



## Fluid-Bed Granulation of Acetaminophen: Effect of Key Process Variables on Granule and Tablet Characteristics

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### OBJECTIVES

- Investigate the independent and interactive effects of key fluid-bed process variables on both finished granulation and resultant tablet characteristics.
- Based on the results obtained, develop a predictive tool for assessing the effect of potential changes in fluid-bed process parameters on product quality and process operation.
- Study the performance of a partially pregelatinized maize starch (Starch 1500<sup>®</sup>) as both binder and disintegrant in a fluid-bed granulation application.

### METHODS

#### Equipment

- Glatt GPCG-3 Fluid Bed
  - Top spray module fitted with a 1.2mm Schlick nozzle
- 16 qt. Twin-shell blender
- Piccola (Riva) 10 station instrumented tablet press
  - 3/8" standard concave, type B tooling
  - Mechanical powder feed

#### Materials

- Acetaminophen powder U.S.P.
  - Rhodia
- Magnesium stearate
  - Mallinckrodt
- Starch 1500<sup>®</sup> partially pregelatinized maize starch
  - Colorcon
- Stearic acid powder
  - Spectrum Chemical

### Design of Experiments

- CARD<sup>®</sup> DOE (S-Matrix Corp.) software was used to generate an experiment design to evaluate the fluid-bed process variables.
- A computer algorithm process design was identified by the software as the optimum design type for this study.
- Data analysis and optimization functions were also handled through this software.

### Experiment Variables and Ranges

- |   |          |
|---|----------|
| • Binder solids (%)                     | 7 to 15  |
| • Atomizing air pressure (bar)          | 1 to 3   |
| • Inlet air temperature (°C)            | 50 to 75 |
| • Fluid delivery (g/min)                | 50 to 70 |
| • Starch 1500 <sup>®</sup> in bowl (%)* | 0 to 50  |

### Experiment Constants

Fluid-bed batch size

- |  |               |
|--|---------------|
| • Acetaminophen                                      | 1700.0g       |
| • Starch 1500 <sup>®</sup> (either dry or in slurry) | <u>300.0g</u> |
| • Total  | 2000.0g       |
- Process air flow - Although not a studied variable, the air flow was controlled at the minimum volume needed to maintain adequate movement of the granulation throughout the process.
  - All granulations were dried to between 1.5% and 2.0% moisture.

\* Because of its partial cold water solubility, the effectiveness of Starch 1500 was examined relative to its use either in the granulation liquid or mixed with the acetaminophen in the bowl.

- Preparation of granulations for tableting
  - Each of the finished granulations was passed through a 12 mesh screen prior to testing and further blending.
  - Each of the finished, sieved, granulations were blended with 2.0% stearic acid for 10 minutes and then blended for an additional 5 minutes with 0.5% magnesium stearate.
  - Other than the initial screening, the granulations were not milled prior to tableting.
  - The target tablet weight was 392.0 mg (325 mg).
- Granulation flow properties
  - Measured using an Erweka funnel type powder flow apparatus in grams/second through a 10mm orifice.
- Finished granule size.
- Mean diameter in microns by sieve analysis.
- Bulk Density
  - g/cm<sup>3</sup>
- Tablet hardness
  - kp at various compaction forces.
- Tablet friability
  - % loss at 100 revolutions @ 25 rpm.
- Tablet disintegration
  - Minutes in 37°C deionized water

### Response Variables

- Maximum moisture content of granulation prior to drying
  - % L.O.D.

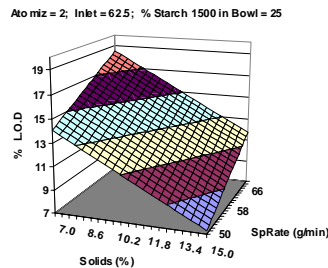
## RESULTS

Summary of observed results over entire range of experimental conditions

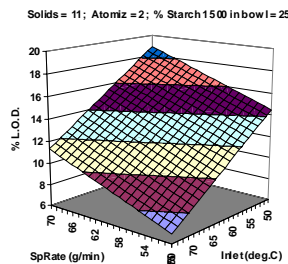
Response Variable	Low	High
Maximum granule moisture (% L.O.D.)	4.1	27.6
Granule flowability (g/sec.)	2.68	9.44
Mean granule size (microns)	136.7	922.1
Bulk density (g/cm <sup>3</sup> )	0.340	0.569
Tablet hardness at 15KN force (kp)	8.2	20.0
Tablet friability at 15KN force (% loss)	0.0051	12.38
Tablet disintegration time (minutes)	0.5	6.82
Product Bed Temperature °C	19	32

### Select Response Surface Graphs Maximum Granulation Moisture Content

Effect of Spray Rate vs. % Solids



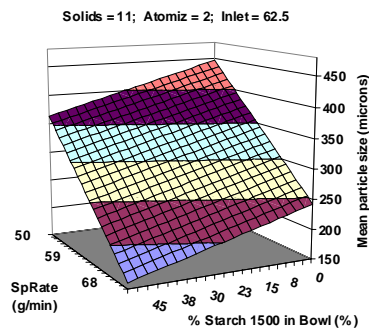
Effect of Spray Rate vs. Inlet Temp.



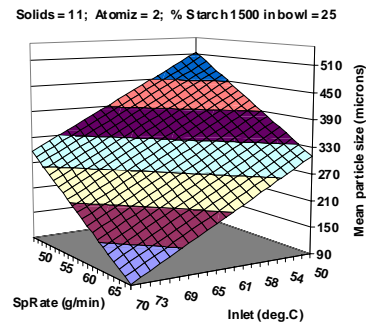
- It is necessary to have sufficient moisture in the process for controlled granule growth. Excess moisture may result in large uncontrolled granule growth while low moisture may result in weak granules subject to high attrition during the drying phase.
- As expected, increasing the solids content of the binder slurry resulted in lower granule moisture content.
- Increases in spray rate and decreases in the inlet temperature resulted in higher granule moisture content.
- It should also be noted that the effect of solids content and spray rate are time dependent. Generally, at a given inlet temperature, the longer the spray cycle, the higher the moisture content.

## Granulation Particle Size

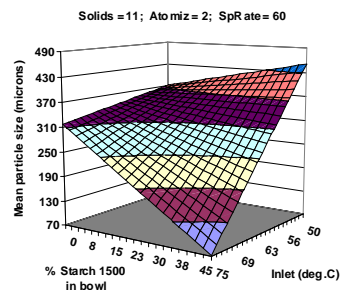
**Effect of Spray Rate vs.  
% Starch 1500 in bowl**



**Effect of Spray Rate vs.  
Inlet Temperature**



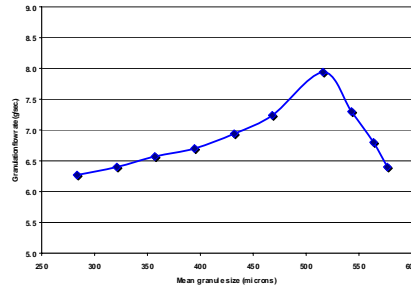
**Effect of % Starch 1500 in Bowl vs.  
Inlet Temperature**



- Lower inlet temperatures, causing higher moisture content, were mostly responsible for increases in the granule particle size.
- Increased spray rates, contributing to higher moisture, also increased the size of the finished granules.
- As the quantity of Starch 1500 in the bowl, rather than in the binder slurry, increased, the granule growth was less. It is inferred that by reducing the Starch 1500 in the binder slurry, the total quantity of liquid to apply is less, resulting in less time for granule formation prior to drying.
- It is also likely that the binding effectiveness of Starch 1500 is diluted when placed in the bowl and the binder liquid is shared by non-binding materials.

# Granulation Flow Properties

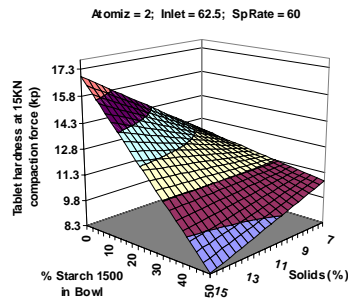
## Granulation Flow Rates Compared to Granule Size



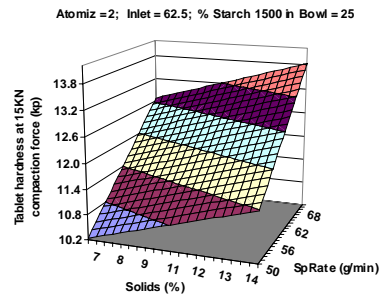
- Almost every trial resulted in improved flow properties over the acetaminophen powder alone.
- The flowability of the final granulations was closely linked with particle size.
- Increasing particle size resulted in faster flow until the size of the granules increased to the point that they began to impede the flow through the 10 mm instrument orifice.

## Tablet Hardness

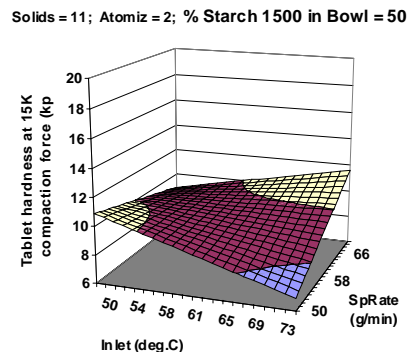
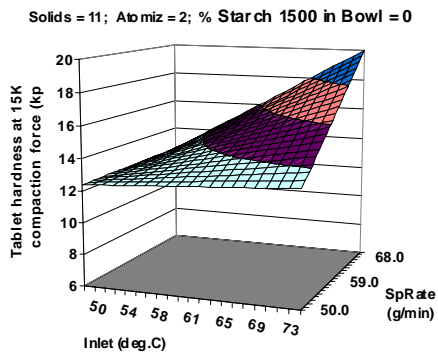
**Effect of % Solids vs. % Starch 1500 in bowl**



**Effect of % Solids vs. Spray Rate**



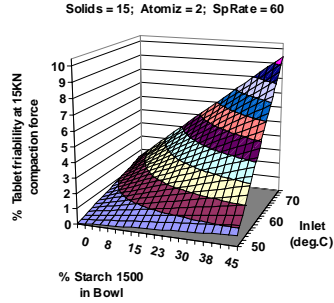
**Effect of Inlet Temperature vs. Spray Rate  
With Either All the Starch 1500 in Slurry or 50% in the Bowl**



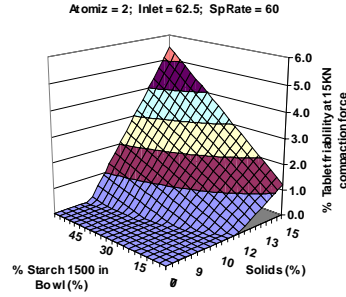
- The hardness characteristics of the tablets could be directly linked to the fluid-bed process conditions.
- Higher levels of Starch 1500 in the binder slurry rather than in the bowl produced harder tablets.
- Increased tablet hardness was also affected by the spray rate used in the granulation. Faster spray rates, resulting in higher granulation moisture content, produced granules with higher compressibility.
- Increasing % solids of the binder slurry, and resultant viscosity, also produced a more compressible granule.

## Tablet Friability

### Effect of Inlet Temperature vs. % Starch 1500 in bowl

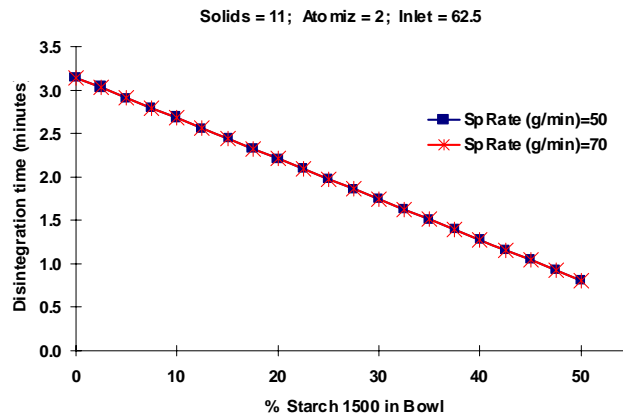


### Effect of % Solids vs. % Starch 1500 in bowl



- Tablet friability was closely associated with tablet hardness but showed that there was very low sensitivity to low % solids binder slurry and any percentage of Starch 1500 in the bowl.
- Only at high % solids and high levels of Starch 1500 in the bowl was there a substantial increase in tablet friability. Again, this is related to the duration of the wet granulation phase and the opportunity for granule growth.
- High inlet temperatures and the resultant lack of granulation moisture also was shown to affect the friability values.

## Tablet Disintegration Time



- Tablet disintegration time was very short over the range of experiments with no sample taking longer than 7.0 minutes.
- Only the quantity of Starch 1500 in the bowl or in slurry had any effect. Using all of the Starch 1500 in the slurry tended to increase hardness of the tablets as well as the resultant disintegration time.

## **CONCLUSIONS**

- Using acetaminophen as a model of a high dose, poorly compressible active, it was demonstrated that changing fluid-bed process conditions can have a direct and significant effect on finished tablet quality.
- It was found that one of the most significant affectors in granule formation and resultant tablet quality is time. Where increasing % solids (and higher viscosity) provided more robust granules at lower spray rates, the effect was the opposite at high spray rates.
- By understanding the interactions of the fluid-bed process variables we were able to study what process changes would have a significant impact on product quality.
- Design of experiments provides an effective tool for the rapid assessment of process variables on product quality.

## **ACKNOWLEDGMENTS**

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