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Evaluation of the Performance of a New Continuous Spheronizer

João F. Pinto and Cristina N. Abreu
Dep. Tecnologia Farmacêutica, Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto, P-1649-003 Lisboa, Portugal

ABSTRACT This study aims to evaluate the performance of a new continuous spheronizer with multiple concentric chambers. The characteristics of the pellets produced in the different chambers (moisture content, mechanical strength, density, sphericity, size, release of a drug) were compared by multivariate analysis of variance (MANOVA), when different times of spheronization and chambers were considered. The statistical analysis has shown that both the diameter of the chambers and the time of spheronization affected the properties of the pellets, and, thus, they must be considered when the spheronizer is used. To minimize these effects all the forming pellets should be processed in all chambers for a defined period of time.

KEYWORDS Continuous spheronizer, Extrusion, MANOVA, Pellet, Spheronization

INTRODUCTION

The production of pellets for the delivery of drugs at an industrial level should be continuous to increase the yield and product uniformity with both lower production costs and higher benefits for patients. Among the different technologies available to produce pellets, extrusion and spheronization of wet masses is commonly used by the pharmaceutical industry to produce highly spherical and uniform-in-size pellets (Mollen, 2003). This process involves the preparation of a wet mass that is extruded and shaped into rods of uniform diameter. These rods are placed in a spheronizer (also known as marumeriser) where they are cut into smaller rods, ideally of equal lengths, and then rounded into spherical pellets due to the centrifugal and frictional forces provided by a rotating plate (Conine & Hadley, 1970, Rowe, 1985, Newton, 1989). These pellets are then dried and given to patients in hard gelatine capsules or tablets. Originally described in 1964, spheronization became widely known in the early 1970s after a publication by Reynolds (1970) who suggested that "the operation may be a batch or a continuous process." However, up to now, spheronization by this technology has always been regarded as a discontinuous process and no continuous equipment is available commercially. Such equipment would allow the continuous processing of the extruded material, offering advantages such as higher production rates and less variability between pellets (Naohisa, 1993). Other examples of spheronizers found in the literature do not enable the

Address correspondence to João F. Pinto, Dep. Tecnologia Farmacêutica, Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto, P-1649-003 Lisboa, Portugal; Tel: (+351) 217 946 434; Fax: (+351) 217 946 470; E-mail: jfpinto@ff.ul.pt

operator or the automated procedure to accommodate changes such as different batch sizes or different products that might require different processing conditions. A common approach requires a minimum quantity of material in a chamber before part of it can move to the next chamber. Baert et al. (1993) identified the important parameters in the process of spheronization: the most important ones were the spheronization time and the spheronization angular speed (proportional to the linear speed) of the friction plate, which affected significantly the quality of the pellets produced, namely a decrease on the sphericity or a larger size distribution, promoting high variations on the release of drugs from the pellets that ultimately will affect the therapeutic value of the medicine.

The design of the equipment suggested in this research incorporates a single friction plate that can rotate at different preset speeds, above which three concentric chambers can be built in such a way that they can move upward and downward independently, at a defined time interval to allow the movement of the spheroids to the next chamber in a cascade-like movement. The flexibility of the equipment is assured by its particular design, which allows the use of a different number of chambers; the movement of the chamber's wall can vary and different speeds of rotation for the plate can be considered (Fig. 1). It follows that these variables can be adjusted to particular product requirements, by opposition to the commercially available equipments. However, as Baert et al. (1993) stated, it is critical to prove that pellets produced in each chamber present the same standard of quality, independently of differences on either the chamber's diameter or the plate's linear speed.

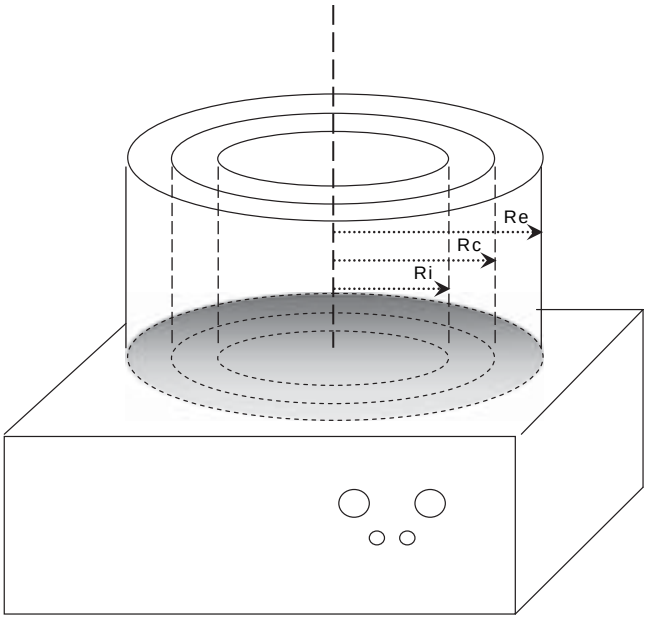

FIGURE 1 Schematic Representation of the Continuous Spheronizer. R_O, R_e = control and external chambers; R_c = central chamber; R_i = internal chamber.

The present study aims to identify differences between pellets produced in each chamber of the equipment when the extrudates produced in the same conditions are processed in the spheronizer. In case the properties of the pellets would be equal from one chamber to the other, it would be possible to come to the conclusion that the spheronizer can work continuously and the forming pellets can rest in any chamber for a preset period of time.

MATERIALS AND METHODS

Materials

Microcrystalline cellulose (MCC) (Avicel® PH-101, FMC Corp., Cork, Ireland), lactose (LAC) (Granulac 230, Meggle, Wasserburg, Germany), both EP grade and propranolol hydrochloride (PRO) (supplied by Capsifar, Oeiras, Portugal) were used as received. Demineralized water (W) was used as the liquid phase.

Methods

Preparation of the Extrudates

The powders (5 MCC:4 LAC:1 PRO) were mixed in a planetary mixer (Kenwood Chef, UK) for 5 min. Subsequently 5.5 parts of water were added to the mixed powders and homogenization was carried out for a further 5 min. Extrusion was performed in a ram extruder, using a 1-mm diameter (D) and 4-mm length (L) die (L/D = 4), fitted to a mechanical press (Lloyd Instruments, LR 50K incorporating a 50 KN load cell, UK). Extrusion was set for a maximum load of 20 KN and a constant speed of the cross head of 200 mm/min.

Spheronization

Spheronization followed immediately on a modified in house spheronizer (main components made by GB Caleva, UK). The final configuration of the spheronizer considered had three chambers (Fig. 1) and the original chamber, as a control: the external chambers

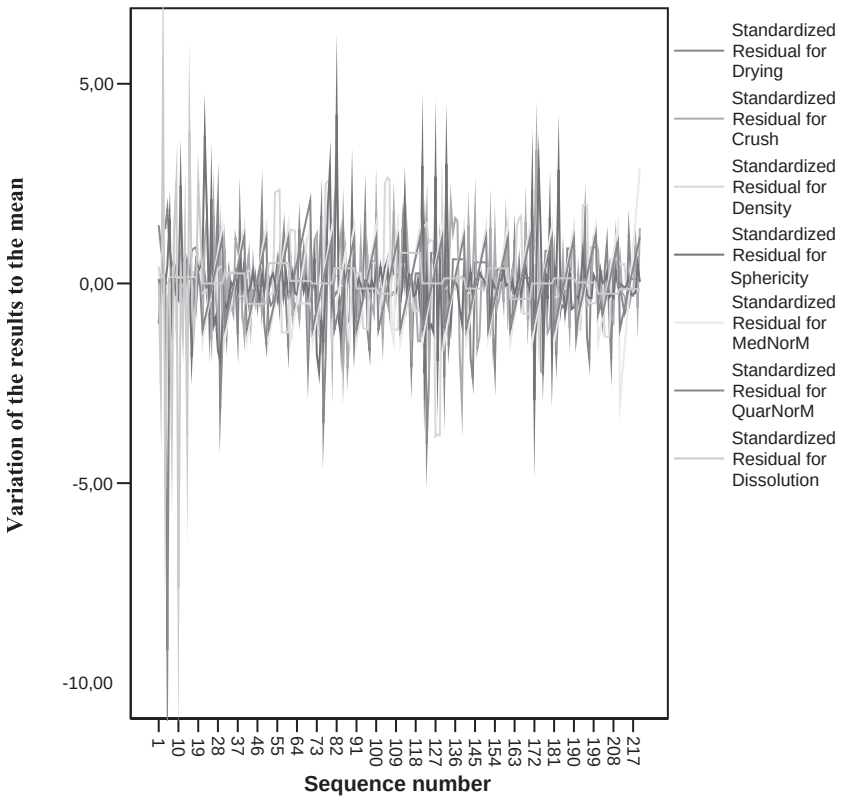

FIGURE 2 **Standardized Residuals as a Function of the Case Number. Standardized residual for loss on drying (——), crushing force (——), apparent density (——), sphericity (——), median particle size (——), interquartile range (——), and dissolution (——).**

(R_0 and $R_e = 11.5$ cm radius), a central chamber ($R_c =$ 9.5 cm radius), and an internal chamber ($R_i = 7.6$ cm radius). The plate was set to rotate at 1000 rpm for different times (30, 60, 120, 300, and 600 sec). This range of times is in agreement with the ones considered commonly for a proper spheronization of the materials (Gamlen, 1985). A total of 100 g of extrudates were placed in each one of the chambers (R_0, R_e, R_c, or R_i) in different runs according to the preset values of both parameters, time and speed. On no occasion were the same extrudates allowed to move from the internal to the central and then to the external chambers, because that was not the aim of the work. The wet pellets were collected after the run and dried in a fluid bed dryer at 60ºC for 30 min (UniGlatt, Glatt, Germany).

Characterization of Pellets

Pellets were characterized for loss on drying, sizing, crushing strength, density, sphericity, and dissolution rate of the propranolol hydrochloride, as follows: (1) the water content, presented as the loss on drying, was determined in a Sartorius moisture balance ($n = 3$; Sartorius, Germany); (2) sizing of the pellets (100 g) was performed by sieve analysis on a vibrating sieve shaker (Retsch As 200, Retsch, Germany), for 5 min and median vibrating amplitude. The fraction between 1.00- and 1.40-mm diameter was collected for further analysis. Median particle size and interquartile range (IQR) were derived from the undersize representation of the results; (3) the mechanical strength, determined as the diametrical compression force necessary to break a pellet, was measured with a strength tester ($n = 15$, CT5, Engineering Systems, Nottm Ltd., UK) fitted with a 5-kg load cell; (4) the density of the pellets was determined by helium pycnometry ($n = 3$, Accupyc 1330, Micromeritics, USA); (5) the sphericity of the pellets was assessed by measuring the length and the breadth (aspect ratio) of pellets by optical microscopy ($n = 50$, Olympus microscope; Olympus, Japan); (6) dissolution tests were performed according to the USP 27 (type 1 apparatus, $n = 3$, Sotax AT7, Switzerland). Pellets containing 20 mg of propranolol hydrochloride were placed in a dissolution vessel containing 1000 mL of HCl 10 g/L at 37ºC, pH 1.0, and stirred at 100 rpm. Samples were collected and the drug was quantified by spectrophotometry at 290 nm (Hitachi U-2000, Japan). The maximum amount of the drug

released (in percentage) within 30 min was considered as representative of the batch.

Statistical Analysis

Experiments were run according to a multifactor experimental design and the results were analyzed by a multivariate analysis of variance test (MANOVA) test to assess the effect of individual variables and their interactions on the properties of the pellets produced. The MANOVA was performed with a SPSS software (Statistical Package for Social Sciences, version 12.0; SPSS Inc., Chicago, IL, USA) for a limit of significance of $p < 0.05$. The independent variables or factors considered were the size of the chamber of the spheronizer and the time of spheronization. The loss on drying, the crushing force, the apparent density, the sphericity, the median particle size, the interquartile range, and the percentage of drug released within 30 min were the dependent variables in the experimental design (Table 1).

RESULTS AND DISCUSSION

General Discussion

The production of pellets was carried out from extrudates produced under the same pressure applied to wet masses containing the same moisture content, to avoid variations on the properties of the extrudates. By doing this, variations on the quality of the pellets were only due to pelletization and not to extrusion (Kleinebudde & Lindner, 1993). Extrudates have shown smooth surfaces and constant length, characteristics required for a proper spheronization (Rowe, 1985). The results from the assessment of the properties of the pellets prepared in the different chambers and for the different times of spheronization are presented in Table 2. Provided the extrudate is cylindrical in shape, presents a smooth surface, and is produced under the same pressure, it is possible to obtain dense spheres with a narrow size distribution (Rowe, 1985). It was possible to confirm by visual inspection the breakage of the extrudates into uniform size segments in all chambers anticipating the production of pellets with good quality. Also, it is important to point out that, due to the design of the equipment considered in the study (single plate), the rotational speed of the friction plate had to be kept constant for all chambers and spheronization times considered. However, for some authors (Lovgren & Lundberg, 1989), the plate's peripheral linear velocity should be the same to avoid changes on the quality of pellets and to minimize scaling-up difficulties that might occur with the production of pellets (Chariot et al., 1987; Newton et al., 1995a). Consequently, differences in the properties of the pellets produced in the different chambers should be anticipated. However, as it will be shown, variations in the properties of the pellets were not significantly different, as anticipated. A possible explanation derives from the fact that the differences between the diameters of the chambers considered were small.

TABLE 1 Variables Considered in the Study

Type of variable	Name of variable
Independent (nominal)	Diameter of the spheronizer's chamber
	Time of Spheronization
Dependent (numeric)	Loss on drying (%)
	Crushing strength (N)
	Apparent density (g/cm^3)
	Sphericity
	Median particle size (μm)
	Interquartile range (IQR) (μm)
	Dissolution (%)

For all batches produced the yield was higher than 97.9% (the range was 97.9–99.3%) proving the efficacy of the process (Table 2). In the present work the yields for individual chambers were high and the differences observed were randomized. It can be assumed that the use of the equipment at an industrial scale will also provide a high yield for any and all chambers. It has been reported that different peripheral speeds and loads affect the yield (Chariot et al., 1987). However, with this equipment, at the end of the process all the forming pellets have been submitted to the same conditions. Thus, changes in loads and speeds at individual chambers will not be reflected in the properties of the pellets. The new equipment is flexible enough to allow different loads in each chamber according to the characteristics of the material being processed. The effect of the load in each chamber affects the quality of the pellets. Some authors (Hellen & Yliruusi, 1993) come to the conclusion that a higher spheronization load lowers the size and bulk density of the pellets, whereas Hasznos et al. (1992) reached a different conclusion.

The results for the weight loss on drying (Table 2) have shown a decrease of the moisture content of the pellets along with the time of spheronization, indicating that drying of the wet extrudate occurs throughout

TABLE 2 Results of Experiments

	Spheronization time (s)	Diameter of the chamber of the spheronizer[a]			
		R_0(control)	R_e	R_c	R_i
Yield (%)	30	98.3	97.9	99.3	99.3
	60	98.5	98.6	99.2	98.1
	120	99.1	98.1	98.5	97.9
	300	99.3	98.3	98.2	98.1
	600	98.1	99.1	99.1	98.3
Loss on drying (%)	30	33.2 (2.50)	33.9 (1.66)	34.8 (2.97)	34.6 (1.46)
	60	33.1 (1.49)	33.5 (1.35)	35.0 (1.92)	34.1 (1.66)
	120	32.7 (1.78)	33.0 (1.74)	34.2 (2.02)	33.4 (2.02)
	300	32.0 (1.60)	32.1 (0.77)	32.9 (1.51)	32.6 (1.56)
	600	29.9 (1.93)	29.9 (1.59)	30.5 (1.01)	30.2 (0.94)
Crushing strength (N)	30	19.0 (1.59)	17.3 (1.55)	18.3 (1.34)	17.9 (2.27)
	60	18.9 (1.07)	16.3 (2.17)	18.4 (2.19)	16.8 (1.06)
	120	17.1 (0.70)	16.2 (1.11)	17.0 (1.40)	15.8 (0.87)
	300	16.7 (0.45)	16.5 (1.18)	16.5 (1.19)	15.1 (0.84)
	600	17.2 (0.95)	15.2 (1.58)	15.8 (0.85)	15.6 (0.93)
Apparent density (g/cm^3)	30	1.507 (0.0029)	1.489 (0.0125)	1.516 (0.0185)	1.508 (0.0048)
	60	1.462 (0.0232)	1.471 (0.0009)	1.479 (0.0013)	1.468 (0.0021)
	120	1.481 (0.0015)	1.476 (0.0055)	1.479 (0.0021)	1.494 (0.0097)
	300	1.489 (0.0116)	1.489 (0.0126)	1.470 (0.0021)	1.485 (0.0065)
	600	1.474 (0.0064)	1.470 (0.0036)	1.485 (0.0078)	1.481 (0.0023)
Sphericity	30	1.60 (0.40)	1.86 (0.36)	1.59 (0.42)	1.74 (0.43)
	60	1.15 (0.10)	1.34 (0.38)	1.25 (0.24)	1.23 (0.23)
	120	1.09 (0.06)	1.10 (0.04)	1.12 (0.05)	1.09 (0.09)
	300	1.12 (0.06)	1.12 (0.07)	1.05 (0.08)	1.09 (0.07)
	600	1.07 (0.05)	1.14 (0.15)	1.08 (0.05)	1.06 (0.05)
Median particle size (μm)	30	1.19 (0.003)	1.19 (0.003)	1.19 (0.003)	1.20 (0.002)
	60	1.20 (0.003)	1.21 (0.003)	1.21 (0.003)	1.23 (0.004)
	120	1.21 (0.003)	1.21 (0.003)	1.22 (0.003)	1.26 (0.004)
	300	1.21 (0.003)	1.21 (0.003)	1.23 (0.003)	1.27 (0.003)
	600	1.20 (0.003)	1.21 (0.003)	1.21 (0.003)	1.26 (0.006)
Interquartile range (μm)	30	0.222 (0.0003)	0.224 (0.0003)	0.226 (0.0003)	0.230 (0.0003)
	60	0.233 (0.0003)	0.230 (0.0003)	0.239 (0.0003)	0.253 (0.0003)
	120	0.236 (0.0003)	0.232 (0.0003)	0.238 (0.0003)	0.274 (0.0003)
	300	0.225 (0.0003)	0.225 (0.0003)	0.241 (0.0003)	0.307 (0.0002)
	600	0.225 (0.0012)	0.225 (0.0003)	0.226 (0.0003)	0.265 (0.0003)
Dissolution (%)	30	96.5 (0.00)	95.3 (0.00)	96.1 (0.00)	95.1 (0.00)
	60	96.7 (0.06)	95.6 (0.09)	96.2 (0.03)	95.1 (0.03)
	120	96.1 (0.12)	95.2 (0.03)	96.0 (0.03)	95.1 (0.01)
	300	96.9 (0.12)	95.1 (0.06)	96.4 (0.09)	94.9 (0.06)
	600	96.5 (0.12)	95.8 (0.18)	95.8 (0.09)	95.0 (0.03)

[a]Results expressed as mean values and standard deviations (SD).

the process. For instance, the values tend to decrease from 34.2% (average of 30 sec results) to 30.1% (average of 600 sec results) continuously, suggesting that pellets lose water while being spheronized. In fact, the open chambers of the continuous spheronizer and the continuous toroidal movement of the pellets promote the loss of water. The largest decrease of the moisture content occurs during the first minutes of spheronization. At this stage drying may interfere with the process of spheronization by changing the plastic properties of the forming pellets. However, drying of the pellets is of most importance for their mechanical properties (Bashaiwoldu et al., 2004). On the other hand, the speed of spheronization did not affect this property of the pellets, although the values observed for the central chamber seem to be slightly higher

than for the others. Regarding the diameter of the chamber, mean values for each chamber were not significantly different, suggesting that for this variable the process of drying the pellets was independent of the chamber considered.

The strength of agglomerates such as pellets can be assessed by the force required to crush them individually at an equatorial plan. The force to crush the granules depends on the strength and number of bonds between the particles of the granules, that is, depends on their structure. This force between the particles derives from the compression of materials required for extrusion followed by the centrifugal forces in the process of spheronization that promoted the bonding between the particles. At the beginning of the process of spheronization pellets have shown higher crushing forces than later in the process. Generally, results have shown a decrease on the strength of the granules throughout the process (e.g., 17.9 N, 30 sec to 15.6 N, 600 sec, for R_i; Table 2). This observation may well be related to the shape of the granules. In fact, the dumbbell shape, observed at initial stages of spheronization, offers a larger surface to fracture and thus a larger resistance for the applied force. Another possible explanation for the observation derives from the fact that, as the spheronization proceeded, the amount of water present in the pellets decreased. The fact that pellets were made of hydrophilic materials suggests that the presence of water strengthens the bonds between the particles, either by dissolving partially the materials or by strengthen hydrophilic bonds in the forming pellets (Chien & Nuessle, 1985): the higher the amount of water present, the higher the strength of the bonds after pellets were dried. However, these variations were not significantly different ($P < 0.05$).

As mentioned, densification of extrudates occurs throughout their spheronization due to centrifugal forces applied to the pellets in the chambers. All pellets presented high densities approaching those of the raw materials. Unlike reported previously (Newton et al., 1995b), the density of the granules had not increased significantly with the residence time (Table 2). Even for small times of spheronization high densities could be observed, suggesting that densification occurred at early stages of processing. The effect of the spheronization time over the bulk and tapped densities of the pellets is contradictory, as reported previously (Hileman et al., 1993).

The process of spheronization is a time-dependent process whereby an increase on sphericity of pellets can be observed. Cylindrical pellets are molded into spheres at a rate dependent on the formulation of the forming materials and processing conditions. The sphericity, assessed by the aspect ratio (whereby a perfect sphere presents a value of unity), increased throughout the process. Similarly to other pellets made by other equipment, which sphericity has been assessed by alternative methods of shaping particles, the results for the aspect ratio have shown the same pattern, that is, a large decrease within the first 120 sec followed by a smaller decrease over 10 min (Fielden et al., 1992). In fact after the second minute the process seems to be nearly complete in all chambers. Not only the means of the results approached unity, but, also, the standard deviation approached zero. It is commonly accepted that the higher the spheronization time, the higher the sphericity of the pellets. However, the degree of sphericity depends on the properties of the forming pellets' material, among other factors (Hellen & Yliruusi, 1993).

Between 82% and 88% of the pellets produced in each chamber were found to be within the range of 1.00–1.40 mm, the expected size since a die 1 mm in diameter was used to produce the extrudates from the masses. This is an expected result since the spheronization occurs by a decrease on the pellets length and an increase on the other two orthogonal dimensions, and finally a rounding effect over them. Furthermore, no significant differences on the particle size distributions for each residence time were observed between pellets produced in the different chambers, although an increase in the median particle size as the chamber size decreases has been observed at up to 5 min of spheronization, which is in agreement with previous observations (Wan et al., 1993). Afterward, a decrease on the median sizes was observed, as reported previously. Results have also shown that an increase on the spheronization time increased the size of the pellets. A possible explanation may be derived from both the swelling of pellets up to a certain extent and by incorporation of powdered material from other pellets. The smaller chamber has produced pellets with the higher sizes, suggesting a smaller densification of the materials. The results for the interquartile range tend to follow the results for the median particle size, that is, there are no significant differences between pellets produced in the different chambers, although pellets produced in the internal chamber have shown a slight increase in the size distribution.

The release of the model drug, expressed as a percentage of the drug released within 30 min, has

shown almost a complete release. In either case the release was not dependent on the spheronization time or size of the chamber. In fact, the amount of drug recovered was identical for the pellets produced in the different chambers and was almost complete within 30 min. Due to the fact that the release of a drug is very sensitive to changes in the structure of solid matrices such as the pellets, smaller changes in the pellet's structure would have affected the release of the drug. The fact that results were not significantly different suggests that the pellets produced in the different chambers were identical with respect to this property.

Statistical Analysis

The statistical analysis of the results was performed at two levels. First, the ability of the statistical analysis to provide a good evaluation of the study was carried out. Only when it was proved adequate was analysis of the results pursued.

The assessment of the quality of the statistical analysis has shown that it was possible to accept the results from the analysis and proceed with the evaluation of the process of spheronization, as follows:

- The Box's M test has shown that the matrices of covariance for the dependent variables were equal across groups (sig. = 0.000; Table 3). This test evaluates the null hypothesis, reflecting the fact that the observed variance matrices of the dependent variables were equal across the groups. Furthermore, the test has identified the model for the analysis, which included the *"Intercept,"* the *"Diameter of the Chamber,"* the *"Time of Spheronization,"* and their interaction *"Diameter of the chamber* Time of pelletization."*

TABLE 3 **Assessment of the Quality of the Statistical Analysis**

Equality of Covariance Matrices (Box's M Test)	
Box's M	301.5
F	2.403
Degrees of freedom 1	84
Degrees of freedom 2	3629.2
Significance	0.000

Test of Normality of the Results

Standardized Residual	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	*Df*	Significance	Statistic	*df*	Significance
Loss on drying	0.100	220	0.000	0.944	220	0.000
Crushing force	0.075	220	0.004	0.991	220	0.169
Apparent density	0.151	220	0.000	0.902	220	0.000
Sphericity	0.185	220	0.000	0.856	220	0.000
Median particle size	0.093	220	0.000	0.975	220	0.001
Interquartile range	0.103	220	0.000	0.752	220	0.000
Dissolution	0.268	220	0.000	0.557	220	0.000

Equality of Error Variances (Levene's Test)

	F	*df*1	*df*2	Significance
Loss on drying	1.389	19	200	0.135
Crushing force	3.004	19	200	0.000
Apparent density	14.023	19	200	0.000
Sphericity	9.798	19	200	0.000
Median particle size	1.079	19	200	0.375
Interquartile range	1.468	19	200	0.100
Dissolution	2.400	19	200	0.001

df = Degrees of freedom.

- The second set of tests assessed and confirmed the normal distribution of the results. For this purpose the Kolmogorov-Smirnov's (for the residuals) and the Shapiro-Wilk's (for the independent variables "diameter" and "time of spheronisation") tests (Table 3) confirmed the adhesion of the results to normality.
- Finally, the Levene's test (to confirm the equality of the variances of errors) evaluates the null hypothesis to assure that the error variance of the dependent variables was equal across groups (Table 3).

All the results from the tests performed have confirmed that the assumptions for the statistical analysis have been fulfilled, allowing the complete interpretation and discussion of the experimental results.

Very often when a MANOVA analysis is considered it is common to perform simultaneously a multivariate analysis of covariance (MANCOVA) statistical analysis to enhance the power of the analysis promoting the clarification of the results. Unfortunately, in the present work the MANCOVA did not improve the quality of the analysis and was, therefore, not pursued.

By the simultaneous observation of box and residual plots (graphs not shown) and representations of the residuals for each case (Fig. 2), it was possible to identify the presence of several outliers and confirmation of the normal distribution of the residuals. Altogether 8 outliers were found of 220 cases analyzed (3.6%). A second analysis was run without the 8 cases corresponding to the outliers, but the pattern of the results remained constant; thus it was decided to accept the results from the first analysis, which are presented in Tables 4 and 5.

Table 4 presents the results of the Pillai's Trace, the Wilk's lambda, the Hotelling's T^2, and the Roy's largest root for the assessment of the intensity of the relationship between the dependent and independent variables considered. From these results it can be said that the independent variables (diameter of the spheronizer's chamber, time of spheronization) and their interaction have a significant effect on the set of dependent variables (properties of the pellets) considered.

The most practical information observed in Table 5 is related to the properties of the pellets that were dependent on the factors considered. Results have shown that the diameter of the spheronizer's chamber affected the density, the median particle size and the interquartile range, and the dissolution rate of the drug (sig. = 0.000). Less significant was the effect of the diameter of the chamber on the force required

TABLE 4 **Multivariate Tests[d]**

Effect		Value	*F*	Hypoth. *df*	Error *df*	Sig.	Noncent. Parameter	Observed Power[a]
Intercept	Pillai's Trace	1,000	65189946[b]	7,000	194,000	0,000	456329627	1,000
	Wilks' Lambda	0,000	65189946[b]	7,000	194,000	0,000	456329627	1,000
	Hotelling's Trace	2352214	65189946[b]	7,000	194,000	0,000	456329627	1,000
	Roy's Largest Root	2352214	65189946[b]	7,000	194,000	0,000	456329627	1,000
Diameter	Pillai's Trace	2,244	83,1	21,000	588,000	0,000	1745	1,000
	Wilks' Lambda	0,000	1695	21,000	557,613	0,000	29685	1,000
	Hotelling's Trace	2920	26792	21,000	578,000	0,000	562635	1,000
	Roy's Largest Root	2880	80651[c]	7,000	196,000	0,000	564560	1,000
Time of	Pillai's Trace	3,005	84,9	28,000	788,000	0,000	2378	1,000
Spheronization	Wilks' Lambda	0,000	440	28,000	700,899	0,000	9075	1,000
	Hotelling's Trace	749	5151	28,000	770,000	0,000	144251	1,000
	Roy's Largest Root	738	20789[c]	7,000	197,000	0,000	145523	1,000
Diameter*	Pillai's Trace	3,030	12,72	84,000	1,400,000	0,000	1068	1,000
Time of	Wilks' Lambda	0,000	71,0	84,000	1,196,168	0,000	4534	1,000
Spheronization	Hotelling's Trace	1382	3165	84,000	1,346,000	0,000	265895	1,000
	Roy's Largest Root	1372	22883[c]	12,000	200,000	0,000	274598	1,000

[a]Computed using alpha = 0.05.
[b]Exact statistic.
[c]The statistic is an upper bound on F that yields a lower bound on the significance level.
[d]Design: *Intercept + Diameter + Time of Spheronization + Diameter * Time of Spheronization*.

TABLE 5 Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	*df*	Mean Square	*F*	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	Loss on Drying	127.17[b]	19	6.693	1.53	0.173	29.2	0.673
	Crushing Strength	0.442[c]	19	0.023	2.91	0.011	55.4	0.951
	Apparent Density	0.009[d]	19	0.000	45.46	0.000	863.8	1.000
	Sphericity	3.214[e]	19	0.169	1.46	0.204	27.7	0.644
	Median Particle Size	0.020[f]	19	0.001	305.37	0.000	5802.1	1.000
	Interquartile Range	0.017[g]	19	0.001	2319.00	0.000	44061.1	1.000
	Dissolution (AUC)	13.734[h]	19	0.723	25.70	0.000	488.3	1.000
Intercept	Loss on Drying	44355.6	1	44355.6	10196	0.000	10196.9	1.000
	Crushing Strength	114.4	1	114.4	14358	0.000	14358.4	1.000
	Apparent Density	87.8	1	87.8	8069618	0.000	8069618.7	1.000
	Sphericity	67.2	1	67.2	580	0.000	580.3	1.000
	Median Particle Size	59.1	1	59.1	17033800	0.000	17033800.5	1.000
	Interquartile Range	2.3	1	2.2	5770281	0.000	5770281.9	1.000
	Dissolution (AUC)	366848.9	1	366848.9	13043516	0.000	13043516.4	1.000
Diameter of the Chamber	Loss on Drying	12.640	3	4.2	0.96	0.427	2.9	0.225
	Crushing Strength	0.095	3	0.032	3.98	0.022	11.9	0.753
	Apparent Density	0.001	3	0.000	26.58	0.000	79.7	1.000
	Sphericity	0.225	3	0.075	0.64	0.594	1.9	0.161
	Median Particle Size	0.012	3	0.004	1111.8	0.000	3335.6	1.000
	Interquartile Range	0.010	3	0.003	8519.9	0.000	25559.8	1.000
	Dissolution (AUC)	13.217	3	4.4	156.6	0.000	469.9	1.000
Time of Spheronization	Loss on Drying	80.293	4	20.0	4.61	0.008	18.4	0.881
	Crushing Strength	0.229	4	0.057	7.17	0.001	28.6	0.980
	Apparent Density	0.006	4	0.002	144.0	0.000	576.3	1.000
	Sphericity	2.508	4	0.627	5.41	0.004	21.6	0.930
	Median Particle Size	0.006	4	0.002	435.0	0.000	1740.2	1.000
	Interquartile Range	0.003	4	0.001	1765.6	0.000	7062.6	1.000
	Dissolution (AUC)	0.111	4	0.028	0.98	0.438	3.9	0.255
Diameter*Time of Spheronization	Loss on Drying	34.243	12	2.8	0.65	0.771	7.8	0.252
	Crushing Strength	0.118	12	0.010	1.23	0.328	14.7	0.481
	Apparent Density	0.002	12	0.000	17.31	0.000	207.7	1.000
	Sphericity	0.481	12	0.040	0.34	0.968	4.1	0.141
	Median Particle Size	0.003	12	0.000	60.52	0.000	726.2	1.000
	Interquartile Range	0.005	12	0.000	953.21	0.000	11438.5	1.000
	Dissolution (AUC)	0.406	12	0.034	1.20	0.346	14.4	0.469

(Continued)

TABLE 5 (Continued)

Source	Dependent Variable	Type III Sum of Squares	*df*	Mean Square	*F*	Sig.	Noncent. Parameter	Observed Power[a]
Error	Loss on Drying	86.998	200	4.3				
	Crushing Strength	0.159	200	0.008				
	Apparent Density	0.000	200	0.000				
	Sphericity	2.316	200	0.116				
	Median Particle Size	0.000	200	0.000				
	Interquartile Range	0.000	200	0.000				
	Dissolution (AUC)	0.563	200	0.028				
Total	Loss on Drying	44569.774	220					
	Crushing Strength	115.017	220					
	Apparent Density	87.898	220					
	Sphericity	72.746	220					
	Median Particle Size	59.213	220					
	Interquartile Range	2.295	220					
	Dissolution (AUC)	366863.17	220					
Corrected Total	Loss on Drying	214.174	219					
	Crushing Strength	0.601	219					
	Apparent Density	0.010	219					
	Sphericity	5.530	219					
	Median Particle Size	0.020	219					
	Interquartile Range	0.017	219					
	Dissolution (AUC)	14.296	219					

[a]Computed using alpha = 0.05. [b]R^2 = 0.594 (adjusted R^2 = 0.208). [c]R^2 = 0.735 (adjusted R^2 = 0.483). [d]R^2 = 0.977 (adjusted R^2 = 0.956). [e]R^2 = 0.581 (adjusted R^2 = 0.183). [f]R^2 = 0,997 (adjusted R^2 = 0.993). [g]R^2 = 1.000 (adjusted R^2 = 0.999). [h]R^2 = 0.961 (adjusted R^2 = 0.923).

to crush the pellets (sig. = 0.022), whereas the water lost on drying (sig. = 0.427) and the sphericity (sig. = 0.594) were very much independent of the chamber where they were produced. The time of pelletization/spheronization, on the other hand, affected significantly the majority of the properties of the pellets considered (loss on drying, crushing strength, density, particle size and interquartile), but not the dissolution (sig. = 0.438). A possible explanation for the observation is based on the fact that dissolution data of drugs can be affected by the other properties (porosity, crushing strength), that they have either opposite or compensatory effects over the dissolution rate.

CONCLUSIONS

The study has shown that pellets were produced by breakage of extrudates into uniform sizes before spheronization. Results indicate that the production of homogeneous and good quality drug-loaded pellets in the continuous spheronizer was carried out successfully. The pellets presented the same characteristics as the ones produced in a batch-type spheronizer, namely, well-defined size and narrow size distribution, high sphericity, density and resistance to crushing forces, and well-defined release of the drug.

The statistical analysis performed on the results has shown that (1) the statistical methodology considered was robust to allow the analysis of the experimental observations; (2) the diameter of the chamber, the time of spheronization and their interaction had to be taken into consideration upon designing the formulation and the processing conditions; and (3) the tests carried out to assess the equality of the covariance matrices, the normal distribution of the results, and the equality of the error variances have shown a sound experimental design and analysis. It can be said that the multivariate approach considered provided a very satisfactory and complete insight-of-the-complex process of production of pellets in contrast to the one-at-a-time experimental design often considered for this type of study.

The study has demonstrated that the characteristics of the pellets produced in either one of the three chambers considered were not significantly different; thus it can be concluded that spheronization of extrudates can start in the inner chamber and by the time they reach the outer chamber, before leaving the spheronizer, they have been transformed into pellets. The process is continuous in nature and the movement of the forming pellets occurs in a cascade-type fashion. Furthermore, the new spheronizer offers other advantages such as lower variability between batches and higher throughputs. By changing the number of chambers in the continuous spheronizer the production yield can be changed according to the manufacturers' needs.

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