

# 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 ( $\Delta T$ ) 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), $\mu\text{m}$ | 1182      | 1056      | 1054      |
| D50 (FB), $\mu\text{m}$   | 1148      | 1040      | 1064      |
| $\Delta T$ , °C           | 13.3      | 12.3      | 12.3      |

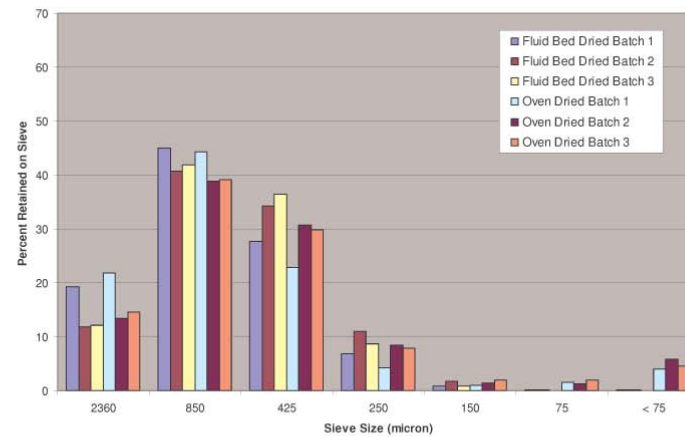
CR Formulation B Summary

| Parameter                 | 1st Batch | 2nd Batch | 3rd Batch |
|---------------------------|-----------|-----------|-----------|
| D50 (Oven), $\mu\text{m}$ | 761       | 794       | 721       |
| D50 (FB), $\mu\text{m}$   | 826       | 790       | 767       |
| $\Delta T$ , °C           | 13.3      | 13.0      | 13.4      |

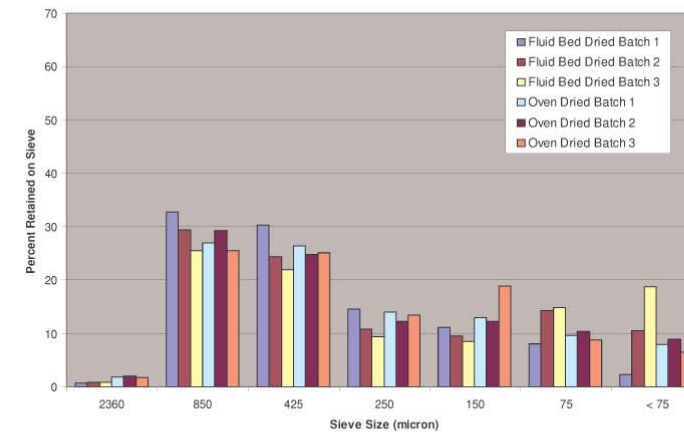
IR Formulation C Summary

| Parameter                 | 1st Batch | 2nd Batch | 3rd Batch |
|---------------------------|-----------|-----------|-----------|
| D50 (Oven), $\mu\text{m}$ | 1147      | 1377      | 1545      |
| D50 (FB), $\mu\text{m}$   | 1157      | 1444      | 1525      |
| $\Delta T$ , °C           | 21.8      | 22.9      | 24.0      |

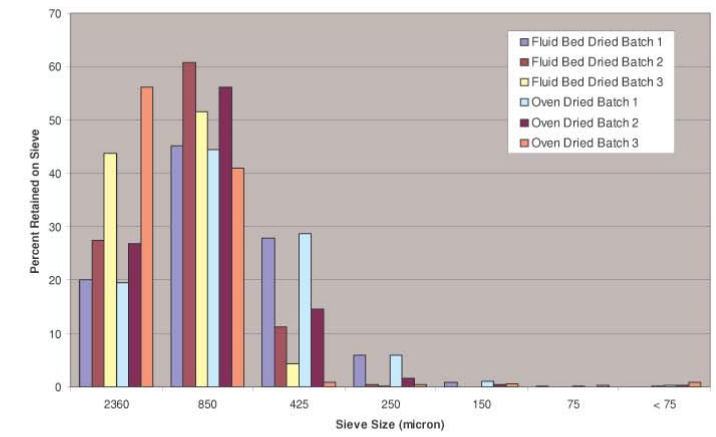
Particle Size Distribution - CR Formulation A



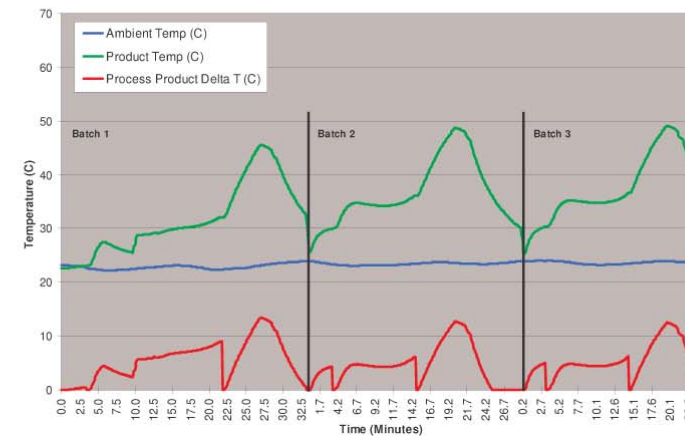
Particle Size Distribution - CR Formulation B



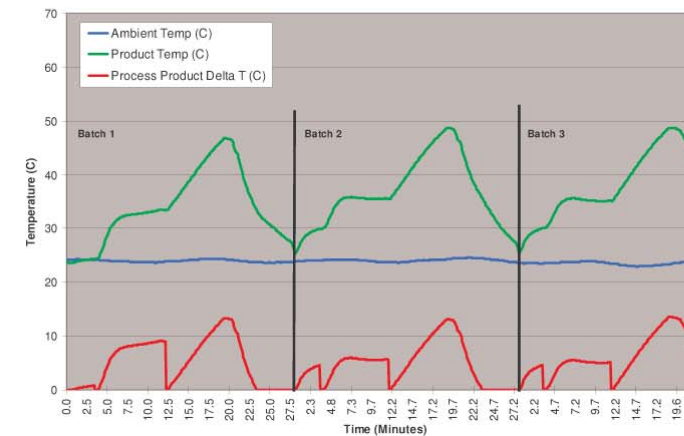
Particle Size Distribution - IR Formulation C



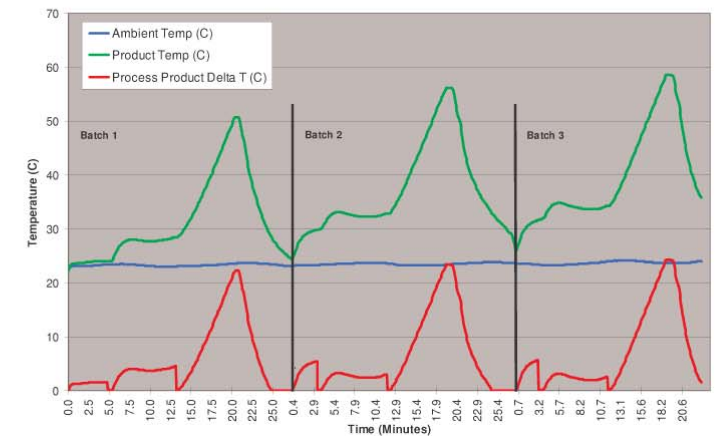
Thermal Trend - CR Formulation A



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 ( $\Delta T$ ) 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  $\Delta T$  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.

## ACKNOWLEDGMENT

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# ADDENDUM

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

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### PURPOSE

To incorporate wet-mass, or high shear, mixer blade power consumption information.

### METHODS

In addition to the methods reported in the original poster, the mixer blade power was also monitored. Power trends were overlaid on the "Thermal Trends" graphs previously reported. Revised graphs are shown in the Results section.

Note: Formulations and process parameters are reprinted for reference in Tables 1 and 2.

### RESULTS

#### REVISED CR Formulation A Summary

| Parameter                       | 1st Batch | 2nd Batch | 3rd Batch |
|---------------------------------|-----------|-----------|-----------|
| D50 (Oven), $\mu\text{m}$       | 1182      | 1056      | 1054      |
| D50 (FB), $\mu\text{m}$         | 1148      | 1040      | 1064      |
| $\Delta T$ , $^{\circ}\text{C}$ | 13.3      | 12.3      | 12.3      |
| Peak Power, KW                  | 3.6       | 3.8       | 3.5       |
| Time to Reach Peak Power, Min   | 0.3       | 0.3       | 0.3       |

#### REVISED CR Formulation B Summary

| Parameter                       | 1st Batch | 2nd Batch | 3rd Batch |
|---------------------------------|-----------|-----------|-----------|
| D50 (Oven), $\mu\text{m}$       | 761       | 794       | 721       |
| D50 (FB), $\mu\text{m}$         | 826       | 790       | 767       |
| $\Delta T$ , $^{\circ}\text{C}$ | 13.3      | 13.0      | 13.4      |
| Peak Power, KW                  | 2.8       | 2.6       | 2.8       |
| Time to Reach Peak Power, Min   | 2.7       | 2.3       | 1.6       |

#### REVISED IR Formulation C Summary

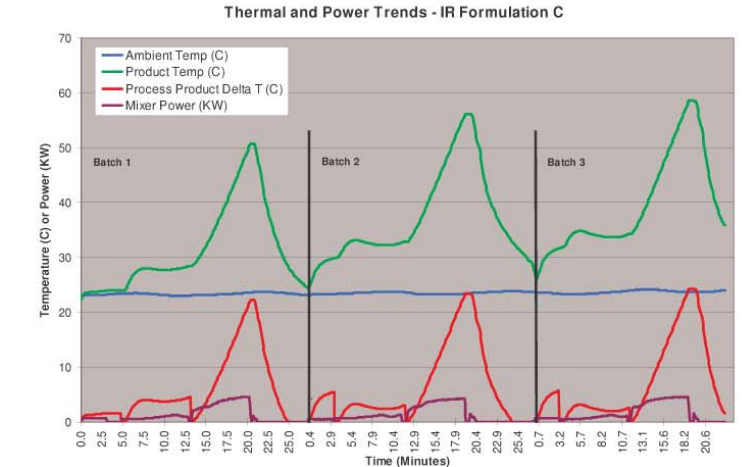
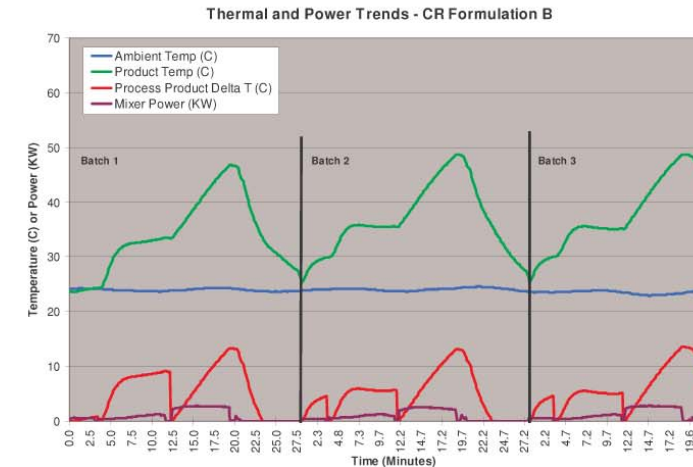
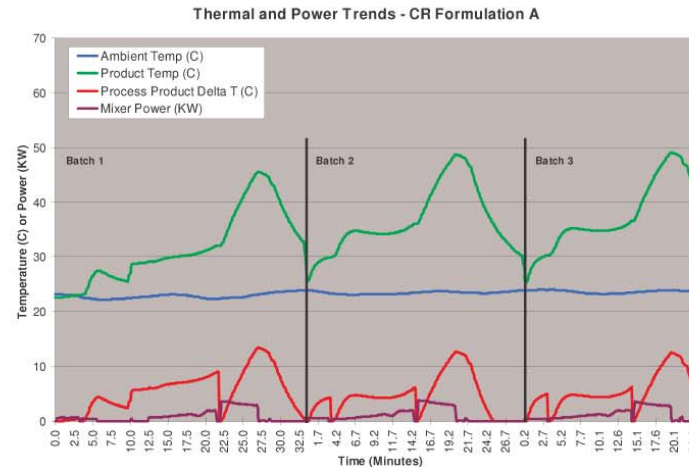
| Parameter                       | 1st Batch | 2nd Batch | 3rd Batch |
|---------------------------------|-----------|-----------|-----------|
| D50 (Oven), $\mu\text{m}$       | 1147      | 1377      | 1545      |
| D50 (FB), $\mu\text{m}$         | 1157      | 1444      | 1525      |
| $\Delta T$ , $^{\circ}\text{C}$ | 21.8      | 22.9      | 24.0      |
| Peak Power, KW                  | 4.6       | 4.3       | 4.6       |
| Time to Reach Peak Power, Min   | 6.2       | 6.5       | 6.0       |

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      |



### CONCLUSIONS (REGARDING MIXER POWER)

Mixer power trends were slightly different for each of the formulations. Mixer power for CR Formulation A rose almost immediately to peak power during the wet-mass stage and then gradually reduced in magnitude, whereas CR Formulation B rose rapidly, leveled off, and did not reach peak power until 23 - 39% of the wet-mass time was completed. IR Formulation C did not reach peak power until almost the end of the wet-mass time. The small rise and fall of the mixer power at the end of each granulation occurred during the discharge of the product. For the formulations used in this study, temperature rise during wet mass ( $\Delta T$ ) appeared to provide a better endpoint correlation to particle size than peak mixer power.

### ACKNOWLEDGMENT

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# 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.

## 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 ( $\Delta T$ ) 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), $\mu\text{m}$ | 1193 | 1096 | 1434 |
| D50 (FB), $\mu\text{m}$   | 981  | 1065 | 1505 |
| $\Delta T$ , °C           | 9.1  | 10.0 | 9.9  |

Table 4 – Formulation B Summary

| Parameter                 | 50%  | 75%  | 100% |
|---------------------------|------|------|------|
| D50 (Oven), $\mu\text{m}$ | 819  | 866  | 766  |
| D50 (FB), $\mu\text{m}$   | 699  | 809  | 686  |
| $\Delta T$ , °C           | 12.5 | 11.9 | 12.8 |

Table 5 – Formulation C Summary

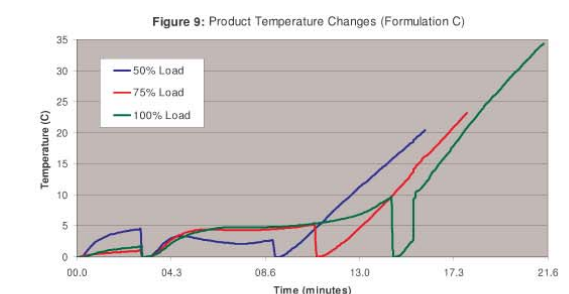
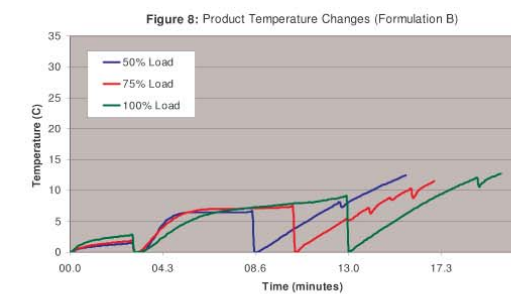
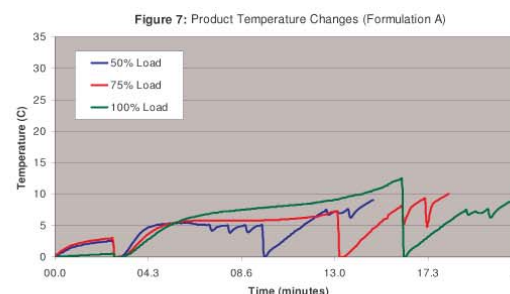
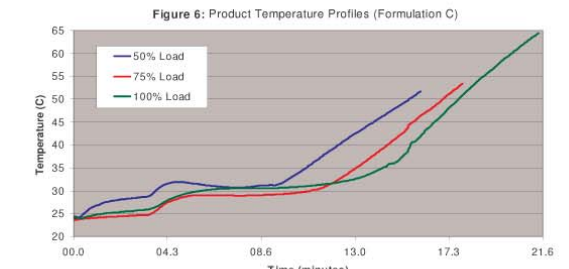
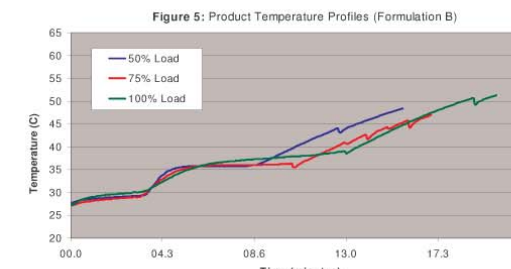
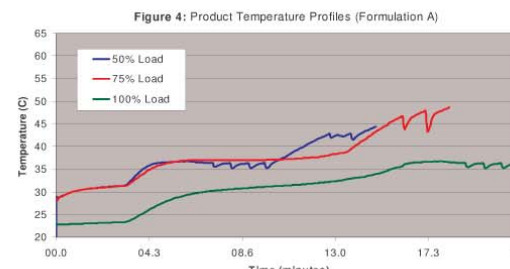
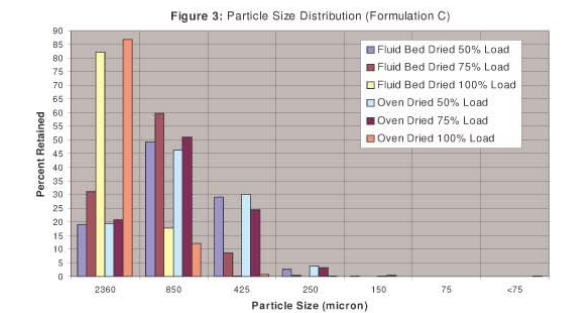
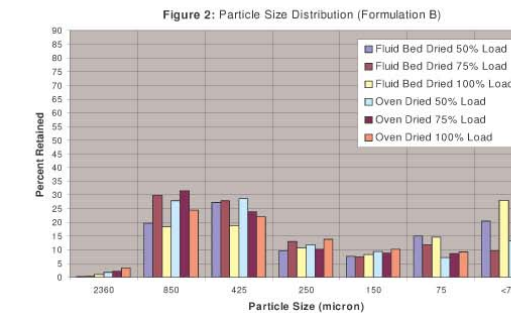
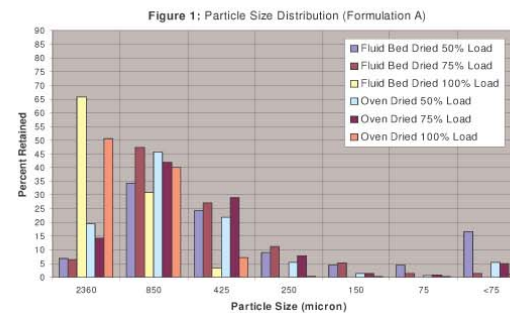
| Parameter                 | 50%  | 75%  | 100% |
|---------------------------|------|------|------|
| D50 (Oven), $\mu\text{m}$ | 1176 | 1247 | 1472 |
| D50 (FB), $\mu\text{m}$   | 1216 | 1474 | 1478 |
| $\Delta T$ , °C           | 20.4 | 23.2 | 34.4 |

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%                 |
| <b>Bulk Density (g/cc)</b> | 0.423                | 0.447                | 0.489               |

Table 2 – Processing Conditions

| Formulation     | A     |       |       | B     |       |       | C     |       |       |
|-----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                 | 50    | 75    | 100   | 50    | 75    | 100   | 50    | 75    | 100   |
| 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   |



## 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.

## ACKNOWLEDGMENT

Authors extend their thanks to Mr. Paul Sheskey of the Dow Chemical Company and Colorcon, Global Technical Support for their contribution in this study.

