



# AN INVESTIGATION OF CORRELATION BETWEEN THE LENGTH OF THE EXTRUDATES AND SPHERONIZATION PARAMETERS ON QUALITY OF PELLETS OBTAINED BY THE EXTRUSION-SPHERONIZATION PROCESS USING STARCH 1500®

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## INTRODUCTION

Extrusion spheronization process has gained considerable interest since its invention in 1960. The unique advantages of this process makes it suitable for developing immediate release formulations. In our previous work, we prepared acetaminophen pellets with 80% drug loading without a binder, using different process parameters. Generally at high drug loading, the formulation requires a strong binder. The presence of a binder in the formulation increases the plasticity of the wet mass and reduces the friability of the resulting pellets. This is particularly true for formulations with high drug loading in which the concentration of microcrystalline cellulose is low [1].

In 1970, Reynolds revealed the requirement of capillary or adhesive type binder in this process [2]. Funck *et al.* [3] showed that low levels of binders such as Na-CMC, Starch, HPC, HPMC, PVP, and carbomer could be used to produce spheres with high drug-loading using microcrystalline cellulose (MCC). However, a slight increase in the concentration of these binders in the formulation greatly affected the rheological properties of the extrudates. According to the authors, the wet mass with high consistency and low plasticity could be extruded, but not readily spheronized [4,5,6].

The objective of this study was to find a correlation between spheronization conditions and extrudate length on physical properties of pellets. Three different lengths of extrudates were obtained with three different concentrations of Starch 1500® as a binder. Five different spheronization conditions (selected based on a factorial design) were used to spheronize extrudates of different lengths. Relationships between extrudate length and spheronization conditions, and physical properties of pellets were evaluated in this study.

## EXPERIMENTAL

### 2.1. Design of Experiment

APAP beads with 85% drug loading were prepared from three different lengths of extrudates. The extrudates were prepared with three different concentrations (5%, 7.5%, 10%) of Starch 1500® as a binder. A 2 x 2 x 3 factorial design was used to prepare a total of 12 initial batches of pellets. In order to estimate the quadratic effects of the process parameters such as spheronization speed and time on physical properties of pellets, three additional batches were prepared at the mid level of process variables, i.e. spheronization speed of 1120 rpm and spheronization time of 2 minutes. Thus, a total of 15 batches of pellets were prepared in this study. The composition and process parameters of these batches are shown in Table 1.

### 2.2. Extrusion-Spheronization process

Appropriate quantities of APAP and Avicel® PH-101 containing were mixed in a high shear mixer-granulator (Model: 3VG, Robot-Coupe, Inc.) in the reverse mode for one minute at 1000 rpm. A slurry of 5% w/w Starch 1500® was then added to the powder mixture in the bowl using a Masterflex® peristaltic pump, while the mixture was stirred at 1000 rpm in the forward mode to obtain a wet mass. Massing of the resulting wet mass was performed at 500 rpm for one minute after adding all the binder. The wet mass was then extruded through a dome extruder fitted with 1 mm screen, at specified operational speeds using the single screw extruder (Multigranulator®, Model: MG-55, LCI Corporation, NC). The cylindrical extrudates were immediately spheronized using a Marumerizer® (Benchtop Marumerizer®, Model: QJ-230T-1, LCI Corporation, Charlotte, NC) at specific speeds and time. The resulting pellets were dried in a tray dryer at 50°C for 12 h. Formulations containing 7.5% and 10% w/w of Starch 1500® were also prepared according to the method described above. However, additional starch (i.e. 2.5% and 5%) was added in the powder form.

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

**2.3.1. Sieve analysis:** Particle size distribution of the pellets was determined by sieve analysis using Gilsonic Autosiever (Model GA-1A, Gilson Lewis Center, OH). Sieves (US Std.) with 10, 12, 16, 20, 40, 60 and 80 meshes were used.

**2.3.2. Bulk and Tapped density:** Known weight of pellets were filled into a graduated cylinder to specific volume and leveled. The pellets were then tapped in Vanderkamp® Tap density tester (Vankel Industries, Edison, NJ) until no further change in volume was recorded. Bulk density of the pellets was calculated as the ratio of the weight of 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 volume after tapping.

**2.3.3. Sphericity (Aspect ratio):** Carl Zeiss stereomicroscope (Model Semi SVII, Carl Zeiss Gruppe, Jena, Germany) was used for analysis of 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 100 individual pellets in each batch were used for determining the sphericity of the pellets.

**2.3.4. Friability of the pellets:** Friability of the pellets was tested using a friability tester according to the method described by Satoru *et al.* [7]. Ten grams of pre-screened pellets retained on a 20-mesh sieve were used for testing. The friabilator was operated at 25 rpm for 20 min. After the test, the pellets were screened through the 20-mesh sieve to remove the fines. The weight-loss was recorded, and the percent friability of the pellets was calculated from the weight loss data.

**2.3.5. Data Analysis:** The effect of varying spheronization speed and time on the physical properties of the pellets prepared with three different extrudate lengths was evaluated using separate slopes (univariate) ANCOVA model. STATISTICA QC & Text Miner 7.1 software was used to build and test the model (Table 2).

Table 1. Composition and process conditions used to prepare APAP pellets

Batch No.	APAP (% w/w)	Avicel® PH 101 (% w/w)	Starch1500® (% w/w)	Spheronization Speed (rpm)	Spheronization Time (min)
NT01	85	10	5	750	1
NT02	85	10	5	750	3
NT03	85	10	5	1500	1
NT04	85	10	5	1500	3
NT05	85	10	5	1120	2
NT06	85	7.5	7.5	750	1
NT07	85	7.5	7.5	750	3
NT08	85	7.5	7.5	1500	1
NT09	85	7.5	7.5	1500	3
NT10	85	7.5	7.5	1120	2
NT11	85	5	10	750	1
NT12	85	5	10	750	3
NT13	85	5	10	1500	1
NT14	85	5	10	1500	3
NT15	85	5	10	1120	2

Table 2. Significance of parameter estimates of ANCOVA model

Physical Property	SS	ST	SS*ST	SS*EI	ST*EL	SS*ST*EL
Geometric Mean diameter	S	NS	NS	S	NS	NS
Size distribution	NS	S	S	S	S	S
Bulk Density	NS	S	NS	NS	NS	S
Tap Density	S	S	S	NS	NS	S
Aspect ratio	S	NS	NS	S	S	NS
Friability	S	S	S	NS	NS	NS

S (Significant) (P<0.05); NS (Not significant); SS (Spheronization Speed); ST (Spheronization Time); EL (Extrudate length);

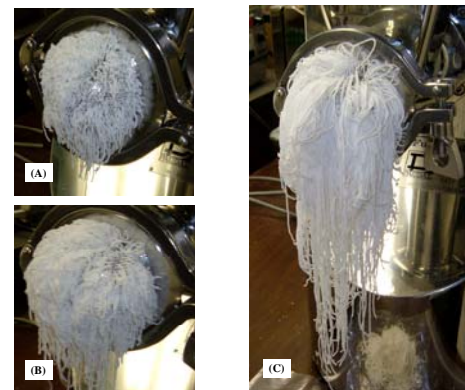


Figure 1: Extrudates of different lengths: (A) Small; (B) Medium; (C) Large

## RESULTS AND DISCUSSION

### 3.1 Mean pellet size

The geometric mean pellet diameter was significantly influenced by spheronization speed and interaction between spheronization speed and extrudate length. The response surface plot (Figure 2) indicated that the mean pellet diameter increased with increasing extrudate lengths. However, if the pellets were prepared with long extrudates (more than 50 mm in length), then the increase in the pellet size was marginal. The figure also showed that larger pellets would be formed at spheronization speeds of less than 1100 rpm when the length of the extrudates is in the range of 30 to 80 mm.

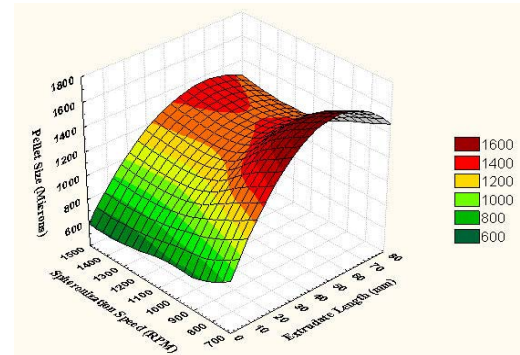


Figure 2: Response surface plot of pellet size (µm) x spheronization speed (rpm) x extrudate length (mm)

### 3.2 Pellet size distribution

Geometric standard deviation was influenced by spheronization time, and interactions between spheronization speed, spheronization time and extrudate length. Pellets with the widest size distribution were obtained at a high spheronization speed (1500 rpm) and spheronization time (3 min). However, at a low spheronization speed (750 rpm), the size distribution of pellets decreased with increasing extrudate lengths. This could be because, at low spheronization speeds, long extrudates produced pellets with a high aspect ratio. Longer spheronization time resulted in the formation of pellets with a wider size distribution. Thus, spheronization time must be considered simultaneously with the spheronization speed for preparing pellets with a narrow size distribution.

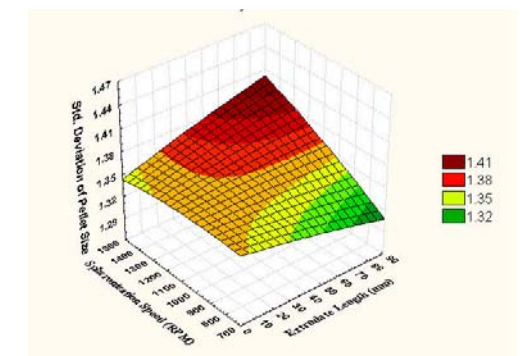


Figure 3: Response surface plot of pellet size distribution x spheronization speed (rpm) x extrudate length (mm)

### 3.3 Bulk and Tapped densities

Bulk density of the pellets was significantly influenced by spheronization time and the interaction between spheronization speed, spheronization time and extrudate length. Packing characteristics of pellets determine the tap density of pellets. A linear relationship was observed between spheronization speed, spheronization time and tap density. This study identified that, although the extrudate length (which is linearly correlated with binder concentration) was not a major determinant of bulk or tap density, extrudates of different lengths will densify to different extent under similar spheronization conditions, i.e. spheronization speed and spheronization time.

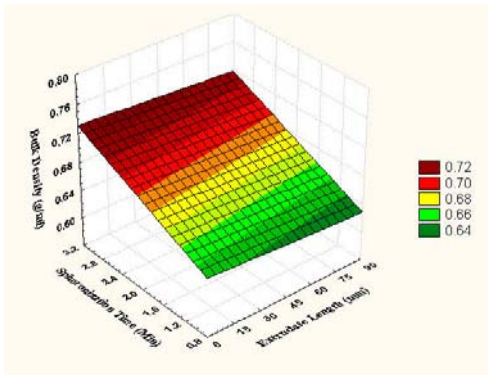


Figure 4: Response surface plot of bulk density (g/ml) x spheronization time (min) x extrudate length (mm)

### 3.4 Aspect Ratio

Aspect ratio of pellets was significantly influenced by spheronization speed, interaction between spheronization speed and extrudate length, and interaction between spheronization time and extrudate length. Figure 5 indicated that dumbbell shaped pellets were formed when long extrudates (88 mm) were processed at a spheronization speed of less than 1100 rpm. However, when long extrudates were processed at 1500 rpm, they formed pellets with a low aspect ratio of less than 1.2. These results indicated that spherical pellets can be prepared from extrudates (obtained from formulations shown in Table 1) of any length ranging from 5 mm to 90 mm by optimizing spheronization speed.

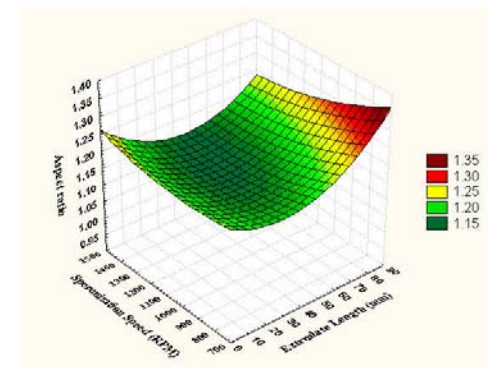


Figure 5: Response surface plot of aspect ratio x spheronization speed (rpm) x extrudate length (mm)

### 3.5 Friability

Friability was significantly influenced by spheronization speed, spheronization time and interaction between spheronization speed and time. The response surface plot shown in Figure 6 indicated that pellets prepared at higher spheronization speed (over 1300 rpm) were friable. Since friability is a measure of pellet strength, pellets with good mechanical strength could be prepared at low spheronization speed (below 1100 rpm). Extrudate length did not influence the friability significantly. This implied that the relationship between spheronization conditions and friability was similar for pellets prepared from extrudates of different lengths.

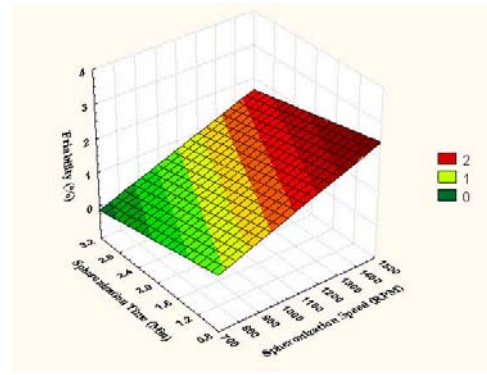


Figure 6: Response surface plot of friability (%) x spheronization time (min) x spheronization speed (rpm)

## CONCLUSION

Pellets could be successfully prepared from extrudates of three different lengths ranging from 5 mm to 90 mm. Moreover, a correlation between spheronization conditions and extrudate length on physical properties of pellets was obtained using a univariate ANCOVA model. For preparation of spherical pellets from long extrudates, high spheronization speed was mandatory. However the pellets prepared at this speed were friable. Therefore, optimum spheronization speed and time must be identified to prepare pellets with good sphericity and mechanical strength. Since the univariate ANCOVA model used in this study considered each physical property separately, it was used only to identify significant effect of spheronization conditions on individual physical property of pellets, prepared from extrudate of different lengths. Since the physical properties of pellets were inter dependent, multivariate statistical models or neural network models must be used for optimization..

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