

# STUDY ON THE EFFECT OF PROCESS VARIABLES ON THE PHYSICAL CHARACTERISTICS OF ACETAMINOPHEN PELLETS

PREPARED BY EXTRUSION AND SPHERONIZATION

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## 1. INTRODUCTION

Oral administration of medications is the most common, convenient and comfortable way of delivering drugs to body<sup>1</sup>. Among many oral dosage forms, pellets offer technological and therapeutic advantages such as the dose-volume ratio, spherical shape, possibility for high drug loading, and uniform distribution throughout the gastrointestinal tract<sup>2,3</sup>.

Extrusion-spheronization process is one of the most commonly used methods to prepare Pellets. The process consists of five unit operations, such as dry powder blending, wet massing, extrusion of the wet mass, spheronization of the extrudate, and drying. Screw and ram extruders are commonly used in the pharmaceutical pelletization processes. Three different extrusion assemblies that can be chosen for screw extruders are radial, axial and dome. Differences in extrusion assemblies along with process variables such as screw speed, spheronization speed and spheronization time typically influence the physical characteristics of the obtained pellets. Moreover, the physical characteristics of the spherical pellets will affect further manufacturing processes such as film coating, capsule filling or tabletting, and the quality of final dosage forms and their biological performance.

The effect of process parameters on the physical characteristics of the pellets prepared using different extrusion assemblies has not been explored. Therefore, the objective of the present study is to investigate the effect of process variables, such as extrusion assemblies (radial and dome), screw speed, spheronization speed, and spheronization time on the physical characteristics of acetaminophen pellets. The study was designed statistically to minimize the number of experiments that need to be carried out to understand the effects of aforementioned process variables on the physical characteristics of the acetaminophen pellets.

## 2. MATERIALS AND METHODS

Acetaminophen (APAP) (Mallinckrodt, St. Louis, MO) was used as the model drug. Microcrystalline cellulose (MCC) (Avicel® PH-101) (FMC Corporation, Newark, DE) was used as the spheronizing agent. All the formulations were prepared using 40% APAP and 60% MCC.

### 2.1. Experimental design

The effect of process variables such as screw speed, spheronizer speed and spheronization time on the physical properties of the pellets, such as pellet size distribution, surface area, bulk, tap and true densities, porosity, friability, flow rate, crushing strength, and shape of the pellets (sphericity) was evaluated in this study. A 2-level-4-factor full factorial (2<sup>4</sup>) design including one center point for each categorical variable (type of extrusion assembly) was adopted for the study. JMP 5.1 software (SAS Institute, Cary, NC) was used for designing the experiments. The level of all factors and process conditions are given in Tables 1 and 2. For comparison, the same process variables were evaluated with the single screw extruder equipped with two different extrusion assemblies, namely either the dome or radial extrusion assembly. All formulations were prepared with 40% APAP and 60% Avicel® PH-101 and wet-massed using the same process conditions. The aforementioned physical properties of the pellets were evaluated after the pellets were prepared and dried. Multiple linear regression model consisting of appropriate linear and interaction terms were fitted to the data. Stepwise regression procedure was used for model development. The selected models were hierarchical in nature, i.e. if an interaction term was appropriate for the model, the associated linear terms were also retained regardless of their significance levels.

Table 1: Levels of process variables used for 2<sup>4</sup> factorial design

Name of the Factor	Low Level	High Level
Screw Speed (RPM)	25	75
Spheronizer Speed (RPM)	600	1400
Spheronization Time (Min)	1	10

Dome and radial extrusion assemblies were used in a single screw extruder

Table 2: Process conditions for all the designed formulations

Batch Code	Screw Speed (rpm)	Spheronizer Speed (rpm)	Spheronization Time (min)	Type of Extrusion Assembly
10	25	600	1	Dome
11	25	1400	1	Dome
12	25	1400	1	Dome
13	75	1400	1	Dome
14	50	1000	5.5	Dome
15	25	600	10	Dome
16	75	600	10	Dome
17	25	1400	10	Dome
18	75	1400	10	Dome
19	25	600	1	Radial
20	75	600	1	Radial
21	25	1400	1	Radial
22	75	1400	1	Radial
23	50	1000	5.5	Radial
24	25	600	10	Radial
25	75	600	10	Radial
26	25	1400	10	Radial
27	75	1400	10	Radial

## 2.2. Extrusion-spheronization process

APAP and Avicel® PH-101 were mixed in Robot Coupe® (Model: 3VG, Robot-Coupe) high shear mixer-granulator in the reverse mode for one minute at 350 rpm. The batch size for all formulations was 300 g (dry weight). Purified water (200 mL) was added to the bowl using Masterflex® peristaltic pump (Cole-Parmer Instrument Company, Vernon Hills, Illinois) at a flow rate of 240 mL/min to obtain a wet mass with 40% wet weight. The mixture at 50 rpm in the forward mode. Massing of the resulting wet mass was not performed after addition of all the water. The wet mass was extruded through either a dome or radial extrusion assembly with 1 mm orifice at specified operational speeds using the single screw extruder (MultiGranulator®, Model: MG-55, LCI Corporation, NC) (Table 1). The resulting cylindrical extrudate was immediately spheronized using a spheronizer (Spheronizer®, Model: QJ-230T-1, LCI Corporation, Charlotte, NC) at specific speeds and times for different formulations (Table 2). Pellets were dried in a tray dryer at 50°C for 12 h.

### 2.3. Moisture content determination

Moisture content of the Pellets was determined using an Infrared moisture balance (Model: AD-4714 A, ANDO Corporation, Milpitas, CA). The sample was dried at 90°C for 20 minutes. Approximately 5-6 g of Pellets were used to determine the moisture content in the Pellets.

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

#### 2.4.1. Sieve analysis

Pellet size distribution was determined by sieve analysis (Gisicon Autoisizer, Model GA-1A, Global Gilson, Lewis center, OH). The average geometric mean diameter of the pellets was calculated as the ratio of the volume of the pellets.

#### 2.4.2. Determination of tap density

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

#### 2.4.5. Apparent pellet density and porosity

The true densities of the powder mixture and pellets were determined using a pycnometer (AccuPyc 1330, Micromeritics, Norcross, GA) with helium as the gas. The porosity of the pellets was calculated using the following equation: Porosity = 1 - (Pellet density/Powder density) X 100

#### 2.4.6. Shape evaluation

Carl ZEISS stereomicroscope (Model Sem 5VII, Carl Zeiss Gruppe, Jena, Germany) was used for evaluating the shape of the pellets. Digital photographs of the pellets were taken using Associan MRC's digital camera attached with the microscope and pictures were processed using Axiovision4.1 software. The aspect ratio of the pellets was calculated using Genesis Phase Analysis software Version 3.60 (EDAX Inc, Mahwah, NJ). The aspect ratio is defined as the ratio between the longest Feret diameter and the Feret diameter perpendicular to this measure. Aspect ratios of 150 individual pellets obtained from each batch were used for determining the sphericity of the pellets. A value of aspect ratio deviating from unity indicates the degree of spheroid elongation.

#### 2.4.7. Evaluation of 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 a lot of Pellets by pouring it through a stainless steel funnel. Pellets were allowed to flow through the orifice opening into beaker placed on an electronic balance (Sartorius LA Pro®, Bradford, MA). Flow rates were calculated using WinWedge V 3.0 (TAL Technologies, Philadelphia, PA) software.

#### 2.4.8. Crushing strength test

The crushing strength of the pellets was determined using AMETEK force measurement system (Model TCD 200, Chaitillon Inc., Greensboro, NC) attached with a 0.05 Kg load cell. A load was applied on the pellets at 50 mm/sec. The load (kilogram force) required to crush each batch was recorded with a digital gauge (DFCS 100, Chaitillon Inc., Greensboro, NC). The crushing strength of the pellets was then calculated using Windows based software (Nxygen 2.0, Chaitillon Inc., Greensboro, NC).

## 3. RESULTS AND DISCUSSION

All the evaluation results for the pellets prepared with different process variables are listed in Table 3. The effect of process variables on each physical property of APAP pellets was evaluated separately using multiple linear regression analysis. The effect of individual parameters or interaction between two parameters was considered to be significant at P<0.05. Only significant parameters including the main parameters and interaction effects were interpreted. Significant values (P-values) showing the effect of process variables and interactions between process variables on physical properties of APAP Pellets are listed in Table 4.

### 3.1. Bulk density

The bulk density of the pellets was significantly influenced by spheronizer speed, spheronization time, and the type of extrusion assembly used during the spheronization process. Interaction between spheronizer speed and the type of extrusion assembly used during the spheronization process also had a significant effect on the bulk density of the pellets (Table 4).

Table 3. Results of Physical evaluation tests for pellets

Batch	True Density (g/cc)	Tap Density (g/cc)	Flow Rate (g/sec)	Bulk Density (g/cc)	Porosity (%)	Bead Size (µm)	Crushing Strength (kg)
10	1.326	0.809	5.2	0.777	44.8	1129.7	6.1
11	1.437	0.783	5.4	0.761	45.5	1066.5	7.0
12	1.408	0.856	4.9	0.791	42.2	1312.2	8.0
13	1.395	0.846	5.6	0.775	44.8	934.7	6.1
14	1.368	0.851	5.5	0.776	44.6	1015.1	6.4
15	1.404	0.866	4.8	0.776	43.7	1433.8	4.4
16	1.400	0.852	5.1	0.778	43.6	1319.0	5.1
17	1.378	0.843	4.6	0.607	58.0	620.4	2.5
18	1.378	0.843	4.9	0.626	56.5	687.4	4.7
19	1.443	0.711	5.5	0.711	49.7	691.3	4.7
20	1.440	0.724	6.5	0.749	47.2	782.3	3.7
21	1.413	0.829	6.1	0.776	44.4	839.8	4.4
22	1.418	0.854	5.7	0.696	51.3	647.5	2.0
23	1.395	0.872	5.4	0.716	50.4	697.9	5.3
24	1.429	0.795	6.0	0.805	43.0	1078.1	4.8
25	1.443	0.817	4.9	0.771	44.5	1075.1	4.0
26	1.413	0.869	5.2	0.777	44.8	1129.7	6.1
27	1.387	0.859	5.4	0.761	45.5	1066.5	7.0

Table 4. Significant values (P-values) showing the effect of process variables and interactions between process variables on physical properties of APAP pellets

Process Variables	Bulk Density	Tap Density	Porosity	Pellet Size	Flow Rate	Crushing Strength	Aspect Ratio
Screw speed (A)	>0.25	>0.25	>0.25	>0.25	>0.25	0.09	0.05
Spheronizer speed (B)	0.00	0.00	0.20	>0.25	0.07	0.66	0.00
Spheronization Time (C)	0.00	0.00	>0.25	0.00	0.16	0.18	>0.25
Extruder type (D)	0.00	0.04	0.02	>0.25	0.01	0.00	0.02
Interactions							
A X B	>0.25	>0.25	0.15	>0.25	>0.25	0.08	>0.25
B X D	0.02	0.07	>0.25	>0.25	0.21	0.07	>0.25
C X D	0.15	0.22	>0.25	0.25	0.25	0.11	>0.25
B X C	0.13	0.01	>0.25	0.00	0.00	>0.25	0.06
A X C	>0.25	>0.25	>0.25	>0.25	0.05	>0.25	0.16

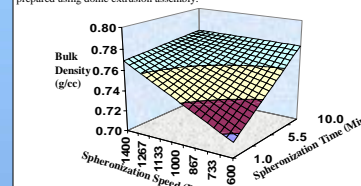
P<0.05 indicates significant effect of the process variable or interaction between the process variables on the physical properties of APAP pellets at level

The effect of spheronizer speed and spheronization time was positive, i.e., change in the bulk density of pellets was directly proportional to the change in spheronizer speed or spheronization time. However, the extent of change in bulk density of pellets was different, depending on the type of the extrusion assembly used to prepare the pellets. While moderate increase in the bulk density of pellets prepared using the dome extrusion assembly was observed with increasing spheronizer speed, significant increase in bulk density of pellets prepared using the radial extrusion assembly was observed when the spheronizer speed was increased (Figure 1). However, there was no change in bulk density of the pellets prepared with radial extrusion assembly when the spheronizer speed and spheronization time were at low level. A significant increase in the bulk density of pellets was observed when the spheronizer speed and spheronization time were at high level.

### 3.2. Tap density

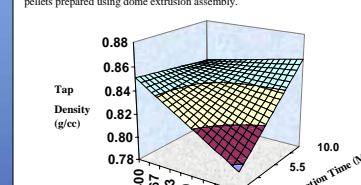
Spheronizer speed, spheronization time and the type of extrusion assembly used in the extrusion-spheronization process had a significant (P<0.05) influence on the tap density of the APAP pellets. Also, interaction between spheronizer speed and spheronization time had a significant effect on tap density. A significant interaction between spheronizer speed and the type of extruders had a significant effect on tap density of the pellets. Spheronizer speed and spheronization time had a positive impact on the tap density, i.e., as the spheronizer speed and spheronization time increased, the tap density of the pellets also increased. Changing the extrusion assembly from dome to radial significantly reduced the tap density of the pellets. Furthermore, a significant increase in the bulk density of the pellets prepared using dome extrusion assembly at different spheronizer speed when the spheronization time was at low level (Figure 2). There was no change in bulk density of the pellets prepared with dome extrusion assembly at different spheronizer speed when the spheronization time was at high level.

Fig 1: Effect of Spheronization speed and spheronization time on Bulk density of pellets prepared using dome extrusion assembly.



Although the effect of increasing spheronizer speed at low spheronizer speed on tap density was significant, no such difference in tap density of the Pellets was observed with different spheronization times at high spheronizer speeds. However, when the dome extrusion assembly was used, an increase in the tap density of the Pellets prepared at increasing spheronizer speed was significantly greater than the tap density of Pellets prepared when the radial extrusion assembly was used. APAP Pellets prepared using the radial extrusion assembly had a transient "no-effect region", thus indicating that changes in either the spheronizer speed or spheronization time in this region (spheronizer speed of 600 to 1300 rpm, and spheronization time of 1 to 8 minutes) did not significantly affect the tap density of the Pellets.

Fig 2: Effect of Spheronization speed and spheronization time on the tap density of pellets prepared using dome extrusion assembly.



### 3.3. Porosity

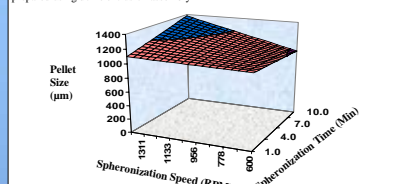
The porosity of the pellets was significantly (P<0.05) influenced by spheronizer speed, spheronization time, and the type of extrusion assembly used to prepare the pellets. Spheronizer speed and spheronization time had a negative influence on the porosity of the pellets, i.e., an increase in any one of these two process variables reduced the porosity of the pellets. Changing from dome to radial extrusion assembly increased the porosity of the pellets. Interaction between spheronizer speed and the type of extrusion assembly was statistically significant. This indicates the effect of spheronizer speed on porosity is different when different extruder dies were used. The results indicate that the degree of change in the porosity of the pellets prepared with radial extrusion assembly was greater than the change in the porosity observed when the dome extrusion assembly was used to prepare the pellets.

### 3.4. Pellet size

Spheronizer speed and spheronization time, type of extrusion assembly, and interaction between spheronizer speed and spheronization time were significant factors influencing the particle size distribution of the pellets. Spheronizer speed and spheronization time had a positive influence on the pellet size (P<0.05). Change in the type of extrusion assembly from dome to radial significantly reduced the pellet size. Interaction between spheronizer speed and spheronization time indicated that the effect of spheronizer speed on the average particle size of pellets was different at different spheronization time. In both types of extruders, at low spheronizer speed, no significant change in the particle size of the pellets was observed at short and long spheronization times. However, a significant increase in pellet size was observed at higher spheronizer speed when the spheronization time was increased from short to long.

This indicates that the pellet size distribution of the Pellets can be controlled by controlling the spheronization time at high spheronizer speeds using either the dome or the radial extrusion assembly (Figures 3). Nevertheless, the size of pellets prepared with radial extruder was smaller than the Pellets prepared with dome extruder.

Fig 3: Effect of spheronization speed and spheronization time on pellet size of pellets prepared using dome extrusion assembly



### 3.5. Flow rate

The type of extrusion assembly, and the interaction between spheronizer speed and spheronization time were found to significantly affect the flow rate of the Pellets. Flow rate of the pellets prepared using the radial extrusion assembly was higher than the flow rate of the pellets prepared using the dome extrusion assembly. This phenomenon could be attributed to smaller sizes of pellets obtained with the radial extrusion assembly (Table 3). Smaller pellets flow more easily than larger pellets through the orifice of a flow tester, assuming that the same amount of each particle size of pellets are used for the test (50 g). At low spheronizer speed, when spheronization time was increased from low to high, significant increase in the flow rate of the pellets was observed. However, at high spheronizer speed, when spheronization time was increased from low to high, the increase in flow rate of the pellets was insignificant. This indicated that if the spheronization process has to be optimized at low spheronizer speed, then high spheronization time will be required to obtain pellets with good flowability. However, if higher spheronizer speed is used during the spheronization process, then spheronization time is not a critical factor to be considered to obtain pellets with good flow characteristics.

### 3.6. Shape evaluation

Aspect ratio, i.e. the ratio between the length and width of the pellets, was used as the criterion for evaluating the shape of the pellets. When the pellets are perfectly spherical in shape, an aspect ratio is equal to one. A value of aspect ratio deviating from one indicates that the pellets are elliptical in shape. Spheronizer speed, spheronization time and screw speed were the main variables in determining the sphericity of the pellets. The effect of process variables such as spheronizer speed, spheronization time and screw speed on the sphericity of the pellets was in the following descending order: spheronizer speed>spheronization time>screw speed. Surprisingly, the extrusion assembly did not have a significant effect on the sphericity of the pellets. Thus, the results of this study indicated that irrespective of the type of extrusion assembly used to prepare the pellets, it is possible to get spherical pellets by adjusting processing conditions such as spheronizer speed and spheronization time.

### 3.7. Crushing strength

The type of extrusion assembly used to prepare the pellets was found to be the only process variable, which significantly influenced the crushing strength of the pellets. The crushing strength of the pellets obtained using the dome extrusion assembly was significantly greater than the crushing strength of the pellets obtained when the radial extrusion assembly was used.

## 4. CONCLUSIONS

This study indicated that extrusion assembly (dome or radial), spheronizer speed and spheronization time were the most influential parameters influencing the physical properties of the pellets. The effect of spheronization time and spheronization speed was dissimilar in different extrusion assemblies. Although earlier studies using ram extruders indicated that extrusion speed had a profound effect on bead density, this study indicated that for screw extruders, extrusion speed is not an important variable in determining the bead characteristics. In conclusion, this study confirmed that the most desirable bead characteristics could be obtained using optimum extrusion-spheronization process variables.

## 5. REFERENCES

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