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Differences in Characteristics of Pellets Prepared by Different Pelletization Methods

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Pellets are currently a very popular dosage form for oral application. They can be prepared by several pelletization techniques. Extrusion/spheronization, commonly used in the pharmaceutical industry, and modern agglomeration in a rotoprocessor were the methods chosen for pellet preparation in our study. Theophylline (in 10% to 65% concentration) was the model drug, lactose monohydrate was used as filler, microcrystalline cellulose Avicel® PH 101 was thespheronization enhancer, and the wetting agent was purified water. Both techniques led to the formation of pellets of appropriate shape and mechanical properties. Pellets of a higher density, hardness, lower friability, and slightly slower dissolution profiles were obtained by extrusion/spheronization. This method of pelletization also led to production of particles with narrower size distribution and bigger yield of pellets with the requested size.

Keywords extrusion and spheronization; rotoagglomeration; pellets; theophylline monohydrate; microcrystalline cellulose

INTRODUCTION

Traditionally, the word pellet has been used to describe a variety of systematically produced geometrically defined agglomerates obtained from diverse starting materials utilizing different processing conditions. Pellets for pharmaceutical purposes are usually produced in the size range of 0.5 to 1.5 mm (Ghebre-Sellasie, 1989). The final oral multiple-unit dosage form can be either a hard gelatin capsule filled with pellets or a tablet composed of carefully compressed pellets (Bechgaard & Nielsen, 1978). Pellets are prepared using different technologies such as layering of the drug solution, suspension or powder on the inactive cores, extrusion/spheronization, agglomeration in rotogranulators or rotoprocessors, compression, spray drying, or spray congealing (Ghebre-Sellasie, 1989).

Extrusion/spheronization is a technique often used in industrial pellet production. The technique is based on an agglomeration by compaction. It is advantageous as it enables the preparation of pellets with a high content of the drug—up to 90%; it does not require inactive cores as pelletization starters; and reproducibility of this method is very good (Gandhi, Lal Kaul, & Panchagnula, 1999). It involves however several steps using different equipment and therefore it is more difficult to achieve GMP conditions during pellet preparation (Newton, 1990; O'Connor & Schwartz, 1989). In an extrusion powder, mixture of excipients and drug is wetted and kneaded to obtain a plastic mass, which is converted by pressure developed by forcing through extrusion die into long rods called extrudate. In spheronization extrudate is broken into the smaller cylinders, which are next rounded due to the frictional and centrifugal forces of the rotating disk of the spheronizer. The pellets are then dried until they achieve final moisture content (Vervaet, Baert, & Remon, 1995). All process steps are dependent on each other and are joined by the number of individual process variables (Peréz & Rabišková, 2002; Umprayn, Chitropas, & Amarekajorn, 1999).

Rotoagglomeration is one of the novel methods of pellet production based on an agglomeration by movement. It involves the conversion of a moving wetted mixture of the drug and excipients into pellets due to the centrifugal, fluidization, and gravity forces (Kristensen & Shaefer, 1993). All the pelletization process is held in one closed system called a rotoprocessor. It is the main advantage of this technique compared with extrusion/spheronization, because the dust problems and the contamination risks can be avoided and time, equipment, energy, laboratory space, costs, and machine operators can be saved. Pellets can be coated immediately in the same equipment. This method also does not need the nonpareils to start the process and a high drug loading of up to 65% can be achieved (Vetchý & Rabišková, 2002). The rotoprocessor unit of Multiprocessor MP-1, produced by the Swiss company Niro-Aeromatic, was used in our study. Pellet formulation

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proceeded in two phases. In the first phase, the rotoprocessor worked in a "closed position" to disable a transmission of the prepared agglomerates into the space between the inner and outer wall of the unit. During this step a non-perforated rotating disc imparted the kinetic energy to the particles of the loaded material, which traveled in a spiral motion around the inner wall. The binder solution was simultaneously sprayed on at a constant speed, therefore the particles were sticking together and spheronizing at the same time. Once the pellets were formed, the inner wall lifted up and the rotoprocessor came to the second "open position" phase, in which pellets fluidizing in warm air were dried. The disadvantages of this method are the great sensitivity of the process to the formulation and the process parameters and therefore difficult optimization of the pellet formulation; high costs of the equipment; and a broader particle size distribution (Pišek, Planinšek, Tuš, & Srčič, 2000; Vetchý & Rabišková, 2002).

Although there are many papers describing the extrusion and spheronization technique, and some concerning the rotoagglomeration method of pellet preparation, there is no article focused exclusively on the comparison of the pellet characteristics prepared by these techniques. That is why the aim of our study was to observe the influence of the pelletization technique—well-established extrusion/spheronization and modern rotoagglomeration—on the shape, yield, mechanical, and flow properties and dissolution profile of uncoated and coated pellets.

MATERIALS AND METHODS

Materials

The theophylline monohydrate (Lehmann & Voss, Germany) was used as the model drug, lactose monohydrate (Granulac® 200, Meggle, Germany) was a filler, microcrystalline cellulose Avicel® PH 101 (FMC, United States) acted as the spheronization enhancer, and purified water was used as the wetting agent. The film of the coated pellets was composed of ethylcellulose (Sigma Aldrich, United States) and a plasticizer, polyethylenglycol 1500 (Fluka, United States). The mixture of ethanol 96% with dichloromethane in the ratio 4:1 served as a coating solvent.

Material Characterization

The size distribution of theophylline was determined by sieving with a set of sieves with apertures of 45, 90, 180, and 355 μm (Retsch, AS 200 control, Germany; 60 amplitudes for 10 minutes). The results were expressed as the percentage of the weight retained on each sieve size. Mean particle diameter $\bar{d}$ was calculated from the results of sieve analysis by applying the following formula (Carstensen, 2001, p. 56; Haznos, Langer, & Gyamathy, 1992):

$$\bar{d} = \sum x_i n_i / 100 \tag{1}$$

where x_i is the arithmetic mean of the upper and the lower limits of i sieve fraction (determined by the aperture size of used sieves); and n_i is the percentage of the particles' weight of i sieve fraction.

As the sieving of fine powders in a dry state may be a problem owing to the cohesive nature of these powders, the particle size of fine excipients was determined by light microscopy and liquid paraffin was used to make dispersion (microscope, TH4, Lambda, Czech Republic). Five hundred particles were measured for the computation of particle mean diameter.

For each substance, pycnometric density was measured according to Ph. Eur. 4 using a helium pycnometer (Pycnomatic - ATC, Porotec GmbH., Germany). The test is intended to determine the volume occupied by a known mass of powder (7.5–10.5 g depending on the volume; the cell no. 30) by measuring the volume of gas displaced under defined conditions. The sample volume is determined after degassing the examined powder mass and its pressurization using the following formula:

$$V_s = V_c - \frac{V_r}{\frac{P_i - P_r}{P_f - P_r} - 1} \tag{2}$$

where V_s is the sample volume, V_c is the cell volume, V_r is the reference volume, P_i is the initial pressure, P_r is the reference pressure, and P_f is the final pressure. The density of the powder mass ρ is given by the equation:

$$\rho = m / V_s \tag{3}$$

The characteristics of the drug and excipients used are shown in Table 1.

Pellet Formulation

Samples 1 to 7 contained from 10% to 65% of active ingredient. The content of microcrystalline cellulose was constant at 35% and the rest of a formulation was lactose. The amount of water used to obtain damp mass depended on the content of the drug in formulation and the preparation method. The actual composition of pellets prepared is shown in Table 2. The preparation of each sample was repeated three times. The samples of the "ES" pellets were prepared by extrusion/spheronization. Following this technique the powder mixture of the drug and excipients was first blended in the mixer (Tefal Kaleo, France). Then in the next phase, the liquid was continually sprayed at the speed of 30 g/minute in the same equipment. The extrusion was performed on a one-screw axial extruder (Pharmex 35T, Wyss & Probst, Germany). The plastic mass was fed through the hopper on a rotating screw at a standard extruder speed of 110 rpm. The diameter of the perforations in the extrusion

TABLE 1
Properties of Used Drug and Excipients

	Particle Mean Diameter (μm)	Pycnometric Density (g/cm^3)	Solubility in Water[a] (g)
Theophylline	277.5	1.468 ± 0.001	8.3[b]
Lactose	29.0	1.534 ± 0.001	216.0[c]
Microcrystalline cellulose	76.2	1.547 ± 0.001	Insoluble[c]

[a]Solubility in 1.0 L of water at 25°C.
[b]Kim & Fasshi, 1997.
[c]Rowe et al., 2003, pp. 323–332, 108–111.

TABLE 2
Composition of the Pellet Samples and Formulation Water Amount

Sample	Theophylline (%)	Lactose (%)	Microcrystalline Cellulose (%)	Watter Amount[a] (%)
ES1 / RA1	10	55	35	33.2 / 31.0
ES2 / RA2	20	45	35	34.6 / 31.0
ES3 / RA3	30	35	35	35.7 / 31.5
ES4 / RA4	40	25	35	36.7 / 32.0
ES5 / RA5	50	15	35	37.2 / 34.4
ES6 / RA6	60	5	35	38.7 / 38.3
ES7 / RA7	65	–	35	40.2 / 38.3

ES = pellets prepared by extrusion/spheronization. RA = pellets prepared by rotoagglomeration.
[a]Expressed as % of the wet weight of the mixture.

screen was 0.8 mm; its width was 1 mm. After extrusion, 200 g of the extrudate were placed into the spheronizer (Pharmex 35T, Wyss & Probst, Germany) with a 23-cm diameter serrated plate. The spheronization speed was 640 rpm and the spheronization time was 15 minutes. Prepared pellets were dried using the ventilated oven (Hoffman, Type 0488, Germany) at 60°C for 20 minutes. The second set of samples marked as "RA" was prepared by the rotoagglomeration. The load of 1,000 g of theophylline and excipients was placed on the textured disc in the rotoprocessor (Multiprocessor MP-1, Niro Aeromatic, Switzerland). Powders were mixed for 5 minutes until the internal temperature reached 30°C. The wetting speed of the water was 30 g/minute and the atomization pressure was 80 KPa. The rotor speed during the agglomeration phase ranged between 160 and 1,360 rpm depending on the product movement. When the wetting phase was finished, the spheronization was processed for 2 minutes at the spheronization rotor speed 1,800 rpm. The pellets were then dried at the temperature of 60°C for 20 minutes. The conditions of the pellet preparation were optimized for both technologies.

Samples of pellets containing 50% of theophylline were coated in a laboratory Wurster type coater (Medipo ZT, Czech Republic). The amount of the pellet coating was 8% of the total pellet weight. The pellet coating was composed of the ethylcellulose (94.9%) and the polyethylenglycol 1500 (5.1%). The batch size of the pellets within the size range of 0.50 to 0.80 mm was 150.0 g. The inlet air temperature was 30°C, the speed of the film solution spraying was 0.50 g/min, and atomization pressure was 80 KPa. Coated pellets were dried at 30°C for 20 minutes.

The preparation of each sample was repeated three times to ensure reproducibility of the process.

Pellet Evaluation

The pellet size distribution was determined by the sieve analysis (Retsch, AS 200 basic, Germany) using the sieve apertures of 0.25, 0.50, 0.80, 1.00, and 1.25 mm, and their mean diameter was calculated according to equation 1. The requested pellet size fraction lay between 0.50 and 0.80 mm and was defined as the usable yield. Pellets obtained in this range were used for further evaluation. The pellet shape was observed by a binocular lens (Intracho-Micro, Czech Republic) and confirmed by the pellet sphericity *S*, determined by the image analysis (Leco IA 32, Leco Instruments, USA) of 500 pellets according to the following formula (Sienkiewicz, Pereira, Rudnic, Lausier, & Rhodes, 1997):

$$S = \frac{4\pi \times area}{perimeter^2} \quad (4)$$

Mechanical properties were characterized as the pellet friability and hardness. A 10-g sample was placed into the metal pan of the abrasion tester adapted for pellet testing (Erweka, TAR 10, Germany), together with 200 pieces of 4-mm glass beads, and rotated 200 times for 10 minutes. The tablet hardness and compression tester fitted with 5-kg load cell (Hardness C5 tester, Engineering System, England) was used for the determination of the pellet hardness. Ten pellets of each formulation were tested; the hardness mean value and standard deviation were calculated. Pycnometric density of the pellet samples was determined by the same method used for material characterization—the gas displacement technique using a helium pycnometer (equation 2). Pellet flow properties were evaluated by the measurement of bulk and tapped densities according to Ph. Eur. 4 using a tapped density tester (Erweka, SVM 102, Germany). The bulk density was determined by measuring of the volume occupied by 50 g of sample filled into a 100-ml graduated cylinder of the density tester. The tapped density was determined from the volume of pellets after 1,250 taps of the cylinder. The values of densities were calculated from the measured volume and its weight according to equation 3. Achieved values of densities were used for calculating the Hausner ratio *HR*—the next parameter for evaluation of flow properties—as follows (Sinha, Agrawal, & Kumria, 2005):

$$HR = \rho_{\text{bulk}} / \rho_{\text{tapped}} \tag{5}$$

The flowability of produced spheres is represented also by the repose angle. Pellet sample (50 g) was placed in a glass funnel with a stem. The funnel was maintained upright so that the stem terminated 10 cm above a flat solid underlay protected from vibrations. Pellets flowed out of the funnel and formed a cone. Its height h and base diameter d were measured. The repose angle value α was calculated using the following equation:

$$\alpha = \text{arc tg}(2h / d) \tag{6}$$

The content of theophylline was measured from the crushed pellet samples using a spectrophotometer (Perkin Elmer, UV/VIS spectrophotometer, United States) at a wavelength of 273 nm. The dissolution profiles of the uncoated and the coated pellets were determined using basket dissolution method and 900.0 ml of the distilled water as a dissolution medium (Sotax, AT 7 Smart on line, Switzerland). The dissolution profile evaluation of the coated pellets was compared according to the recommendations of similarity factor *F*. If the factor value is higher than 50, than the dissolution profiles are more than 90% identical and they are considered similar (Gray, Brown, Dressman, & Leeson, 2001; Shah, Tsong, Sathe, & Williams, 1999).

The friability, pellet densities, repose angle, and drug content of the pellet samples were carried out in triplicate and standard deviations were calculated.

RESULTS AND DISCUSSION

Material Characteristics

Drug and excipient particle size, density, and solubility were considered (Table 1) before pelletization. The largest particles were determined with theophylline ($đ$ = 277.5 μm) having the lowest density and solubility of 8.3 g/l; smaller particles were observed for insoluble MCC ($đ$ = 76.2 μm) with the highest density; and the smallest ones were measured for lactose $đ$ = 29.0 μm), which had highest solubility 216.0 g/l. Material characterization was performed due to particle size, and solubility of the single compounds have an impact on amount of wetting agent used for preparation of pellets with optimal size by both techniques (Hilemann, Upadrashta, & Nean, 1997; Newton, 1996). Particle size of insoluble or slowly dissolving compounds and their ratio is substantial with respect to total moist surface. Freely soluble substances are dissolved during the homogenization phase; increasing the concentration of slightly or less soluble substances demands a higher amount of water (Table 2) necessary for preparation of either plastic mass during extrusion and spheronization process (Lustig-Gustafson, Kaur Johal, Podczeck, & Newton, 1999; Tomer, Podczeck, & Newton, 2001) or uniform particle surface damping (Vetchý & Rabišková, 2002), which is fundamental for successful pellet formulation.

Pelletization and Pellet Characteristics

A total of 14 samples of the uncoated pellets and 2 samples of the coated pellets were prepared by extrusion/spheronization and rotoagglomeration techniques in our experiments. Samples 1 to 7 contained from 10% to 65% of theophylline monohydrate; each sample contained 35% of microcrystalline cellulose and the rest was lactose monohydrate. The composition of the pellets prepared is represented in Table 2. The amount of water used in the formulations was slightly higher in the extrusion/spheronization samples than the rotoagglomeration samples, probably due to different requirements on dampening mass characteristics between these two techniques. The higher amount of wetting agent during extrusion and spheronization is related to the capability of the plastic mass to compress and flow through an extrusion die and additionally to this, the particles must cohere into cylindrical rods (Jerwanska, Alderborn, Newton, & Nystrom, 1995). While at rotoagglomeration, pellets arise by formation of liquid and after drying solid bridges between individual particles, and by coalescence of agglomerates arising during processing (Holm, Bonde, & Wigmore, 1996; Vonk, Guillaume, Ramaker, Vromans, & Kossen, 1997).

Table 3 indicates the size distribution and the mean diameter of the prepared pellets. The usable yield (pellet size 0.5–0.8

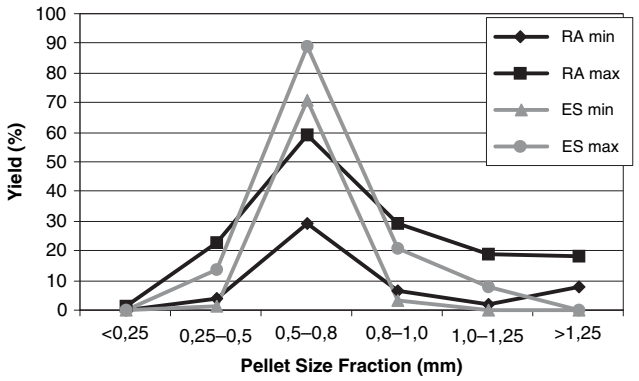

FIGURE 1. Influence of pelletization technique on pellet size distribution. ES min = minimal yield of pellets prepared by extrusion/spheronization. ES max = maximal yield of pellets prepared by extrusion/spheronization. RA min = minimal yield of pellets prepared by rotoagglomeration. RA max = maximal yield of pellets prepared by rotoagglomeration.

mm) prepared by extrusion/spheronization ranged within the interval from 71.14% to 88.94%, while that one of the rotoagglomeration was smaller within the interval from 29.40% to 58.90%. The bigger yield and the narrower size distribution of particles after spheronization at ES samples (Table 3 and Figure 1) are due to the extrusion die perforations, which produce uniform smooth coherent extrudate strands, fragile enough to be broken into smaller cylinders of the same size (Vervaet et al., 1995). With rotoagglomeration, the pellet formation is based on the mechanism of particle growth and that is why the particle size is more adventitious (Wan, Heng, & Liew, 1995). The mean diameter of pellets prepared by both technologies was almost the same, in the interval 0.66 to 0.81 mm (Table 4). Sample RA 1 of the pellet mean diameter 0.91 mm was the exception caused by the higher percentage of the arisen agglomerates (Table 3).

The different pelletization techniques contributed also to the differences in mechanical properties of the pellets. Pellet hardness and pycnometric pellet density values were slightly higher in the extrusion/spheronization samples than in the rotoagglomeration samples with the exception of the samples containing 10% of theophylline (Tables 4 and 5; Figure 2). Different values of these parameters might be explained as a result of the higher screw pressure affecting the plastic mass during extrusion (Vervaet et al., 1995), in contrast to the pressure caused by the forces (centrifugal, fluidization and gravity) acting on the wetted particles during the rotoagglometration process (Vetchý & Rabišková, 2002). The values of the pellet density and hardness within the extrusion/spheronization samples were also getting higher—slightly increasing with the increasing drug content—from 1.353 g/cm^3 to 1.429 g/cm^3 and from 4.72 N to 7.13 N, while the samples obtained by rotoagglomeration showed more or less opposite tendency (Tables 4 and 5). Such tendency of pellets prepared by rotoagglomeration has been recently reported (Krejčová et al., 2006). The decreasing pellet hardness (Figure 2) can be caused by the decreasing content of lactose, which acts as a binder when is wetted (Rowe, Sheskey, & Weller, 2003, pp. 323–332). Prepared pellets showed low friability—under 0.71%, which is considered appropriate (Vertommen & Kinget, 1997). Significantly lower values, again caused probably by the higher pressure during

TABLE 3
Pellet Size Distribution

	Size Distribution[a] (mm)					
Sample	< 0.25 (%)	0.25–0.50 (%)	0.50–0.80 (%)	0.80–1.00 (%)	1.00–1.25 (%)	>1.25 (%)
ES1	0.60 ± 0.34	13.65 ± 2.71	*82.22 ± 4.02*	3.39 ± 1.72	0.15 ± 0.09	0.00 ± 0.00
ES2	0.23 ± 0.11	6.60 ± 2.52	*71.14 ± 4.48*	14.89 ± 2.83	7.14 ± 2.07	0.00 ± 0.00
ES3	0.31 ± 0.27	4.60 ± 0,98	*87.31 ± 3.99*	7.24 ± 2.06	0.55 ± 0.33	0.00 ± 0.00
ES4	0.00 ± 0.00	2.38 ± 0.96	*75.36 ± 4.65*	20.75 ± 3.01	1.51 ± 0.39	0.00 ± 0.00
ES5	0.00 ± 0.00	2.01 ± 0.43	*70.52 ± 3.97*	19.76 ± 2.94	7.71 ± 1.43	0.00 ± 0.00
ES6	0.00 ± 0.00	1.40 ± 0.34	*74.15 ± 4.26*	20.15 ± 4.11	4.29 ± 1.01	0.00 ± 0.00
ES7	0.16 ± 0.19	4.40 ± 1.68	*88.94 ± 3.53*	5.15 ± 2.43	1.33 ± 0.44	0.00 ± 0.00
RA1	0.00 ± 0.00	4.40 ± 1.83	*29.40 ± 6.47*	28.90 ± 6.61	18.90 ± 3.74	18.40 ± 4.18
RA2	0.20 ± 0.19	15.00 ± 4.92	*58.90 ± 9.78*	13.20 ± 4.63	4.30 ± 1.56	8.40 ± 2.75
RA3	0.40 ± 0.27	21.50 ± 5.36	*57.60 ± 10.43*	9.10 ± 4.78	2.80 ± 0.83	8.60 ± 2.69
RA4	0.70 ± 0.43	16.70 ± 5.22	*51.60 ± 10.07*	10.60 ± 4.51	5.30 ± 2.04	15.10 ± 3.34
RA5	0.20 ± 0.36	18.00 ± 5.97	*58.90 ± 10.74*	6.70 ± 3.82	1.90 ± 0.80	14.30 ± 4.03
RA6	1.10 ± 0.35	23.00 ± 6.01	*57.60 ± 11.03*	8.30 ± 4.03	2.00 ± 1.11	8.00 ± 2.41
RA7	0.70 ± 0.29	3.70 ± 1.90	*50.40 ± 9.89*	26.70 ± 7.13	5.50 ± 2.23	14.00 ± 3.62

ES = pellets prepared by extrusion/spheronization. RA = pellets prepared by rotoagglomeration.
[a]Each sample was done in triplicate and ± standard deviation was calculated.

TABLE 4
Pellet Characteristics

Sample	Hardness[a] (N)	Friability[a] (%)	Repose Angle[a] (°)	Mean Diameter[a] (mm)	Sphericity
ES1	4.72 ± 0.89	0.09 ± 0.01	23.34 ± 0.74	0.62 ± 0.01	0.864
ES2	5.04 ± 0.58	0.04 ± 0.01	22.07 ± 0.51	0.70 ± 0.01	0.905
ES3	5.12 ± 0.67	0.06 ± 0.02	21.03 ± 0.47	0.66 ± 0.01	0.876
ES4	5.38 ± 1.06	0.01 ± 0.00	21.52 ± 0.94	0.70 ± 0.01	0.883
ES5	5.34 ± 0.49	0.06 ± 0.01	21.44 ± 0.53	0.71 ± 0.01	0.871
ES6	6.27 ± 0.85	0.07 ± 0.01	21.03 ± 0.61	0.72 ± 0.01	0.879
ES7	7.13 ± 0.73	0.09 ± 0.02	21.87 ± 0.88	0.66 ± 0.01	0.880
RA1	4.83 ± 0.70	0.29 ± 0.05	19.40 ± 1.70	0.91 ± 0.02	0.877
RA2	4.57 ± 1.50	0.26 ± 0.07	22.56 ± 0.39	0.71 ± 0.02	0.883
RA3	3.83 ± 1.69	0.39 ± 0.13	23.92 ± 0.68	0.68 ± 0.02	0.892
RA4	3.54 ± 1.16	0.55 ± 0.15	22.57 ± 0.26	0.74 ± 0.02	0.872
RA5	3.53 ± 0.81	0.27 ± 0.08	21.73 ± 0.51	0.71 ± 0.02	0.867
RA6	2.49 ± 0.46	0.71 ± 0.08	20.94 ± 0.98	0.66 ± 0.02	0.886
RA7	3.45 ± 0.40	0.26 ± 0.01	20.17 ± 1.24	0.81 ± 0.02	0.882

ES = pellets prepared by extrusion/spheronization. RA = pellets prepared by rotoagglomeration.
[a]Each sample was done in triplicate and ± standard deviation was calculated.

TABLE 5
Densities of Prepared Samples, Hausner Ratio and Drug Content

Sample	Bulk Density[a] (g/cm^3)	Tapped Density[a] (g/cm^3)	Hausner Ratio[a]	Pycnometric Density[a] (g/cm^3)	Drug Content[a] (%)	Theoretical Content Difference (%)
ES1	0.772 ± 0.016	0.830 ± 0.011	1.08 ± 0.01	1.353 ± 0.006	9.79 ± 0.29	–0.21
ES2	0.844 ± 0.011	0.862 ± 0.006	1.02 ± 0.01	1.378 ± 0.009	19.52 ± 0.33	–0.48
ES3	0.793 ± 0.007	0.854 ± 0.005	1.08 ± 0.00	1.388 ± 0.005	29.37 ± 0.46	–0.63
ES4	0.819 ± 0.013	0.874 ± 0.008	1.06 ± 0.01	1.397 ± 0.012	39.20 ± 0.51	– 0.80
ES5	0.818 ± 0.006	0.871 ± 0.007	1.06 ± 0.00	1.392 ± 0.005	48.74 ± 0.24	–1.26
ES6	0.829 ± 0.008	0.878 ± 0.013	1.06 ± 0.01	1.413 ± 0.008	58.61 ± 0.45	–1.39
ES7	0.817 ± 0.009	0.886 ± 0.005	1.08 ± 0.01	1.429 ± 0.004	63.67 ± 0.38	–1.33
RA1	0.762 ± 0.006	0.803 ± 0.009	1.05 ± 0.00	1.376 ± 0.009	9.83 ± 0.42	–0.17
RA2	0.749 ± 0.011	0.789 ± 0.014	1.04 ± 0.01	1.287 ± 0.009	19.27 ± 0.56	–0.73
RA3	0.751 ± 0.004	0.782 ± 0.007	1.04 ± 0.00	1.272 ± 0.011	29.40 ± 0.39	–0.60
RA4	0.739 ± 0.003	0.778 ± 0.008	1.05 ± 0.00	1.256 ± 0.008	39.17 ± 0.44	–0.83
RA5	0.801 ± 0.010	0.836 ± 0.012	1.04 ± 0.01	1.381 ± 0.001	48.81 ± 0.35	–1.19
RA6	0.743 ± 0.005	0.765 ± 0.005	1.03 ± 0.00	1.341 ± 0.005	58.66 ± 0.22	–1.34
RA7	0.721 ± 0.013	0.735 ± 0.015	1.02 ± 0.01	1.373 ± 0.007	63.41 ± 0.38	–1.59

ES = pellets prepared by extrusion/spheronization. RA = pellets prepared by rotoagglomeration.
[a]Each sample was done in triplicate and ± standard deviation was calculated.

extrusion, were obtained in the extrusion/spheronization samples (Table 4 and Figure 3).

The repose angle of all samples below 23° 92' and Hausner ratio under 1.08 (corresponding to the small differences between bulk and tapped densities) reflected the good flow properties of pellets prepared using both techniques (Table 5). The sphericity of the pellet samples was also good as shown in Table 4: values in between 0.864 and 0.905. The spherical shape of pellets was confirmed by the photographs of the samples ES 1 and RA 5 with the lowest sphericity values (Figures 4 and 5).

The theophylline content of each batch prepared by both techniques was slightly lower than the theoretical value: 0.17% to 1.59% (Table 5). Theophylline was completely released from uncoated pellets within 35 minutes. With an increasing amount of theophylline in pellets, a slower release of active

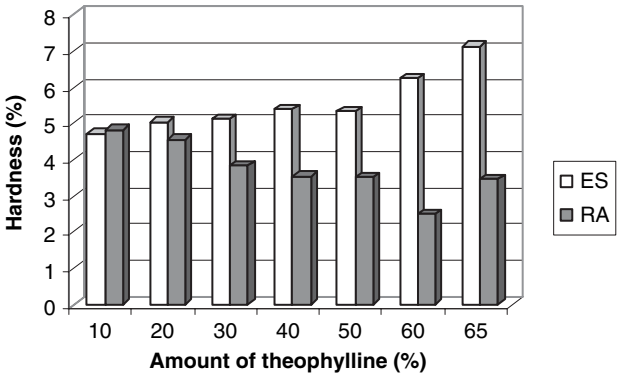

FIGURE 2. Influence of pelletization technique on the pellet hardness. EST = pellets prepared by extrusion/spheronization. RT = pellets prepared by rotoagglomeration.

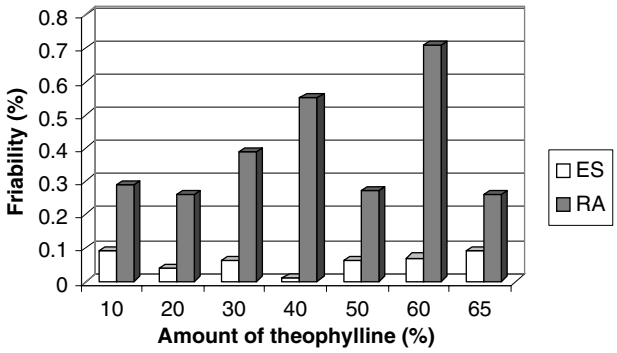

FIGURE 3. Influence of pelletization technique on the pellet friability. ES = pellets prepared by extrusion/spheronization. RA = pellets prepared by rotoagglomeration.

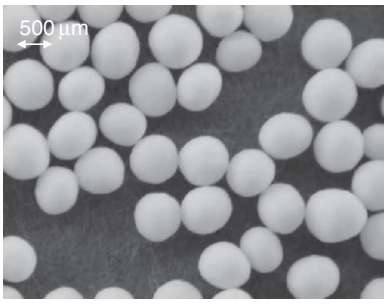

FIGURE 4. Uncoated pellets prepared by extrusion/spheronization.

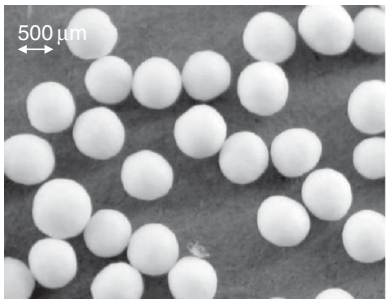

FIGURE 5. Uncoated pellets prepared by rotoagglomeration.

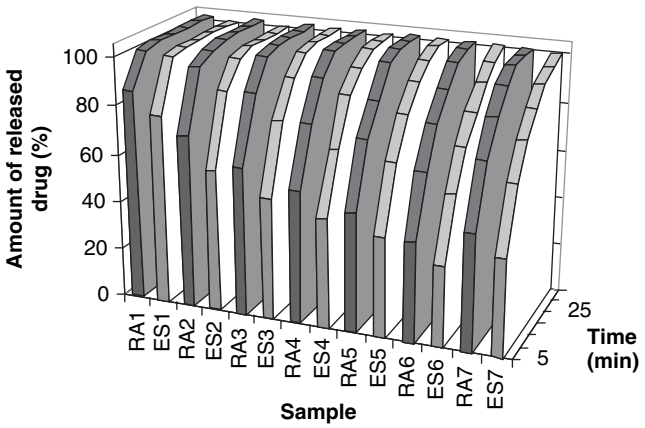

FIGURE 6. Comparison of the dissolution profiles of the uncoated pellets. ES = pellets prepared by extrusion/spheronization. RA = pellets prepared by rotoagglomeration.

ingredient is visible because of its poor solubility in water (Rabišková, Häring, Havlásek, Minzingerová, & Musilová, 2007). This tendency is most apparent after 5 minutes of dissolution test. At samples ES 1 and RA 1, with the lowest drug content, was amount of released theophylline 78.1% and 87.0%, compared with samples ES 7 and RA 7, with the highest drug content, where the amount of released theophylline was only 40.1% and 47.6% (Figure 6). Comparison of dissolution profiles of pellets prepared by both techniques showed slightly slower release of theophylline from the extrusion/spheronization pellet samples (Figure 6). It was probably caused by higher density and hardness values indicating higher compactness of pellets prepared by extrusion/spheronization. The objective of our study was also to observe the influence of the pelletization technique on the release of theophylline from the coated pellets. These tests were performed to find out if there are the same differences as with uncoated pellets. However, drug dissolution profiles from the coated samples ES 5 and RA 5 were similar in the interval of 12 hours (Figure 7) and the value of similarity factor 87.72 does not confirm significant differences (Shah et al., 1999).

CONCLUSION

From the results of our study we can conclude that extrusion/spheronization and agglomeration in a rotoprocessor produced pellets of appropriate shape and mechanical properties. Due to the higher pressure of the screw during extrusion, pellets of higher density, hardness, lower friability, and slightly slower dissolution profile were obtained. Extrusion die also

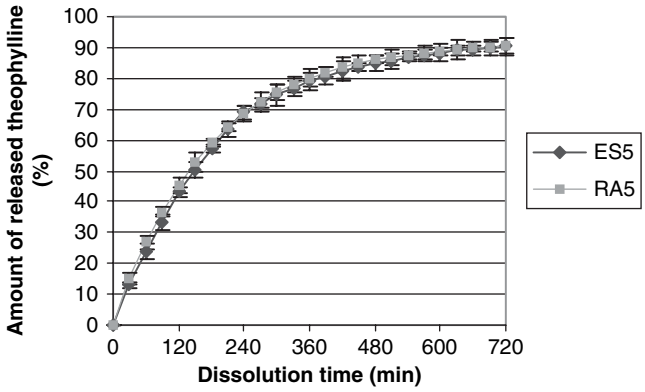

FIGURE 7. Comparison of the dissolution profiles of the coated pellets. ES = pellets prepared by extrusion/spheronization. RA = pellets prepared by rotoagglomeration.

produced uniform extrudate strands giving narrow size distribution of particles after spheronization and therefore a bigger yield of pellets with the requested size. Pellets using both technologies had similar dissolution profiles after coating and showed good ability to modify the drug release within the interval of 12 hours.

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