS

Consecutive batch processing had no significant effect on D_{50} for the controlled released granulations in this study. However, consecutive batch processing did result in an increased D_{50} for the immediate release granulation. The change in product temperature during wet mass (ΔT) appeared to remain relatively constant for the controlled released formulations, but increased slightly for the immediate release formulation. The correlation coefficient between D_{50} and ΔT for the immediate release formulation was 0.97. When processing multiple, consecutive, batches of a product similar to the immediate release formulation, the product temperature rise during the wet mass time should be taken into account if consistent particle size is important.

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FREUND VECTOR

Penwest Pharmaceuticals Co.