



# EFFECT OF DIFFERENT PROCESS FACTORS ON PHYSICAL PROPERTIES OF ACETAMINOPHEN PELLETS WITH HIGH DRUG LOADING PREPARED USING EXTRUSION SPHERIONIZATION-WITHOUT A BINDER

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## INTRODUCTION

Extrusion spherionization is a four-step process involving wet massing, extrusion, spherionization and drying<sup>1</sup>. The successive completion of each of these steps leads to transformation of poorly flowing, fluffy dry powder into spherical shaped pellets. Pellets are multiparticulate dosage forms which offer unique flexibility to the formulator because they can be formed into sprinkles, filled into capsules, or compressed into tablets.

Pellets are appropriate immediate release dosage forms for high dose drugs with poor compressibility and flowability. Acetaminophen (APAP) is one such drug. Preparation of pellets of hydrophobic drugs like APAP with high loading using extrusion-spherionization is difficult. This is because wettability and solubility of drugs and excipients used to formulate the pellets play a critical role in determining the quality of the pellets.<sup>2</sup> Jover *et al.*<sup>3</sup> prepared pellets with high drug loading (80%) using a special grade of microcrystalline cellulose (Avicel® 955) and evaluated the effects of pKa, solubility and freezing point depression of several drugs on pellets prepared using the extrusion-spherionization process. Sonaglio *et al.*<sup>4</sup> studied only the extrusion process at high drug loading, using APAP as the drug.

The influence of process variables such as rate of water addition, massing speed and time in the preparation of wet mass for extrusion and spherionization variables like speed and time on the properties of pellets with high drug loading have not been reported. In addition, interaction among process variables, if any, demands careful optimization of critical manufacturing process like preparation of high drug loaded APAP pellets.

Therefore, the objective of this study was to prepare high drug loaded (80 %) APAP pellets with the most commonly used extrusion spherionizing agent, Avicel® PH 101 without adding any additional binder. Statistical experimental design was used to investigate the effect of different process variables and their interactions on physical properties of the APAP pellets.

## EXPERIMENTAL

### 1. Experimental design

The effects of five process variables such as rate of water addition, mixing speed, massing time, spherionization speed, and spherionization time were investigated in this study (Table 1). Data analysis was done using General Linear Model (Stastica 7.1 *QC&Text Miner* Statsoft Inc., Tulsa, OK).

### 2. Extrusion-Spherionization process

APAP and Avicel® PH-101 were mixed in a high shear mixer-granulator (Model 3VG, Robot-Coupe, Inc., Ridgeland, MS) in the reverse mode for 1 min at 500 rpm. The batch size for all the formulations was 300 g (dry weight). Purified water (129 mL) was added to the bowl at different addition rates using Masterflex® peristaltic pump (Cole-Parmer Instrument Company, Vernon Hills, Illinois) to obtain a wet mass with 30% w/w water while stirring the mixture at 1000 rpm in the forward mode. Massing of the resulting wet mass was performed at specified operational speeds and time, after addition of all the water. The wet mass was extruded through a dome extruder fitted with 1 mm screen, at specified operational speeds (50 rpm) using the single screw extruder (Multigranulator®, Model: MG-55, LCI Corporation, NC). The cylindrical extrudate was immediately spherionized using a Marumerizer (Benchtop Marumerizer®, Model: QJ-230T-1, LCI Corporation, Charlotte, NC) at specific spherionization speeds and times. Pellets were dried in a tray dryer at 50°C for 12 hours.

### 3. Evaluation of the physical properties of Pellets

#### 3.1. Particle size and distribution

Particle size distribution of the pellets was determined by sieve analysis using Gilsonic Autosiever, (Model GA-1A, Lewis center, OH) fitted with sieve numbers 10, 12, 16, 20, 40, 60 and 80. The average geometric mean diameter and the size distribution of the pellets were calculated from the pellets size distribution data.

#### 3.2. Bulk and Tapped density

Pellets were filled in a graduated cylinder to specific volume and leveled. The pellets were tapped in Vanderkamp® Tap density tester (Vankel Industries, Edison, NJ) until no further change in volume was recorded. Bulk densities of the pellets were calculated as the ratio of the weight of pellets to the volume occupied by the pellets in the measuring cylinder before tapping.

Tapped densities of the pellets were calculated as the ratio of the weight of the pellets to its volume after tapping.

#### 3.3. Sphericity of the pellets (Aspect ratio)

The aspect ratio is defined as the ratio between the longest Feret diameter and the Feret diameter perpendicular to this measure. A value of aspect ratio deviating from unity indicates the degree of spheroid elongation. Carl Zeiss stereomicroscope (Model Semi SVII, Carl Zeiss Gruppe, Jena, Germany) was used for analysis of the pellet-shape. Digital photographs of the pellets were taken using Axiocam MRc5 digital camera attached with the microscope and pictures were processed using Axiovision® 4.1 software. The aspect ratio of the pellets was calculated using Genesis Particle/Phase analysis software Version 3.60 (EDAX Inc, Mahwah, NJ). Aspect ratios of 150 individual pellets in each batch were used for determining the sphericity of the pellets.

#### 3.4. Flow properties of the Pellets

Flow rate of the pellets was determined using Flowdex® (Hanson Research Corporation, Chatsworth, CA) equipped with a 10 mm orifice. Cylindrical hopper of the instrument was filled with 50 g of pellets by pouring the pellets through a stainless steel funnel. Pellets were allowed to flow through the orifice opening into a beaker placed on an electronic balance (Sartorius LA Pro®, Bradford, MA). Flow rates of pellets were calculated using Winwedge® V 3.0 (TAL Technologies, Philadelphia, PA) software.

#### 3.5. Friability of the pellets

Friability of the pellets was tested using Redington® friability tester. Ten grams of pre-screened pellets retained on 20-mesh sieve was used for testing. The friabilator was operated at 25 rpm for 20 min. After the test, the pellets were screened through a 20-mesh sieve to remove the fines. The weight-loss was recorded, and the friability of the pellets was calculated using following formula:

$$\text{Percent Friability} = \left( \frac{\text{Initial Weight of Pellets} - \text{Final Weight of Pellets}}{\text{Initial Weight of Pellets}} \right) \times 100$$

Table 1. Process parameters for preparation of the Pellets by Extrusion-Spherionization.

Batch Code	Rate of water addition (mL/min)	Massing time (sec)	Massing speed (rpm)	Spherionization speed (rpm)	Spherionization time (sec)
OA-1	250	60	500	1000	30
OA-2	250	60	1000	1000	180
OA-3	100	30	1000	1000	180
OA-4	100	60	500	1000	180
OA-5	100	30	500	1000	30
OA-6	250	30	1000	1000	30
OA-7	100	60	1000	1000	30
OA-8	250	30	500	1000	180
OA-9	175	45	750	1000	105
OA-10	175	45	750	750	30
OA-11	175	45	750	1250	30
OA-12	175	45	750	750	180
OA-13	175	45	750	1250	180

## RESULTS AND DISCUSSION

### Bulk density and Tap density

Bulk density of APAP pellets was significantly influenced by interaction between the rate of water addition and massing time, spherionization speed, and interaction between spherionization speed and spherionization time.

Tap density was significantly affected by massing time, spherionization speed, interaction between rate of water addition and massing time, and interaction between spherionization speed and spherionization time.

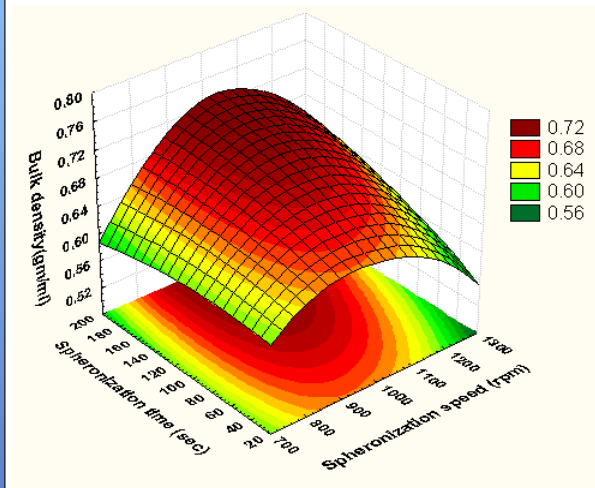


Figure 1. Response surface plot for bulk density as a function of spherionization time and spherionization speed.

### 2. Pellet size

Pellet size was influenced significantly by spherionization time and interaction between spherionization speed and spherionization time. Significant interaction between spherionization time and spherionization speed indicated that the effect of spherionization time on pellet size was not uniform, and depended on the spherionization speeds.

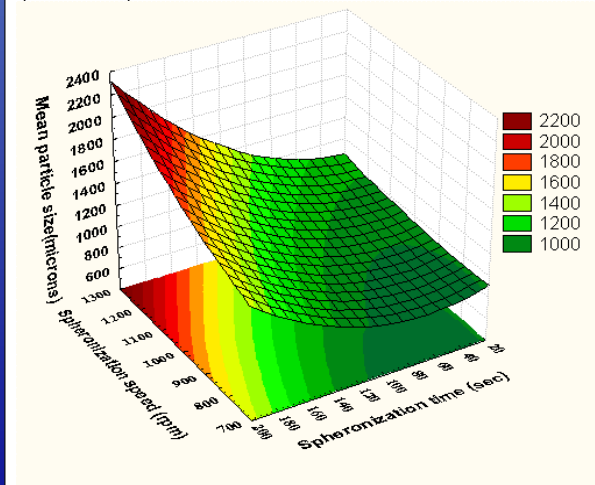


Figure 2. Response surface plot for mean particle size as a function of spherionization time and spherionization speed.

### 3. Pellet size distribution

Standard deviation of geometric particle size was used as a measure for estimating particle size distribution of the pellets. The standard deviation of geometric particle size was influenced significantly by interaction term between spherionization speed and spherionization time. Pellet size distribution was narrow in batches prepared at low spherionization time and higher spherionization speed. When spherionization time and spherionization speed were high, the size distribution was wide.

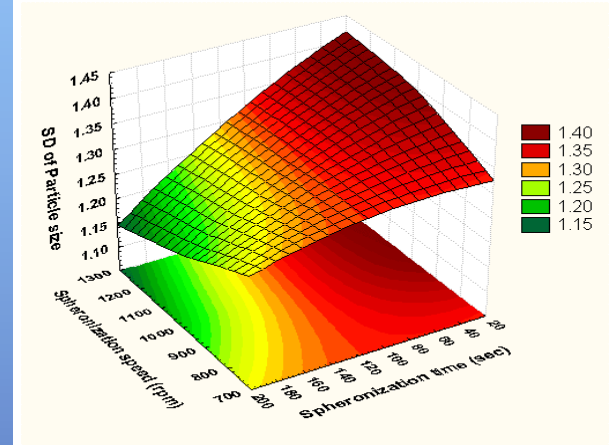


Figure 3. Response surface plot for particle size distribution as a function of spherionization time and spherionization speed.

### 4. Flow rate

The flow rate of the pellets was significantly influenced by spherionization time and spherionization speed. There was a non-linear relationship between flow and the spherionization speed. Flow rate of the pellets prepared at high spherionization speeds and spherionization time was low. Poor flow characteristics were observed from the pellets with large size and wide size distribution.

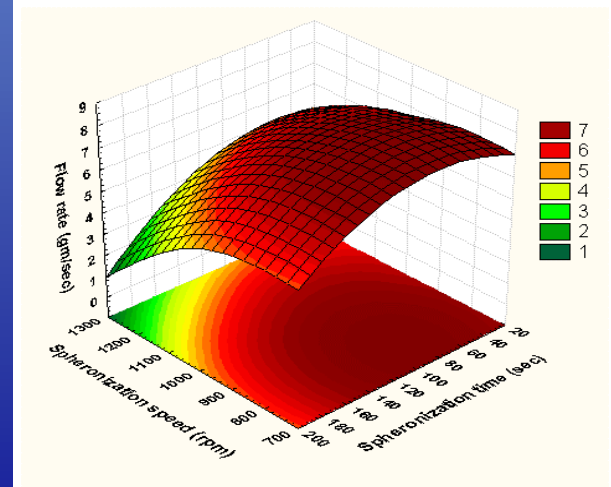


Figure 4. Response surface plot for flow rate of pellets as a function of spherionization time and spherionization speed.

### 5. Friability

Pellet friability was significantly affected by rate of water addition, massing time, interaction between rate of water addition and massing time, and spherionization speed.

An increase in spherionization time decreased the pellet friability. The effect of spherionization speed was different at different spherionization times. Pellets with low friability were obtained at spherionization speed ranging from 900 to 1200 rpm. Pellets with high friability were obtained at spherionization speeds lower than 900 rpm or higher than 1200 rpm. At spherionization speed ranging from 900 to 1200 rpm, the friability of the pellets was the lowest and the bulk density was the highest.

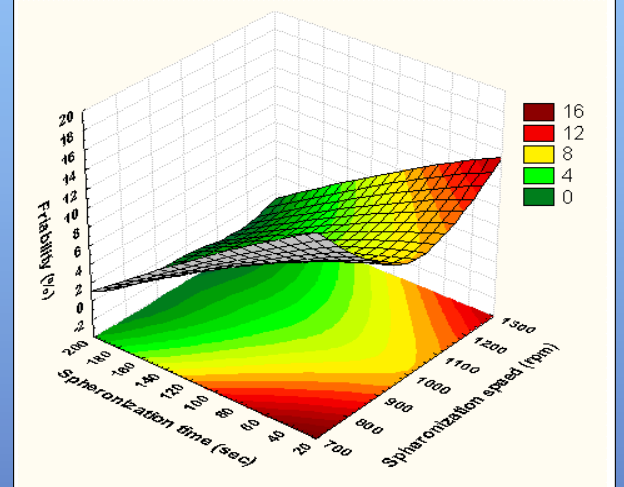


Figure 5. Response surface plot for friability of pellets as a function of spherionization time and spherionization speed.

### 6. Aspect ratio

The aspect ratio of pellets was significantly influenced by all the parameters except interaction between the rate of water addition and massing time. The aspect ratios were in the range of 1.1 to 1.23. Pellets with an aspect ratio less than 1.2 are considered spherical. Therefore, although pellets were prepared using different processing variables, they had good sphericity. However, since all process variables and interactions were significant for preparing spherical pellets of APAP with high drug loading, all process variables in the present study must be controlled adequately to obtain spherical pellets.

## CONCLUSIONS

Pellets with high APAP loading (80%) were successfully prepared with round shape, and good strength and flow properties. The results indicate that the less studied factors like massing time and rate of addition of water can influence the pellets density, friability and aspect ratio. However, these factors did not significantly influence other physical properties such as pellet size, size distribution, aspect ratio and flow rate. The more dominant factors like spherionization time and speed as well as the interaction between them play a major role in determining the physical characteristics of the pellets. Therefore, these factors must be adequately controlled during manufacturing of pellets with high drug loading.

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