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RESEARCH PAPER

Spheronization of Theophylline–Avicel Combinations Using a Fluidized-Bed Rotogranulation Technique

G. Sienkiewicz, R. Pereira,* E. M. Rudnic,†
J. M. Lausier, and C. T. Rhodes

Department of Applied Pharmaceutical Sciences, College of Pharmacy, University of Rhode Island, Kingston, Rhode Island 02881

ABSTRACT

A tangential-spray rotary fluidized-bed granulator was used to test the spheronization potential of microcrystalline cellulose in a process using anhydrous theophylline as a model drug. Three grades of theophylline and three grades of microcrystalline cellulose (MCC) were used together to form spherical pellets in drug potencies up to 90%. Water was used as the granulating agent. The purpose of the investigation was to identify differences between raw materials in the formation of spheres and the effects of increasing levels of drug loading on pellet quality. The materials were judged by their ability to spheronize, while the pellets themselves were characterized by size, density, friability, flowability, drug content, and shape. There were marked differences in the ability of some combinations to form spheres. A qualitative scale of spheronization potential describes the ability of the process to go to completion without rescue. The potential for spheronization of binary systems using anhydrous theophylline and microcrystalline cellulose depended primarily on the choice of theophylline and the level of drug loading. The choice of MCC grade was less important. In concentrations of 50% drug and below, all nine combinations of drug and excipient formed spheres, although often with difficulty. The two finer grades of theophylline were substantially more difficult to spheronize than the coarse grade. Only the coarsest grade of theophylline formed spheres containing 90% drug. Despite substantial differences in spheronization potential, the pellets themselves showed similarities in true den-

*Present address: IVAX Corporation, 8800 NW 36th Street, Miami, Florida 33178
†Present address: PHARMAVENE Inc., 35 W. Watkins Mill Road, Gaithersburg, Maryland 21701

sity, friability, or flowability. Other properties showed significant differences. Sphericity declined when drug loading exceeded 70%. The actual drug content of the pellets declined slightly with increasing theoretical potency and did not vary across sieve fractions.

INTRODUCTION

Drug-loaded spheres are important for the design of some controlled-release dosage forms. Traditionally, spherical drug-containing pellets are manufactured using a four-step process which includes wet granulation, extrusion, spheronization, and drying. Some of the equipment, process, and formulation variables involved in this process have been investigated (1–6). Others (7,8) have studied the process and its effect on tablets made with the compressed spheres.

More recent studies have investigated a newer spheronization process using rotary fluidized-bed equipment which combines several processing steps into a single operation. In this method, material is spheronized atop a spinning rotor plate within a fluidization column. Air rises through a gap between the rotor plate and the column wall, and displaces moistened solid material accumulating at the wall by centrifugal action. Suspended particles return to the rotor surface by gravitational forces. Eventually, the wetted material takes on the appearance of a twisted rope, with individual agglomerates assuming a rounded shape. Once agglomeration is complete, fluidizing air rapidly dries the product.

Jäger and Bauer (9) first described the rotary fluidized-bed technique. More recently, Wan et al. (10) examined sphere formation at different spray rates and gap air pressures, while Vecchio et al. (11) studied different water feed rates, different excipient materials, and various levels of drug loading. Robinson and Hollenbeck (12) compared directly the four-step method with the rotary fluidized-bed technique, finding the results to be comparable. The fluidized-bed technique economizes time and labor but is sometimes more difficult to control.

Regardless of which manufacturing method is used, however, a spheronizing agent often employed is microcrystalline cellulose (MCC). It can be used with or without additional binding agents. It is available in various powdered and colloidal grades from several suppliers. Significant differences exist between grades and between suppliers, even for grades promoted by some manufacturers as "interchangeable" (13).

No studies of the pelletization process to date have focused on the physical grades of the drug substance as well as the spheronizing agent. Differences in size, shape, powder flowability, or other physical properties might have significant effects on the agglomeration process for binary systems, perhaps favoring some combinations of materials over others. In addition, rotary fluidized-bed granulation may present processing difficulties due to lack of accessibility within the fluidization column. The present work examined three grades of MCC and three grades of anhydrous theophylline as a model drug, each differing substantially in particle size and shape. Each of the nine possible combinations of drug and excipient was examined in various proportions in an attempt to maximize drug loading without loss of pellet quality.

EXPERIMENTAL

Materials

Anhydrous theophylline was available in three particle size grades, designated for study purposes as A, B, and C. Theophylline type A was the largest-sized grade; type B was intermediate, and type C was a micronized form. Grades A and B were available from Knoll AG (Germany); anhydrous theophylline grade C was available from Henley (Ger.). Avicel® grades PH-101, PH-102, and PH-200 were used as received (FMC Corp.). All spheronization was performed with purified water as the granulating agent.

Methods

Raw Material Evaluation

Raw materials were analyzed as received for particle size and shape using scanning electron microscopy (JEOL, USA) in conjunction with quantitative image analysis (Structure Probe, Inc., Metuchen, NJ, USA). For each raw material sample, a number-average arithmetic mean size and a number-average volume–surface mean particle size was computed (14). Each particle was also evaluated for shape using the formula described below under "Shape Factor."

Manufacturing Process

Spheronization of 500-g batches was performed using a Glatt GPCG-1 Versaglatt (Glatt Air Techniques, Ramsey, NJ) fitted with a 12-in. rotor insert with waffle plate. The interior of the fluid-bed column contains one tangentially mounted Schlick® nozzle with a 0.8-mm opening. Water was pumped at a rate of 50–60 ml/min using a Masterflex Pump and Flow Controller and sprayed at 1.5 bar pressure.

Water spraying continued for each batch until the same particle size was reached, as determined visually. Drying continued until the exhaust temperature reached 60°C.

Bulk Density

Loose and tapped bulk density was determined using a Vanderkamp Tap Density Tester Model 10700 (VanKel Industries, Chatham, NJ).

True Density

True density determinations were made using a Micromeritics Autopycnometer Model 1320 (Micromeritics Corp., Norcross, GA) using helium as the intrusive gas.

Sphere Flowability

Flowability was estimated using the Carr compressibility index (15). Values below 15% usually indicate good flowability (16).

Actual flow rates of pellets were also determined using an Erweka Flow Tester Model GWF (Erweka Instruments, Milford, CT). The reading is converted to a flowability value by calculating the reciprocal angle of repose.

Friability

Six grams of pellets larger than 30 mesh and 6 g of 3-mm glass beads (Kimble®) were rotated for 10 min in an 8-in. baffled abrasion drum operating at 25 rpm. The pellets were dedusted and reweighed; the weight loss is expressed as a percentage.

Experimental Design

The design for experiment A is given in Fig. 1. It was not possible to produce drug-loaded pellets in all strengths using all grades of materials (see "Spheronization"). Therefore, a second experimental design, experiment B (Fig. 2), was used to test the three Avicel grades with a single grade of anhydrous theophylline (type A) at all levels of drug loading; the experiment was performed in three replicates.

		Theophylline A	Theophylline B	Theophylline C
Avicel PH-101	25%			
	50%			
	70%			
	90%			
Avicel PH-102	25%			
	50%			
	70%			
	90%			
Avicel PH-200	25%			
	50%			
	70%			
	90%			

Figure 1. Experiment A.

Shape Factor (Sphericity)

Computer-aided image analysis was performed for each pellet in a random sample of at least 30 pellets from each batch. Sphericity is calculated using the following formula (a circle = 1, a line = 0):

$$\text{Sphericity} = \frac{4\pi \times \text{area}}{\text{circumference}^2}$$

Shape uniformity was estimated by evaluating the sample standard deviations of the shape factors for each batch of pellets tested. A Scheffe's multiple comparison test compared the means by raw material type.

Drug Content

Theophylline potency in pellets was determined by high-performance liquid chromatography (HPLC; Perkin–Elmer) in conjunction with an ultraviolet (UV) detector measuring absorbance set at 275 nm for potency assay and 220 nm for purity determination.

	THEOPHYLLINE POTENCY (Type A)				
	0%	25%	50%	70%	90%
Avicel PH-101	A B C	A B C	A B C	A B C	A B C
Avicel PH-102	A B C	A B C	A B C	A B C	A B C
Avicel PH-200	A B C	A B C	A B C	A B C	A B C

Figure 2. Experiment B.

RESULTS

Evaluation of Raw Materials

Microscopic analysis of the raw materials was used to determine the size and shape of individual particles. For each sample an arithmetic mean particle size (d_a) and a volume–surface mean particle size (d_{vs}) were computed on a number basis (Table 1). The volume–surface mean particle size is useful when the surface area of the material may be important (14).

Surface–volume mean diameters for the Avicel grades show a less than twofold difference in particle size, while the difference between theophyllines type A and type C is seventyfold (Fig. 3). The increased surface area of the micronized theophylline may predispose it to difficulties in a process involving high shear forces in an inaccessible environment. High surface energies often complicate high-shear processes, and fluid-bed processes also generate substantial static charges (17). On this basis, process differences between the theophylline grades are more likely than differences between Avicels.

The raw materials also differ in particle shape. Mean shape factors for the Avicels indicate a tendency toward increased roundness with increasing size, due to the presence of rounded agglomerates in the 200- to 300-μm range (Figs. 4 and 5). Microscopic examination of the theophylline grades reveals similar particle shapes for all three grades. Individual drug particles are essentially rectangular in appearance. The shape factors of the

Table 1

Particle Sizes and Shape Factors of Raw Materials (μm)

Material	d_a	d_{vs}	Typical Size[a]	Shape Factor
Avicel PH-101	135	180	50	0.41
Avicel PH-102	197	235	100	0.535
Avicel PH-200	310	345	180	0.768
Theophylline A (coarse)	246	428		0.436
Theophylline B (medium)	55	131		0.439
Theophylline C (fine)	3.9	6.1		[b]

[a]Manufacturer's data (18).
[b]Shape factor could not be determined using this method.

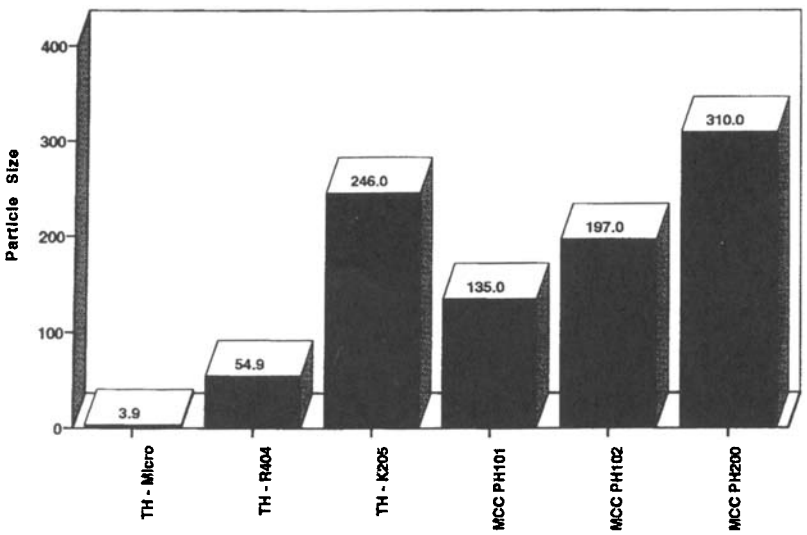

Figure 3. Arithmetic mean particle size of raw materials (μm).

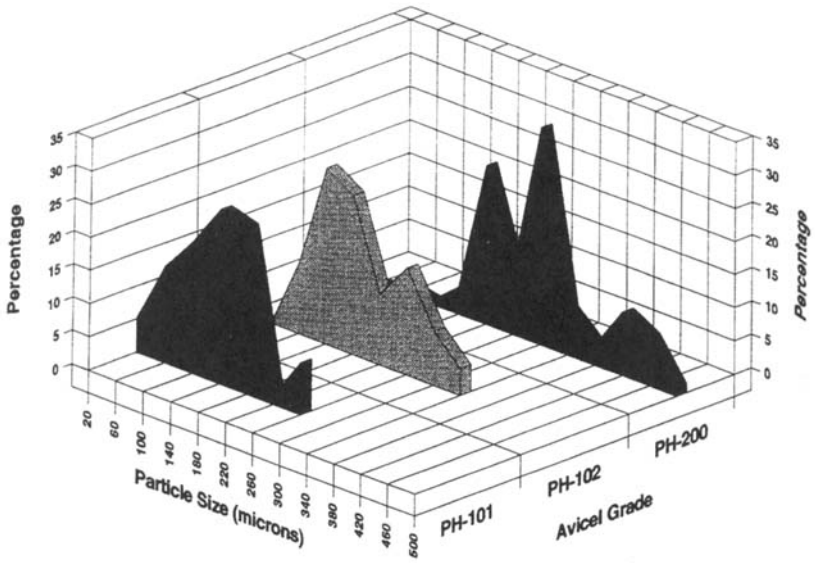

Figure 4. Particle size distributions of three Avicel grades.

two largest grades are similar (0.436 and 0.439). While the shape factor of the micronized grade could not be determined using this method due to its cohesive nature, visual comparisons reveal a similar structure.

Spheronization

There were marked differences in the ability of the various combinations of materials to form spherical pellets. In 8 of the 30 cases (22%), the process yielded no pellets at all. The material adhered strongly to the interior surfaces of the fluidization column despite efforts to rescue the batch. In another 10 cases (28%), spheres could be produced, but the process required at least one interruption to clean off the interior surfaces before restarting. These batches were termed "marginal" (see Fig. 6). The remaining 50% of the cases spher-

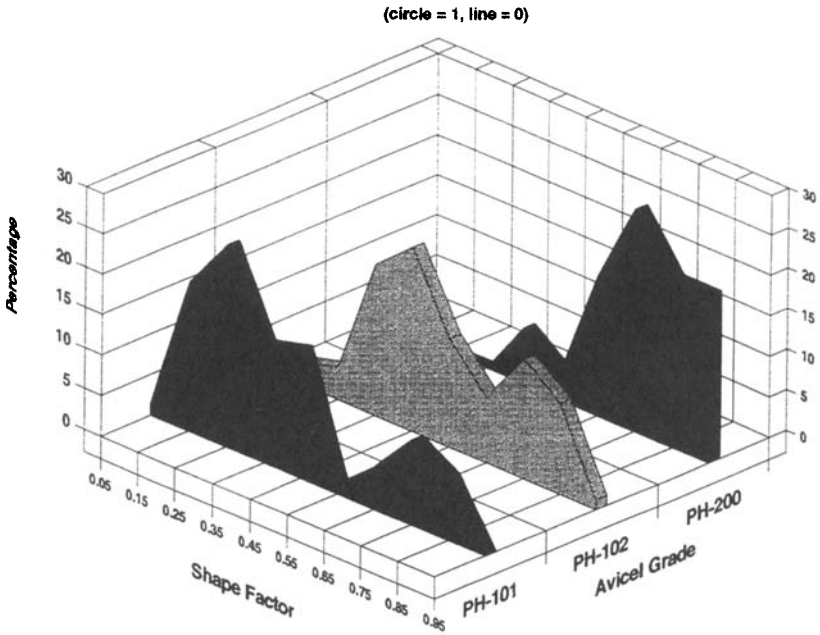

Figure 5. Shape factor (sphericity) distribution for three Avicel grades (circle = 1, line = 0).

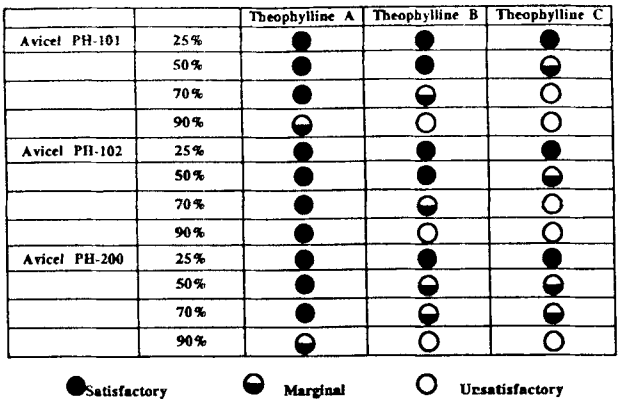

Figure 6. Spheronization potential.

onized well, with the process going to completion without interruption.

Figure 6 shows that the most important single factor in the ultimate success of the process was the choice of theophylline grade. Micronized theophylline type C spheronized poorly, if at all, at drug concentrations above 25%. By contrast, theophylline type A produced spheres at all drug-loading levels, although some 90% batches were considered marginal. The intermediate grade of theophylline (type B) was slightly better than theophylline type C, but was either marginal or unsatisfactory in more than half the cases.

The amount of drug loading was also an important factor. As the proportion of drug increased, the process became more difficult to carry out to completion. Pellets containing 25% drug formed spheres reliably regardless of the materials used. Higher concentrations were strongly affected by the choice of materials. Materials adhered to the column surfaces and failed to form the smooth, twisted-rope configuration necessary for the formation of rounded particles.

The grade of Avicel had a much smaller effect on processing. Avicel PH-200 was judged slightly superior to Avicel PH-101 and about equal to PH-102. Avicel PH-200 produced 70% spheres regardless of choice of theophylline. Moreover, its large particle size resisted dust formation during fluidization, resulting in "cleaner" runs. In this regard, Avicel PH-102 was also superior to Avicel PH-101.

Bulk Density

Pellets made with micronized theophylline had the highest tapped density values. A Scheffe's multiple comparison test (Table 2) indicates the differences are significant (means with the same letter are not different). This may be important for producing smaller dosage units of the same strength. Experiment B results confirm the similarity of Avicel grades, but there were differences due to drug potency levels. These differences, however, followed no clear pattern with regard to pellet strength.

Flowability

The Carr index was used to estimate flowability in experiment A. Spheres made with both larger grades of Avicel had significantly lower compressibility values (Table 3), indicating the potential for better flowability. All three pellet groupings, however, had excellent results and appeared to flow well. There were no differences between theophylline grades.

Flowability was measured directly in Experiment B using a funnel flow method. The results indicate no sig-

Table 2

Tapped Bulk Density for Avicel–Theophylline Spheres: Effect of Raw Material Grade

	Compressibility ± *SD* (%)	Scheffe Grouping
Avicel grade		
Avicel PH-101	0.84 ± 0.10	A
Avicel PH-102	0.87 ± 0.01	A
Avicel PH-200	0.82 ± 0.02	A
Theophylline grade		
Type A	0.798 ± 0.06	A
Type B	0.845 ± 0.03	A,B
Type C	0.881 ± 0.05	B

Table 3

Compressibility Index for Avicel–Theophylline Spheres: Effect of Raw Material Grade

	Compressibility ± *SD* (%)	Scheffe Grouping
Avicel grade		
Avicel PH-101	7.3 ± 1.5	A
Avicel PH-102	4.2 ± 0.9	B
Avicel PH-200	5.3 ± 1.1	B
Theophylline grade		
Type A	5.1 ± 1.7	A
Type B	6.1 ± 2.0	A
Type C	5.7 ± 1.5	A

nificant differences between Avicel grades and no differences due to pellet potency.

Sphere Friability

Smooth, durable pellets facilitate the uniform application of polymeric materials. Pellets from each of the nine combinations of Avicel and theophylline were tested in triplicate, along with pellets containing no drug (theophylline type D), which served as a control.

The results of a Scheffe's test show no differences between Avicels (Table 4). There were, however, statistically significant differences between grades of theophylline, but these differences were small and followed no clear pattern. It appears that the resistance to abrasion and fracture of these pellets in a property unrelated to the choice of materials.

Table 4

Sphere Friability (%) for Avicel–Theophylline Spheres: Effect of Raw Material Grade

	Friability ± *SD*	Scheffe Grouping
Avicel grade		
Avicel PH-101	2.10 ± 1.70	A
Avicel PH-102	1.93 ± 1.29	A
Avicel PH-200	2.99 ± 1.31	A
Theophylline grade		
Type A	3.07 ± 2.19	A
Type B	1.40 ± 1.12	B
Type C	2.48 ± 1.13	A,B
Type D (control)	2.19 ± 0.84	A,B

Sphere Shape

Results indicate that all nine combinations of Avicels and theophylline grades made spheres whose shape characteristics were not statistically differentiable from each other. The mean sphericity values and sphericity uniformity values of theophylline pellets are similar for all three grades of theophylline and microcrystalline cellulose. Scheffe's tests for both "sphericity" and "uniformity" (Table 5) indicate no statistically significant differences. These results are confirmed in experiment B, which finds identical shape factors for the three Avicels (not shown).

The results of experiment B reveal in more detail the effect of drug potency on sphericity. To the unaided eye, pellets containing 50% drug loading or less appeared round and elegant, while those containing 70% or 90% were often judged to be more granular. Computer-aided image analysis confirmed that 70% pellets showed some deterioration in shape. Seventy-percent pellets were sufficiently round to be grouped with all lower strengths (Table 6) but showed enough deterioration in sphericity to also be grouped with the 90% pellets, which were substantially worse.

Sphere Theophylline Content

Pellets made with the three grades of theophylline and MCC were formulated to contain drug loading levels from 25% to 90%. Since fluidization, mixing, and agglomeration must occur simultaneously as spheres are formed (unlike during extrusion–spheronization), segregation of materials may occur, particularly if their properties differ. Some material is lost from the process as

Table 5

Sphere Shape and Shape Uniformity of Avicel–Theophylline Spheres: Effect of Raw Material Grade

	Shape		Shape Uniformity	
	Sphericity	Scheffe Grouping	Uniformity ± *SD*	Scheffe Grouping
Avicel grade				
Avicel PH-101	0.867	A	1.101 ± 0.035	A
Avicel PH-102	0.861	A	1.104 ± 0.008	A
Avicel PH-200	0.861	A	1.113 ± 0.042	A
Theophylline grade				
Type A	0.857	A	1.119 ± 0.030	A
Type B	0.874	A	1.078 ± 0.015	A
Type C	0.858	A	1.122 ± 0.015	A

Table 6

Pellet Shape Factors (Sphericity) for Avicel–Theophylline Spheres: Effect of Percent Drug Loading

Theoretical Potency	Mean Sphericity	*SD*	Scheffe Grouping
0%	0.830	0.038	A
25%	0.836	0.018	A
50%	0.844	0.020	A
70%	0.828	0.027	A,B
90%	0.785	0.044	B

it adheres to the filter bag and column walls. The drug may be retained preferentially within either larger or smaller agglmoerates, depending upon the ability of liquid bridges to hold them together during growth and coalescence. In short, actual pellet potency could vary depending on the grade of the materials used and their proportion.

Each batch of pellets was fractionated by sieve size into three groupings A, B, and C, corresponding to sieve classifications 18/20, 20/30, and 30/40, respectively. A four-way classification analysis of variance was used to estimate the effects of Avicel type, theophylline type, sieve cut, and drug-loading level upon actual potency relative to the theoretical.

Mean assay values for the three types of theophylline and three Avicel grades show only small differences (Table 7)

The results in Table 8 show that drug-loading levels may affect the capacity of pellets to retain drug during processing. Actual potency decreases as theoretical potency increases ($p < 0.0001$), but the differences are small.

Table 7

Pellet Theophylline Content (% Theoretical) for Avicel–Theophylline Spheres: Effect of Raw Material Grade

Raw Material	Mean ± *SD*	Scheffe Grouping
Avicel grade		
Avicel PH-101	92.2 ± 3.11	A
Avicel PH-102	92.0 ± 0.93	A
Avicel PH-200	89.1 ± 3.84	B
Theophylline grade		
Type A	91.4 ± 2.63	A
Type B	92.0 ± 2.77	A,B
Type C	93.0 ± 4.15	B

Table 8

Pellet Theophylline Content (% Theoretical) for Avicel–Theophylline Spheres: Effect of Percent Drug Loading

Potency	Mean ± *SD*	Scheffe Grouping
25%	95.8 ± 1.83	A
40%	91.89 ± 4.01	B
50%	91.29 ± 2.16	B,C
70%	90.36 ± 1.61	B,C
90%	89.38 ± 0.62	C

There is no evidence that the drug content varies with the sieve cut of a given batch. Assay values in Table 9 show the mean assay values to be similar.

SUMMARY

The spheronization of theophylline with microcrystalline cellulose was carried out in a single-unit operation using a fluidized-bed rotogranulation technique. These grades of anhydrous theophylline and three grades of

Table 9

Pellet Theophylline Content (% Theoretical) for Avicel–Theophylline Spheres: Effect of Sphere Size Fraction (U.S. Standard Sieve Cut)

Sieve Cut	Mean ± *SD*	Scheffe Grouping
A (18/20)	92.54 ± 2.22	A
B (20/30)	92.90 ± 3.02	A
C (30/40)	92.90 ± 3.33	A

microcrystalline cellulose, differing considerably in size and shape (but not chemically), were used in all possible permutations and in varying proportions, from 0% drug loading to 90%.

Importantly, it was found that for many of the combinations of materials it was not possible to produce spherical pellets at all. Only half of the possible combinations resulted in a process which could proceed to completion without attempts to rescue the batch. The results indicate that the potential of these materials to spheronize is inversely related to their particle size, and that it was the grade of anhydrous theophylline used which was the controlling factor. Of the four possible drug loading levels (25%-90%), micronized theophylline pelletized at only two of them (a 70% pellet was made using Avicel PH-200, but only with great difficulty). By contrast, the intermediate grade of theophylline spheronized at three of the four levels (up to 70%) with all three Avicel grades. Finally, type A spheronized with all three Avicels at all four strengths.

Differences between the Avicel grades were relatively small. Of the 12 possible combinations for each Avicel, it was possible to pelletize 9 of them (75%) using Avicel PH-101 and Avicel PH-102. Avicel PH-200 was able to form pellets in 10 of the 12 cases (83%).

Where pellets could be produced, an examination of their properties revealed only small differences, if any, attributable to choice of materials. There were no differences in shape, shape uniformity, flowability, or friability due to the combination of materials used. In most instances, the ability of the pellets to retain drug during the agglomeration process did not differ between grades of material, between size fractions, or for different drug loading levels. All pellets tested retained approximately 90% of the drug.

Although pellets made with different materials showed few differences, there were significant differences due to high levels of drug loading. Shape analysis of spheres with drug concentrations of 25% to 90% showed statistically significant decreases in roundness when concentrations exceeded 70%. While mean shape factors for other potencies ranged from 0.828 to 0.844, those containing 90% drug averaged only 0.785, a marked decrease ($p = 0.004$). The worst average shape factor for a single batch was 0.695 (90% drug, 10% Avicel PH-102). By comparison, a shape factor of 0.868 was the highest attainable mean for any single batch, and some individual pellets had shape factors as high as 0.898.

CONCLUSIONS

Fluidized-bed centrifugal pelletization is an efficient, reproducible technique for the production of drug-loaded spheres without starting seeds. With proper choice of starting materials, the process can result in elegant, durable pellets containing up to 90% drug. This study found that larger-sized particle grades of both drug and excipient materials worked best. Micronized theophylline was much more difficult to process and could only produce pellets of modest potencies.

Once formed, the pellets themselves had similar characterisitics, regardless of the starting materials used. There was, however, a deterioration in sphericity when drug concentrations exceeded 70%.

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