



# Effect of different production variables on the physical properties of pellets prepared by extrusion-spheronization using a multivariate analysis

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## ABSTRACT

**Background:** The spheronization process is a rapidly expanding technology which provides a uniform and predictable transport in the gastrointestinal tract and renders pellets having a good flowability, high mechanical strength, and low friability. **Objectives:** The aim of the present study was to evaluate the effects of spheronization rate, spheronization time, and moisture content on shape descriptors and physical properties of pellets produced from microcrystalline cellulose (MCC). **Methods:** Approximately, 50 g of MCC were hydrated, passed through a #8 mesh sieve, and spheronized at rates of 4, 6, 8, 10, and 12 Hz and residence times of 30, 60, 90, 120, and 180 s in 25 experimental runs. In a separate experimental set, moisture levels of 23.1, 37.5, 47.4, 54.5, and 60% were employed at the optimal operational conditions of 12 Hz and 180 s. A microscopy analysis was used to evaluate the shape descriptors using the ImageJ® software. Pellets properties such as compressibility, friability, true density, strength, flow rate, and mass were also evaluated. A multivariate analysis was used to study the effect of these production variables on response variables such as shape descriptors, densification, breaking strength, friability, and porosity. **Results:** Pellets having a large size were obtained employing a high spheronization rate, spheronization time, and high moisture content. Shape descriptors related to size such as area, perimeter, and mean diameter increased with increasing spheronization time and spheronization rate. Further, pellets obtained at a high spheronization rate were more spherical than those obtained at low speeds. Conversely, shape descriptors related to morphology such as circularity and roundness and pellet strength remained virtually unchanged as operational conditions changed. **Conclusions:** The moisture level was the most critical factor to increase pellet size and improved the spherical morphology. On the other hand, spheronization rate was the determining factor for pellet properties such as densification, compressibility, and compactibility.

## INTRODUCTION

Pellets are spherical or semispherical agglomerates of bulk drugs and excipients ranging from 0.5 to 2.5 mm in diameter.<sup>[1]</sup> The extrusion-spheronization is the most commonly used process for pelletization and is used to achieve a controlled drug release.<sup>[2]</sup> The purpose of the pelletization process is to produce spherical particles with a narrow size distribution and acceptable mechanical properties for the desired release pattern.<sup>[3]</sup> Pellets render several advantages since they are freely dispersed in the gastrointestinal tract, and maximize drug absorption providing a homogeneous dispersion of the drug, reducing plasma fluctuations, and minimizing potential side effects. It offers good flow properties ensuring a target content uniformity.<sup>[4]</sup> Further, pellets allow

for the combination of several active ingredients with different release profiles into a single-dosage unit.<sup>[5]</sup>

Only few excipients can be used for the extrusion-spheronization process due to the strict requirements they must fulfill. First, they should form a cohesive plastic mass on wetting. The wet mass should be mechanically strong and brittle enough to be broken down into short lengths in the spheronizer. Microcrystalline cellulose (MCC) is the typical excipient for extrusion-spheronization and its rheological properties are suitable for this process.<sup>[6]</sup> It has a very high internal porosity and a large surface area because of the randomly arrangement of its filamentous microcrystals.<sup>[7]</sup> These phenomena provide a high absorption and moisture retaining properties. The retained water molecules act as

a lubricant during extrusion and control the pellet shape during spheronization. The pelletization properties of MCC are also affected by the chemical composition, degree of polymerization, degree of crystallinity, moisture content, and particle morphology.<sup>[8]</sup> The aim of this study is to evaluate the impact of spheronization rate and time, and moisture level on the morphology and particle properties of the resulting pellets employing a multivariate analysis (principal component analysis [PCA]).

## MATERIALS AND METHODS

### Materials

MCC (lot P205815624, Avicel® PH102) was obtained from FMC Biopolymers (Philadelphia, PA). Deionized water was used as a wetting fluid and liquid binder. Concentrated hydrochloric acid (lot 2612KLHV) was obtained from Mallinckrodt Specialty Chemicals Co. (St. Louis, MO). All ingredients were of analytical grade.

### Preparation of Pellets

Pellets were prepared by the extrusion-spheronization method. Approximately, 50 g of MCC was weighed and wetted with 70 mL of deionized water. Subsequently, the wet mass was passed manually through a #8 mesh sieve (2.6 mm in diameter) with a force  $\leq 11.2$  N/cm<sup>2</sup> measured with a load cell (LCGD-10K, Omega Engineering, Inc., Stamford, CT). The granules thus formed were transferred to a spheronizer (Model 1LA70-4YA60, Siemens) operated at rates of 4, 6, 8, 10, and 12 Hz, and residence times of 30, 60, 90, 120, and 180 s employing a total of 25 experimental runs. The friction plate employed had a grooved cross-hatch surface forming a right angles pattern. These grooves enhance the frictional forces. It has. Pellets were then oven-dried for 24 h at 40°C. It allows for the formation of hard mini granules with low porosity and a homogenous surface. Subsequently, in parallel study the effect of the moisture level from 23.1 to 60% at the optimal operational conditions of 12 Hz and spheronization time of 180 s was studied.

### Physical Properties of Pellets

Shape descriptors were obtained by digital image analysis using an optical microscope (BM 180P, Boeco, Hamburg, Germany) coupled with a digital camera (FinePix S9000, Fujifilm, Tokyo, Japan). The microphotographs were taken at 10× magnification. Approximately, 600 pellets were randomly selected in each micropicture and their projected area, perimeter, Feret diameter, circularity, aspect ratio (AR), roundness, solidity, and sphericity were calculated using the license-free software name as ImageJ® (v. 1.46r, NIH, Bethesda, MD). Particle size distribution plots were then constructed by plotting the frequency percentage vs. the Feret diameter intervals using the Minitab v.16 software (Licence #1369619352118374680, Minitab® Inc., State College, PA). The equations used to calculate these parameters are expressed as follows:

$$\text{Circularity} = \left( \frac{4\pi * \text{Area}}{\text{Perimeter}^2} \right) \quad (1)$$

$$\text{Sphericity} = \left( \frac{4 * \text{Area}}{\pi * \text{Feret diameter}^2} \right) \quad (2)$$

$$\text{Aspect ratio} = \left( \frac{\text{Width}}{\text{Lentgh}} \right) \quad (3)$$

$$\text{Roundness} = 4 * \frac{\text{Area}}{\pi (\text{Feret diameter})^2} \quad (4)$$

$$\text{Solidity} = \frac{\text{Area}}{\text{Convex area}} \quad (5)$$

The moisture content was determined using 3 g of the sample on an infrared moisture balance (Scout Pro, OHAUS Corp., Parsippany, NJ) at 100°C for 10 min. True density and porosity were determined on a Helium pycnometer (AccuPyc II 1340, Micromeritics, USA) with ~3 g of sample. Bulk density was determined on 3 g of sample directly measured on a 10 ml graduated cylinder. Tap density was measured in an AutoTap® density analyzer (AT2, Quantachrome Instruments, Boynton Beach) operated for 250 cycles.<sup>[9]</sup> Volume data for each cycle were fitted to the Kawakita, compressibility model. The flow rate was determined using ~15 g of sample passed through a glass funnel with a neck diameter of 20.6 mm and subsequent measurement of the time flow. The ratio between mass and the respective time was taken as the flow rate.<sup>[10]</sup> The flowability of the pellets is used to assess whether a homogeneous filling of the gelatin capsules would occur. The average mass was obtained on an analytical microbalance (HT224R, Vibra, Denshi Shinko Co, Tokyo) having a 0.1 mg sensitivity.

Friability is the property related to the pellet ability to withstand shock and abrasion without fragmentation. It measures the pellet tendency to flake off during handling leading to the formation of dust.<sup>[11]</sup> This test was performed on ~6 g of sample previously sieved on a #60 mesh. A friabilator (FAB-25 1,351,130, Logan) operated at 25 rpm for 4 min was employed. At the end of the test, only the fraction retained on the #60 mesh sieve was utilized.

The pellet strength was obtained by measuring the force required to break a pellet having a known diameter. A hardness tester (VK200 8-1011-0699, Vankel) with a 0.5 N sensitivity was employed. Data of breaking force were found from the expression 6. The test was conducted on 10 replicate.

$$\text{Pellet strength} = \left( \frac{0.4 * \text{breaking strength}}{\pi * \text{Feret diameter}^2} \right) \quad (6)$$

### PCA

A multivariate analysis known as PCA was used to structure the resulting properties into three linear components or vectors named as PC1, PC2, and PC3. The correlation criterion was used to determine the relationship between the properties. Further, a cluster analysis was used to show a hierarchical structure between variables. The Minitab® v. 16 software (Minitab® Inc., State College, PA, USA) was used for the statistical analysis.

## RESULTS AND DISCUSSION

### Processing Conditions

A constant plate diameter of 30 cm was employed at spheronization rates of 4, 6, 8, 10, and 12 Hz which are equivalent to 240, 360, 480, 600, and 720 rpm and peripheral velocity of 377, 566, 754, 944, and 1131 cm/s, respectively. The spheronization time varied from 30 to 180 s (Table 1). Results indicate that the most spherical pellets were obtained at 12 Hz and 180 s. Other researchers have found a rotational speed in the range between 200 and 400 rpm and long spheronization times as suitable to obtain highly spherical pellets.<sup>[12]</sup> However, most of these studies have been conducted on small plate spheronizers. Thus, Newton *et al.* found an optimal peripheral velocity of about 420 cm/s for a small plate device.<sup>[13]</sup> Further, small plates require higher speeds for an optimal performance. For instance, 800 rpm might be required for a plate size of 21.2 cm with an optimal load of 300 g.<sup>[14]</sup> Therefore, the plate must have an appropriate load to allow for “chopping” of the extrudate after which the fragments move in a toroidal motion. Our preliminary studies (not published) determined 50 g as the optimal drug load for the spheronization time  $\leq 180$  s. If

the load on the plate is too low ( $< 20$  g) an insufficient particle-particle interaction occurs, which results in smaller pellets with low densities and irregular shapes. Conversely, if the plate load is too high ( $> 400$  g) the particles cannot sufficiently interact with the spheronizer plate, taking longer to produce spherical particles (up to 10 min).

The spheronizer rotating plate produced a denser, rounder, and rougher surfaced pellet due to the centrifugal force created by plate rotation, the vertical force created by collision, and the gravitational force allowing for the formation of a toroidal motion. This movement is also described in terms of a rope-like tumbling, twisted rope, and spiral patterns. The increase of spheronization time and rate allowed for the generation of more frictional and rotational forces where the short, oblong and granular particles experienced growth, folding, and edge rounding and subsequently were shaped into dumb bells. These dumb bells were then twisted, broken, rounded, and transformed into spherical pellets. These findings are in agreement with previous studies conducted by other researchers.<sup>[15,16]</sup>

A cross-hatch plate of 30 cm in diameter was employed and produced pellets with a spherical shape and rough surface.

**Table 1:** Effect of processing conditions on pellet properties\*

Rates (Hz)	Time (s)	Compressibility (%)	Friability (%)	Strength (N)	Flow (g/s)	Porosity (%)	Mass (mg)	Bulk density (g/cm <sup>3</sup> )	Tap density (g/cm <sup>3</sup> )	True density (g/cm <sup>3</sup> )
4	30	13.0	4.3	4.1	45.0	76.6	6.1	0.37	0.42	1.58
4	60	14.9	4.6	4.1	42.7	73.5	7.0	0.32	0.37	1.60
4	90	14.5	0.3	12.1	46.1	79.6	3.9	0.32	0.40	1.57
4	120	14.2	0.5	19.0	48.6	74.7	5.8	0.4	0.46	1.58
4	180	9.9	0.8	23.6	47.5	75.4	19.5	0.39	0.43	1.58
6	30	13.5	0.8	3.9	50.3	75.9	6.6	0.38	0.44	1.58
6	60	12.5	0.6	18.2	45.0	73.4	13.7	0.42	0.47	1.58
6	90	12.3	0.8	24.7	41.1	72.8	16.1	0.43	0.49	1.58
6	120	14.0	0.5	26.9	54.6	72.6	11.7	0.43	0.50	1.57
6	180	11.6	0.3	31.3	49.1	70.8	16.2	0.46	0.53	1.58
8	30	13.3	0.7	23.8	55.2	68.2	10.3	0.5	0.57	1.57
8	60	15.6	0.5	33.2	44.3	71.4	21.6	0.45	0.53	1.58
8	90	15.0	0.2	38.4	50.8	71.4	17.9	0.45	0.52	1.57
8	120	12.7	0.6	42.6	47.8	72.0	27.8	0.44	0.50	1.57
8	180	12.8	0.5	50.7	41.9	73.4	26.2	0.42	0.48	1.58
10	30	11.4	0.2	24.8	52.5	74.6	14.7	0.4	0.45	1.58
10	60	13.1	0.3	32.7	52.9	72.8	15.0	0.43	0.49	1.58
10	90	7.5	0.3	36.4	50.8	70.6	32.8	0.44	0.48	1.58
10	120	13.3	0.3	44.5	46.5	71.6	30.9	0.44	0.51	1.55
10	180	12.2	0.2	65.1	42.4	71.5	38.7	0.45	0.51	1.58
12	30	13.0	0.7	24.8	19.6	74.2	12.4	0.41	0.47	1.59
12	60	8.2	0.9	32.5	56.2	72.0	18.2	0.44	0.48	1.57
12	90	9.2	1.2	38.9	50.3	69.5	27.7	0.48	0.52	1.57
12	120	7.3	0.5	50.3	53.3	66.2	24.0	0.53	0.57	1.57
12	180	10.4	0.2	107.2	56.2	67.5	21.2	0.51	0.56	1.57

\*Wetting level: 60% w/w

Some researchers have reported similar findings by using a textured rotor plate obtaining smaller and less spherical pellets with a rougher surface. On the contrary, using a smooth rotor plate and a higher rotor speed results in more spherical pellets with smoother surface.<sup>[17]</sup>

A large spheronization rate and time led to the formation of large pellets. Further, these high spheronization rates and times led to the formation of more regularly-shaped pellets (Figure 1a and b). Conversely, a low spheronization rate and time led to the formation of small and irregular particles leading to the loss of sample at the edge of the rotating plate.

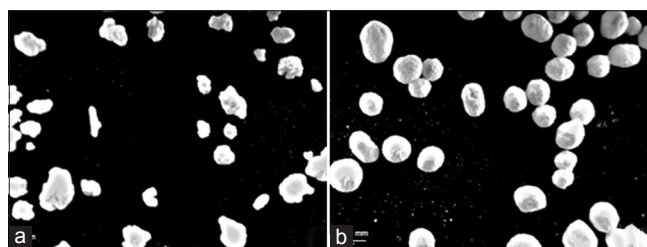
Figure 2a and b show the effect of spheronization rate and time on pellet size distribution. The size distribution was more dispersed when pellets were produced at low spheronization rates (4 and 6 Hz), but at high rates (12 Hz) the resulting pellets were larger and had a narrow size distribution. On the other hand, the spheronization time did not have major contribution on size distribution. Thus, the spheronization rate rather than spheronization time was more determining for pellet growth.

### Effect of Moisture Level

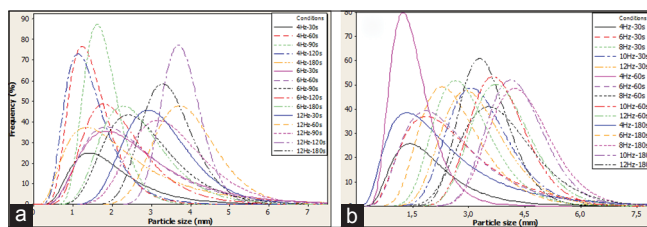
The moisture content is an extremely important parameter in the pelletization process. It is necessary to award plasticity to a powder mass so that it can be extruded and shaped afterward. During wet-massing, coalescence and growth of the particles are induced due to the formation of strong hydrogen bonding interactions.<sup>[17]</sup> In this scenario, water provides the required plasticity to the mass so a permanent bonding occurs. There is a certain limit of moisture content at which pellets having an acceptable quality are produced. A large wetting degree was related to a large increase in pellet size, whereas a low wetting degree made the massless cohesive and more susceptible to be blown up out of the rotating plate. Other researchers have obtained similar results.<sup>[18]</sup> For instance, if the moisture content is less than a certain lower limit, a lot of dust will be introduced during the spheronization process which will be reflected on (i) a large yield of fines due to attrition of the extrudate so that it fall down between the edge of the spheronizer plate and the chamber wall; or (ii) the formation of an extrudate which although is reduced in length, remains as cylindrical or “non-rounded” pellets. On the other hand, if the moisture content is larger than certain upper limit (60% w/w) an overweighed mass and agglomeration of individual pellets occurs due to

the accumulation of excessive water at the surface of pellet. Beyond this value, a very sticky dough was produced which did not pass through the #8 mesh sieve. As a result, the spheronization process becomes very difficult since this mass was not brittle enough to disintegrate and break down. On the contrary, this excessive wetting and hence, plasticity makes the material too tacky resulting in the formation of extremely large pellets under the effect of the centrifugal force.

A high wetting level (>60 mL) also increased the mechanical strength, pellet mass, and flowability, but lowered the friability and porosity of pellets (Table 2). This indicates that the pellet strength was inversely correlated with friability and that strength increased in pellets having a larger diameter (Figure 3). There was an inverse relationship between compressibility and flow rate. However, flow rate and mass showed a direct relationship with the wetting level. For instance, a high pellet weight, size, and flow were obtained when the wetting level was 75 mL (Figure 3). The opposite occurred for compressibility, which decreased as the amount of added water increased. On the other hand, porosity virtually did not change indicating no effect on densification. Similar results have been obtained previously.<sup>[15,19,20]</sup>



**Figure 1:** Effect of spheronization rate and spheronization time on pellet morphology (a) 4 Hz-30 s, (b) 12 Hz-180 s



**Figure 2:** Particle size distribution of pellets produced at: (a) Different spheronization speeds, and (b) different spheronization times

**Table 2:** Effect of wetting level on pellet properties\*

Wetting level (ml) <sup>1</sup>	Moisture content (% w/w)	Compressibility (%)	Friability (%)	Strength (N)	Flow (g/s)	Porosity (%)	Mass (mg)
0 <sup>2</sup>	0	20.2	0.5	3.50	0	81.8	4.7
15	23.1	27.3	0.6	3.50	9.9	76.2	0.1
30	37.5	28.7	0.6	3.50	20.0	77.4	0.1
45	47.4	22.2	0.6	3.50	26.8	74.6	2.7
60	54.5	14.0	0.8	3.50	38.6	67.1	3.5
75	60	10.3	0.2	114.67	39.5	72.1	58.8

\*Rate of 12 Hz and time of 180 s, <sup>1</sup>wetting level is defined as the amount of distilled water added to MCC during the extrusion process, <sup>2</sup>only the powder properties are reported since no pellets were formed. MCC: Microcrystalline cellulose

The morphological analysis included an assessment of the roundness, and the sharpness of the vertices, edges, and sides of the pellet. Descriptors such as circularity, roundness, and AR are related to the shape of the pellet. The AR describes the ratio between the width and length of the pellet. This characteristic is related to the elongation of the particle, whereas sphericity is described by the value of roundness. An ideal sphere should have an AR of 1. Therefore, an AR of 0.9 can be considered as practically spherical.<sup>[21]</sup>

Figure 3a and b depicts the influence of moisture content on properties related to size (a) and morphology (b), respectively. The surface area is defined as the surface area of a cylinder having the same radius and a height corresponding to the diameter to that of the sphere. Perimeter is defined as the linear distance around a two-dimensional geometry. The Feret diameter is the distance between two parallel tangent planes touching the surface of the pellet.<sup>[22]</sup> A direct relationship was found between the moisture content and area, perimeter, and Feret diameter. This effect was much more pronounced at high moisture levels. Thus, a high wetting level results in the formation of more spherical particles having a large particle size. For instance, a slight increase in circularity, roundness, and AR of pellets is obtained at 12 Hz, 180 s and high-moisture content easing the extensive formation of hydrogen bonds facilitating the agglomeration process and hence, pellet growth.

Results indicate that all shape descriptors increased in magnitude with increasing moisture levels, and a value close to the unity for these dimensional factors indicates that the particle is nearly spherical.<sup>[23]</sup> Thus, as these variables increased the granules changed from an irregular shape to oblong and spherical geometry. Further, there was a direct relationship between the moisture level and the resulting size, diameter, and perimeter of the pellets.

## PCA

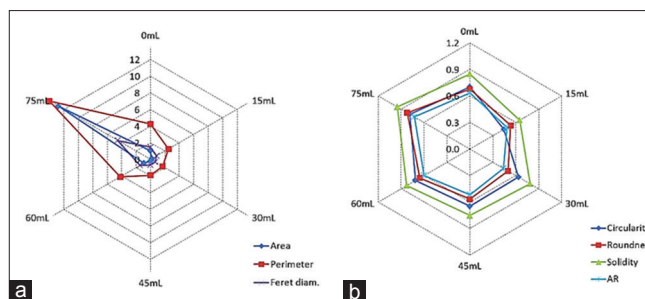
The PCA correlation analysis (PC1, PC2, and PC3) indicates that 72.4% of the variability in the data set is explained by the first three components. This means that most data were structured into these three dimensions. The correlation analysis indicates that there was a linear association between the variables, and it was governed by their standard deviation. The scores for the analysis can be broken down into these vectors:

$$\text{PC1: } 0.27\text{Frequency} + 0.27\text{Strength} - 0.26\text{Porosity} + 0.26\text{Roundness} + 0.28\text{Bulk density} + 0.26\text{Tap density} + 0.27\text{Area} + 0.27\text{Perimeter} - 0.29\text{Aspect ratio}$$

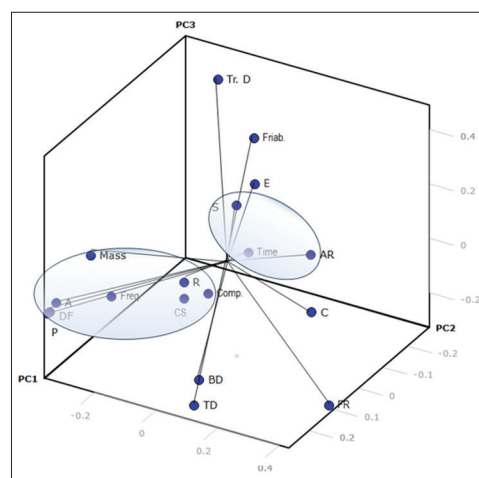
$$\text{PC2: } 0.41\text{Flow} - 0.33\text{Area} - 0.35\text{Perimeter} + 0.4\text{Circularity} - 0.4\text{Feret} + 0.19\text{Time}$$

$$\text{PC3: } -0.33\text{Compressibility} - 0.33\text{Flow} + 0.49\text{True density} + 0.43\text{Solidity} + 0.2\text{Time}$$

The pellet loading plot is shown in Figure 4. This chart shows 3D projections of these properties in three axes named as PC1, PC2, and PC3. The loads are weights of each original property when the main component is calculated. This plot is a linear combination of the original data that maximizes the variance. Thus, each point on the plot determines the particular contribution of this property on these components.



**Figure 3:** Radial plots showing the effect of wetting level on (a) size descriptors and (b) shape descriptors conducted at the spheronization rate and time of 12 Hz and 180 s, respectively



**Figure 4:** Loading plot of pellets properties according to the principal component analysis. A: Area, AR: Aspect ratio, BD: Bulk density, C: Circularity, Comp: Compressibility, CS: Strength, DF: Feret diameter, E: Porosity, FR: Flow rate, Friab: Friability, Freq: Spheronization rate, P: Perimeter, R: Roundness, S: Solidity, TD: Tap density, Time: Spheronization time, Tr.D: True density

Factors such as spheronization time appears near the center of the plot and therefore, had a very little contribution to the overall pellet properties. On the contrary, the spheronization rate is shown on the peripheral and thus was the most influential factor on all properties.

In addition, the bulk and tap densities, true density, friability, and flowability appear on the edges of the plot suggesting that these properties were highly affected by the pelletization process. For instance, the properties highly affected by the spheronization rate formed a cluster in the PC1 vector. This indicates that the spheronization rate was a critical factor to produce pellets of a large mass, pellet strength, roundness, and compressibility. Conversely, the spheronization time mainly affected properties such as strength, sphericity, and AR. The latter appears opposite to the area, perimeter, and diameter vectors as these decreased with increasing spheronization rate and therefore were inversely related. In addition, some properties such as area, perimeter, Feret diameter, and densification seem to be correlated. Other properties that were inversely correlated are densification and porosity. Therefore, it is evident that the correlation analysis that works with the normalized

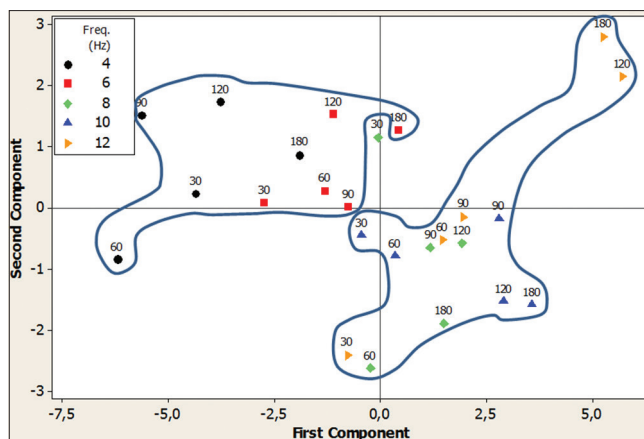
standard deviation determined the spheronization rate as the most influential variable for pellet quality, especially for properties such as the densification, porosity, and some shape descriptors. Thus, as spheronization rate increased, pellets became more densified and spherical and had a less porous surface. Further, the spheronization rate was the most critical factor in PC1. Conversely, in PC2 and PC3, the spheronization time was more relevant to the flowability of pellets, which in turn, was related to the spherical morphology.

The two-dimensional plot of the scores generated by the correlation analysis is shown in Figure 5. This plot classified and structured all the collective properties of the pellets. For instance, two large clusters were formed; the first one is located on the right side and the other one on the left side of the PC1. This stratification was mainly governed by the pelletizing rate. For instance, a low spheronization rate of 4 and 6 Hz appeared on the left side, whereas rates of 8, 10, and 12 Hz were shown in the right side of the plot. On the other hand, no trends were observed for the spheronization time, except for a tiny cluster formed in the upper right side of the plot due to the influence of a large spheronization time and rate of 180 s and 12 Hz, respectively. The spheronization rate is ratified as the most important factor to produce pellets having a large size, density, and flowability. This production factor also rendered pellets of low porosity, high strength, and compressibility. Porosity did not affect pellet strength. In most cases, friability values were < 1%, except in runs conducted at low rates (i.e., 4 Hz) which did not allow for the formation of spherical pellets.

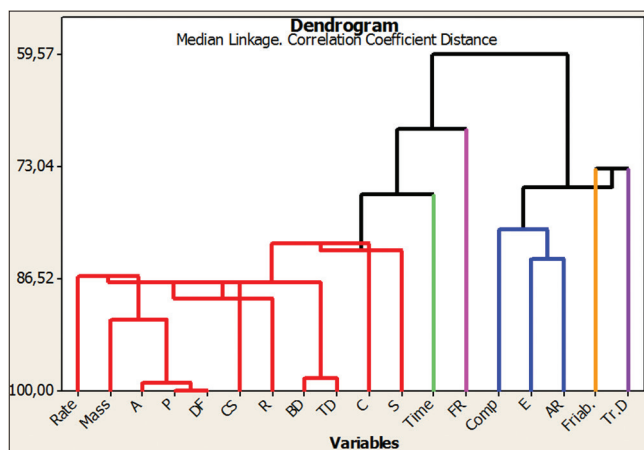
The dendrogram is a tree diagram which separate data into groups having a common property (Figure 6). The similarity degree is shown along the vertical axis by the distance level, and the production variables are listed on the horizontal axis. The plot shows clusters linking individual variables or matches them according to their level of similarity and composition of the respective cluster in the final partition. The cutting point for similarity was taken in the dendrogram above 75%. This is the step where values changed abruptly. The level of similarity is the percentage of minimum distance of this step with respect to the maximum distance between intervariable data. Thus, the dendrogram determined the spheronization rate (depicted in red color) as the variable having a high effect on properties such as area, perimeter, mass, pellet strength, Feret diameter, roundness, circularity, and densification. On the other hand, the spheronization time appears as an isolated variable having no major influence on most pellet properties.

## CONCLUSIONS

The analysis revealed that the spheronization rate was the most critical production variable which influenced most pellet properties. The correlation analysis indicated that at least 72.4% of the data variability were explained by the first three components. Further, the moisture content was also a crucial factor that affected the production of optimal pellets. Moreover, pellets having the best shape, dimensions, and related properties were obtained having a high amount of moisture and spheronization rates.



**Figure 5:** Score plot of pellets properties according to the principal component analysis. The subscript number on top of each tick correspond to the spheronization time (s), Freq: Spheronization rate (Hz)



**Figure 6:** Dendrogram showing the relationship between pellet properties

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