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Feasibility Studies in Spheronization and Scale-up of Ibuprofen Microparticulates Using the Rotor Disk Fluid-Bed Technology

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ABSTRACT The aim of this study was to develop spheronized microparticulates as a drug delivery system using the 1-step closed rotor disk fluid-bed technology, and to scale up the batch spheronization process. Ibuprofen was used as the model drug and microcrystalline cellulose/sodium carboxymethyl cellulose hydrocolloid (Avicel® RC-581 or CL-611) was present as the diluent/binder. The mixture, in 1:1 ratio, was blended with and without 1% sodium lauryl sulfate (SLS) and spheronized with the rotor disk insert, using either water or hydroxypropylmethyl cellulose (HPMC) as binder. Fluid-bed machines (Vector/Freund Flo-Coater model) FLM-1 (with 9-inch rotor insert for 0.75 kg) and FLM-15 (with a 12-inch and 19-inch rotor inserts for 1 kg and 5, 10 kg, respectively) were used. The critical process parameters included inlet air temperature, rotor disk speed and configuration, air flow, and rate of binder application. The 1 kg batch containing SLS that was made with 12-inch smooth stainless steel or waffle teflon plates rotating at 500 rpm had desirable characteristics. The sphericity values were 0.88 and 0.91, with percent yield of 85.4 and 91.2 and drug content values of 94.47% and 91.44%, respectively. The spheroids showed good flow properties with respective rapid drug release (Q20 = 83.27 and 91.75). No difference was seen in the Avicel RC-581 and CL-611. Based on the 1 kg data, Avicel RC-581 and smooth stainless steel and waffle teflon plates (12 inch and 19 inch), the batch was scaled up to 5 and 10 kg. The scale-up parameters included rotor speed (124 -300 rpm) and spray rate (90-140 g/min). The scale-up batches had similar flow characteristics, release rate, and size distribution. The geometric mean diameter increased as batch size increased, and slightly bigger spheroids were obtained using the waffle teflon plate. Ibuprofen spheres with very good physical characteristics were developed using the rotor disk fluid-bed technology, a 1-step closed process that did not require additional unit processes.

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INTRODUCTION

Spheroids are a multiparticulate drug delivery dosage form that could offer not only therapeutic advantages, such as less irritation of the gastrointestinal tract, but also key processing advantages. They demonstrate better flowability, provide less friable microparticulates, can have a narrower particle size distribution, have a very low percentage of fines, and are easy to coat and encapsulate. Moreover, they are suitable for multiple dosage forms because of their spherical shape, their mechanical properties, and their ability to readily release their active constituents [1] from hard gelatin capsules, tablets, and sprinkles.

Extrusion spheronization has been described as the most popular method of producing pellets [2], and the method of choice in the preparation of spherical particles [3]. However, this traditional spheronization method involves 4 different steps:

granulation, extrusion, spheronization, and drying. The success or failure of each of these steps affects greatly the quality of the final pellets or spheres. In contrast, rotor disk fluid-bed technology is a 1-step closed process in which the binder solution is added at a fixed rate onto the powder blend in the fluid bed rotor (a kind of spheronizer). The particles are agglomerated and spheronized simultaneously [2]. This is followed by drying (by inlet air) of the spherical particles until the desired final bed moisture is reached. The fluid-bed technology has been developed to involve the rotor module for several different manufacturing processes [4,5], which now include spheronization.

As shown in Figure 1, rotor disk spheronization is centered around the rotor plate insert, where disk rotation adds centrifugal force to the material on it. As the powder is sprayed tangentially, it is wetted and rolls to the outside of the disk by the centrifugal force (F_c) into a vertical moving air stream (F_v) caused by a gap around the plate, then falls back toward the center of the disk by gravity (F_g), thereby creating a rope-like motion [6]. This process has been demonstrated to be reproducible at the development and pilot stages. Tangential spraying has been shown to be a good choice for producing spheroids that can be coated for controlled release in the same rotor insert [6-8]. Moreover, the prepared spheroids are reported to have a surface morphology (less porous and more spherical) that is more suitable for coating than that of spheroids prepared through a top-spray process.

Scale-up of a process or batch is studied to determine the operating conditions applicable to large-scale production batches, with the goal of obtaining products of the same quality based on previously optimized laboratory -scale experiments. Scale-up of processes that involve powder handling is especially difficult because the dynamic behavior of powders is not very well understood. Moreover, when scale-up is applied to granulation process, the effects of the operational variables on powder properties and granule growth are not clearly known [9]. Therefore, although scale-up processes of materials in the solid state can be based on dimensional analysis, mathematical modeling, and computer simulation, most of the work in this field still depends on trial and error and the principles of geometric similarity [10]. The latter describes the interrelationships among system properties on scale-up; thus, the ratio of some variables in small-scale equipment should be equal to that of similar variables in equivalent larger-scale equipment [11].

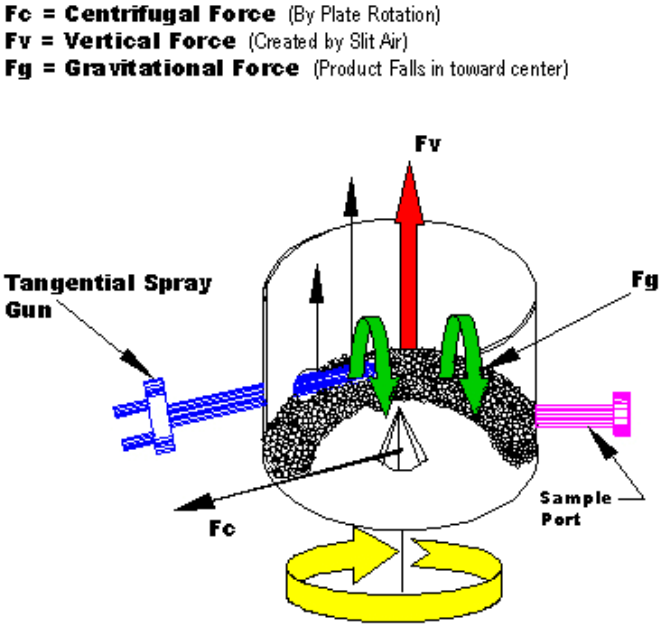

Figure 1 - Schematic representation of rotor disk granulator using tangential spray gun.

Dimensional analysis is an algebraic treatment of variables affecting a process. It does not result in a numerical equation, but experimental data are fitted to an empirical process equation that results in scale-up being achieved more readily. Past experience is required in handling the numerous problems encountered during scale-up in drug development [12].

The aim of this study was to determine the feasibility of developing and scaling up spheronized microparticulates as a drug delivery system using the rotor disk fluid-bed technology and ibuprofen as the model drug.

MATERIALS AND METHODS

Materials

Ibuprofen powder was obtained from Albemarle Corporation (Baton Rouge, Louisiana); Methocel E5 LV or HPMC was purchased from Dow Chemical Co. (Midland, MI), while Avicel® CL-611 and RC-581 were donated by FMC Biopolymer (Princeton, New Jersey). SLS and talc of pharmaceutical grade were bought from Spectrum (Gardena, CA). Carbowax or polyethylene glycol (PEG) was purchased from Union Carbide Corp. (Danbury, CT). Monobasic potassium phosphate, sodium hydroxide pellets, and all other materials and solvents of the highest-purity grade were bought from Fischer Scientific (Hanover Park, IL).

Equipment

Fluid-bed machines Vector/Freund Flo-Coater models FLM-1 (9-inch rotor insert) and FLM-15 (12-inch, 19-inch rotor inserts) were used on site in Vector Pharmaceutical Services in Cranbury, NJ.

Blending and spheronization

Trial spheronization was made on FLM-1 equipment using a teflon plate (9-inch) and a 0.75-kg batch of ibuprofen and RC-581 (1:1), with 1% SLS. Spheroids were successfully made, with the results showing that using our materials, the amount of water needed to provide appropriate consistency was between 50% and 52% of the dry mixture. Based on this, FLM-15 with 12"-inch or 19"-inch plates (Figures 2A and B) was used for 1-, 5-, and 10-kg batches.

Weighed amounts (1:1) of ibuprofen and Avicel® RC-581 or CL-611 sieved through a 16- mesh sieve were blended with and without 1% SLS, and spheronized in FLM-15 using water or HPMC solution as a binder. The critical process parameters are shown in Table 1. The inlet and exhaust flaps were kept open and a frequency drive device was used to fine-tune the control of the air flow. Fluidization of powder blend was achieved by heated air drawn through the gap around the rotor disk. The air volume and velocity of air can be adjusted with the gap-adjustment ring below the disc. This aids in air distribution while the rotor disc is spinning in a clockwise direction. The fine powders, lifted up by the fluidization air, are restricted by polyester air filters (which are intermittently cleaned or cleared by a pulsating jet of air), then returned to the batch. Drying was performed at gradual inlet temperature increases of 10°C every 5 minutes up to 60°C, and until a 50°C product temperature was reached. This staged drying was done to prevent case hardening of the spheroids. The loss on drying (LOD) was measured using a moisture balance (Mettler Pm100 and LP16, Mettler, NJ) at 85°C and the value recorded when it became constant.

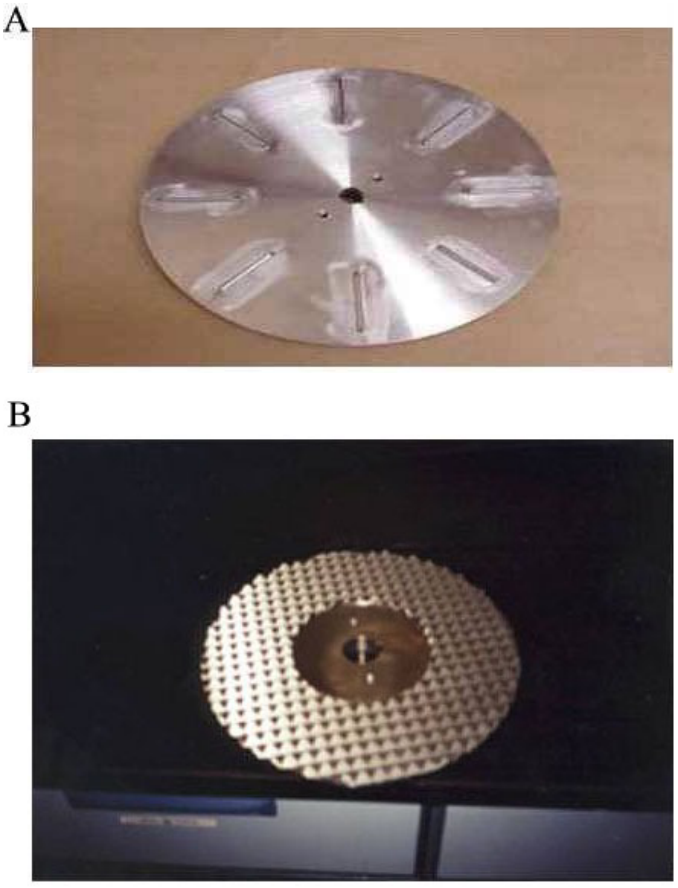

Figure 2 - Rotor disk plates for fluid-bed machines: stainless steel/smooth (A); waffle/teflon (B).

Eleven preliminary 1-kg batches were investigated using formulation and process variables as shown in Table 1. Consequent to data analyses, 8 (trials 1-8)

of the 1-kg batches were replicated twice and analyzed further. This will be discussed under the Results section. Two of these batches (trials 4 and 7) were used to make replicate scale-up batches of 5-kg and 10-kg (trials 12-15) as a result of product

Table 1 - Process and Formulation Variables*

Variable		Batch Number										
Function	Type	1	2	3	**4	5	6	**7	8	9	10	11
Surfactant	SLS (1%)‡	x		x	x	x	x	x	x	x	x	x
Avicel type	CL-611			x								
	RC-581‡	x	x		x	x	x	x	x	x	x	x
Plate material type	*SS‡	x	x	x	x	x	x			x	x	x
	*Teflon‡							x	x			
Plate contour	*Smooth‡				x					x		
	Waffle	x	x	x		x	x	x	x		x	x
Speed (rpm)	*500‡	x	x	x	x		x	x			x	x
	650					x			x	x		
Binder type	*Water‡	x	x	x	x	x		x	x	x	x	x
	HPMC (5%)						x					
Coating	PEG (25%)										x	
Lubricant	Talc (3%)											x

Ibuprofen : Avicel (1:1)

* : Variables used in scale-up
** : Scale-up batches
SS ; Stainless steel

characteristics (yield, particle size, size distribution, sphericity, etc.). Scale-up was based on geometric similarity using the plate radius (R) and centrifugal force (F_c) as similarity factors. This is shown in equations 1 and 2, modifications of the Froude-number equation as reported by Horsthuis et al [13] for rotational speed (V) and centrifugal force, respectively.

$$V = \sqrt{\frac{Fc * R}{W}} \quad (1)$$

$$Fc = \frac{W * V^2}{R} \quad (2)$$

The centrifugal force is directly proportional to the weight (*W*) of the powder blend and the square of the rotational speed and inversely related to the plate radius. The force was calculated for a 1 kg batch at 500 rpm to be 41,667 Newtons. Using this value, the rotational (rotor) speeds during the spheronization phase for 5 kg and 10 kg batches were calculated, with the value of the 5 kg batch rounded up to 300 rpm (Table 2). However, for the drying of the scale-up batches, a reduced rotor speed was used.

Based on the results of the 1 kg batches, and using the air volume indicator present on the equipment, the air volume that gave the desirable fluidization for the scale-up batches was obtained visually by tuning the frequency drive of the exhaust blower to balance the air volume and velocity [11]. This correlated with an increased air volume of 10 cfm for each additional kilogram of powder. The spray rate multiplier for the scale-up batches was determined as the ratio of the 2 air volumes needed for fluidization of both batches, which can also be calculated from known values using equation 3 [11]:

$$B_2 = \frac{A_2 * B_1}{A_1} \quad (3)$$

where A_1 and B_1 are the air volume and binder addition rate, respectively, of the 1-kg batch, while A_2 and B_2 refer to the same parameters for subsequent scale-up batches.

Yield of microparticulates

The yield of the spheroids was taken as a percentage of the ratio of the final weight obtained after the production processes and the initial weight of the powder blend before final sizing.

Table 2 - Spheronization Conditions and Process Parameters

	Parameters			
Batch size		1 kg	5 kg	10 kg
Plate size		12"	19"	19"
Centrifugal force (N)		41,667	41,667	41,667
Plate material type/contour		Stainless steel/smooth	Stainless steel/smooth	Stainless steel/smooth
		Waffle/Teflon	Waffle/Teflon	Waffle/Teflon
Spraying				
	Air volume (cfm) A_1 and A_2 values	50	90	140
	Plate gap (mm)	0.8	3.5	6
	Spray rate (g/min) B_1 and B_2 values	50	90	140
	Rotor speed (rpm)	500	300	200
	Inlet air temperature (°C)	25-30	25-30	25-30
	Product temperature (°C)	18-22	18-22	18-22
	Atomization air pressure (psi)	45	45	45
Drying				
	Air volume (cfm)	85	145	220
	Plate gap (mm)	1.3	5.0	8
	Rotor speed (rpm)	150	124	124

Particle size distribution

The size distribution of the microparticulates was determined using conventional sieve analysis. Spheroids with size ranges between 250 µ and 850 µ (20/60 mesh size) comprising at least 85% of the batch were considered usable products. The percent frequency was the proportion of spheroids obtained in the different sieves relative to the total amount of particles used for the analysis. Using the frequency data, the log-normal distribution on a probability scale was plotted and the geometric mean diameter (*dg*), and the geometric standard deviation (d_g) were calculated.

Density of the spheroids

True density (Wt/V_s) was determined from the sample mass and volume using a Quantachrome multipychnometer® (Vincentown, NJ). The system and samples of known weight (Wt) were purged off of contaminated gas, moisture, and vapor for a minimum of 20 minutes by placing the latter in the instrument using helium as the gaseous medium. Sample volume (V_s) was calculated from cell and reference volumes (V_c and V_r, respectively) obtained by calibration of a reference spherical material, using the protocols and the equation given in the manufacturer's protocol:

$$V_s = V_c - V_r\left[\left(\frac{P_1}{P_2}\right) - 1\right] \qquad (4)$$

where P_1 and P_2 are the pressures obtained from the reference and cell volumes, respectively.

Drug content assay

Standards were prepared in triplicates using a concentration range between 2.5 and 1000 µg/mL of methanol. The regression equation was linear, with a correlation coefficient (R^2) of 0.9998.

The determination of ibuprofen in the spheroids was conducted by extracting the drug twice from known sample weight of the product using 3 mL methanol. Fifty microliters of the extract was directly injected into the the high pressure chromatography column (HPLC) - Shimadzu Scientific Instruments, Columbia, MD, consisting of C18 reverse phase column (100 x 46 mm, 5 µm, Phenomenex,Torrance, CA). Known standard concentrations of ibuprofen were injected separately and analyzed simultaneously with samples. The HPLC method [14] is a modification of Tsao and Savage [15], in which the mobile phase consisted of acetonitrile:water:glacial acetic acid:triethylamine (600:400:1:0.2). The mobile phase was vacuum filtered and degassed simultaneously using a Branson 3200 ultrasonicator (Danbury, CT). Ibuprofen was monitored by UV detector at 265 nm wavelength, and the results were reported as the means of data from 6 replicates of 2 batches.

Dissolution

The dissolution of the produced microparticulates was carried out using the USP apparatus I at a rotation speed of 100 rpm. Known amount of sample was weighed into 3 x 2- cm diameter stainless steel minibaskets with 40 mesh screens that held each sample in the 6 flasks. A 1 mL sample was collected at specific intervals and filtered immediately using a 5 mm hydrophilic nylon filter membrane (B. Braun Medical Inc., York, UK). Simulated intestinal fluid (USP) containing 0.02% Tween 80 (enzyme grade) at pH 7.4 ± 0.05 was used as the dissolution medium with a temperature of 37 ± 0.1 °C. Fifty microliters of the samples were analyzed by HPLC with ibuprofen concentration monitored by UV detector at 265 nm. The results were reported as the means of data from a minimum of 10 dissolution vessels (± 2.10-13.00).

Carr's index determination

The bulk and tap densities of the pellets were determined with Vanderkamp® Tap density tester (Van-Kel Industries, Edison, NJ). The Carr's compressibility index was calculated using the following equation:

$$\%C = \frac{D_r - D_B}{D_T} * 100 \qquad (5)$$

where C is the compressibility index while D_T and D_B are tap and bulk densities, respectively. From the Carr's index the powder flow properties were estimated.

Granule friability test

The friability tester of tablets was used to test the resistance of the pellets to abrasion. Size fraction of 250 μ to 850 μ used for the test with a Erweka Roche friabilator (Apparate-bau-Gm.bH, West Germany) was subjected to a falling shock for 15 minutes at 30 rpm, then sieved for 10 minutes and the weight loss was recorded.

Sphericity and roundness of spheroids

Sphericity and roundness were determined using an image analyzer (Quantimet 500, Leica, Cambridge, UK) interfaced with a microscope (Reichert, Bordersen Instrument, Valencia, PA) in which the roundness, perimeter (P_M), and particle projected area (A) were measured. These were used to calculate sphericity (S), a reciprocal of the roundness factor, as shown in equation 6 below [16]:

$$S = \frac{4A * 3.142}{P_M{}^2} \qquad (6)$$

A perfectly spherical particle will have a value of 1.0, while a nonspherical particle will have a value of 0.1.

Scanning Electron Microscope

The samples were placed on a sample stub containing double-sided transparent adhesive tapes. They were then coated under reduced pressure (~0.8 mbar) with gold for 2 minutes using a Cressington Sputter Coater 108 (Franklin Electric, Bluffton, IN) and observed under a scanning electron microscope (Hitachi S510, Tokyo, Japan) at 10 kV.

Flowability

Weighed amount of spheroids was gently poured into an 8-oz mounted funnel with the orifice covered. The covered end was gently opened so that the spheroids flowed freely onto a dark surface. The diameter and height of the spheroids were measured and the angle of repose calculated using the following equation:

$$\theta = \left(\frac{H}{R}\right)\tan^{-1} \qquad (7)$$

where θ is the angle of repose, and H and R are the height and radius, respectively, formed by the spheroids. The results reported are the means of 6 replicates of 2 batches.

Statistical analysis

The influence of the independent variables on the pellet characteristics was analyzed by standard deviation and relative standard deviation, while the yield variable was also analyzed by Student t test and 1-way analysis of variance (ANOVA) techniques using the JMP IN© version 3.2 statistical software (SAS Institute, Cary, NC).

RESULTS AND DISCUSSION

Physical characteristics of spheroids

The characteristics are for all the different scale levels, (1 kg, 5 kg, and 10 kg), unless otherwise stated.

Yield of spheroids

One-kilogram batches

The 8 selected 1-kg batches had yield values ranging from 58.0% to 91.2%; however, most of the batches yielded spheroids varying from 74% to 85% (Table 3A). This could be considered satisfactory since even with starting materials that are "ideal" in formulating spheres (eg, for 100% Avicel, the

Table 3A - Product Characteristics of 1-Kg Batches

Parameters	Trials (as in Table 1)							
	1	2	3	4	5	6	7	8
% Yield	73.75 ± 2.33	58.0 ± 4.24	71.45 ± 3.89	85.40 ± 6.65	70.10 ± 2.55	80.0 ± 10.32	91.2 ± 32.24	79.05 ± 1.34
% LOD	1.75 ± 0.35	6.56 ± 2.34	1.66 ± 0.91	2.71 ± 1.70	2.96 ± 2.20	2.1 ± 0.43	6.85 ± 2.34	8.1 ± 4.10
% Drug content	93.46 ± 1.17	73.77 ± 3.32	91.69 ± 2.09	94.47 ± 0.65	94.30 ± 3.88	94.3 ± 8.48	91.44 ±1.64	99.95 ± 4.08
Geometric mean diameter (μm)	438 ± 1.57	577 ± 1.43	445 ± 1.59	455 ± 1.57	363 ± 1.95	403 ± 1.63	417 ± 1.80	415 ± 1.78
Sphericity	0.90 ± 0.00	0.92 ± 0.01	0.89 ± 0.01	0.88 ± 0.09	0.87 ± 0.04	0.84 ± 0.01	0.91 ± 0.00	0.90 ± 0.01
Flowability (deg)	21.45 ± 1.05	23.07 ± 0.14	22.09 ± 1.88	23.36 ± 0.75	25.31 ± 1.06	24.84 ± 0.00	22.49 ± 0.83	24.37 ± 0.40
Carr's index (%)	8.56 ± 0.76	6.61 ± 0.4	9.85 ± 0.21	8.92 ± 3.97	9.34 ± 0.05	11.82 ± 1.19	8.92 ± 0.53	10.14 ± 0.25
True density (g/cm^3)	1.29 ± 0.00	1.30 ± 0.00	1.29 ± 0.00	1.30 ± 0.00	1.29 ± 0.01	1.28 ± 0.01	1.31 ± 0.01	1.28 ± 0.00
Bulk density (g/cm^3)	0.67 ± 0.00	0.77 ± 0.02	0.69 ± 0.02	0.64 ± 0.08	0.67 ± 0.05	0.58 ± 0.01	0.66 ± 0.01	0.67 ± 0.00
Q20 (%)	86.74 ± 2.39	74.66 ± 2.92	87.47 ± 4.12	83.27 ± 5.02	90.42 ± 7.64	75.14 ± 1.85	91.75 ± 2.10	85.09 ± 1.71
Friability (%)	0.34 ± 0.47	0.67 ± 0.48	0.17 ± 0.24	1.5 ± 1.66	1.67 ± 1.41	1.17 ± 0.71	0.33 ± 0.71	1.84 ± 0.71

LOD: % loss on drying Two replicate batches used for all trials

process output was approximately 80%) [17]. We also observed that spheroid batches having 50% to 52% binder content at the end of the spheronization process had better product characteristics.

Effect of SLS. The lower yield obtained from trial 2 without SLS (Table 3A) as well as that containing SLS and talc (results not shown) could be due to delay in wetting of the granules during processing, that led to loss on fluid-bed walls and filters.

Binder effect. Use of HPMC as binder improved the yield compared to the standard formulation (Table 3A, trial 6 vs 1). However, there was agglomeration.

Rotor speed effect. Lower disk speed (500 rpm) produced higher yields than higher disk speed (650 rpm, Table 3A, trials 1 and 7 vs 5 and 8, respectively). This could be due to the lower centrifugal forces, which caused the spheres not to collide and agglomerate with the walls of the rotor container, but to be fluidized more efficiently as a result of the reduced rotor speed, as has been reported with the traditional extrusion/spheronization method [18]. Ideal product movement in the rotor increases potential efficiency, thus the need for empirical determination overrides strictly mathematical scale factors.

Rotor disk plate material effect. Higher yield was obtained from the waffle teflon plate batches in comparison to those made with stainless steel waffle plate (trials 7 and 8 vs 1 and 5, respectively). The LOD values for the 2 plates ranged between 6.85% and 8.10% compared to 1.75% and 2.96%, respectively. The higher LOD for the teflon plate could have contributed to the increase in the yield value. The teflon disk tends to insulate the bed from some of the drying medium, thus retaining a higher moisture level, whereas the stainless steel disc allows for better conduction of heat and consequently better heat transfer and drying.

Scale-up batches

The two 1 kg-batches (trials 4 and 7) selected for scale-up (smooth stainless steel 500 rpm and waffle teflon 500 rpm) are highlighted in Table 3B. The scale-up batches were trials 12 and 13 for the stainless steel smooth plate and trials 14 and 15 for waffle teflon plate. The yield values were similar for 1, 5, and 10-kg for the batches made with stainless steel smooth plate: 84% -to 87% (Table 3B). For the teflon plate, the values were higher (88% -96%) than those of the stainless steel plate, though with higher LOD values as mentioned earlier. However, Student t test and 1-way ANOVA of the teflon plate data did not indicate any statistical difference between the yield result

Table 3B - Product Characteristics of 1-Kg Batches

Plate material/contour	Stainless steel/smooth plate			Teflon/Waffle plate		
Batch Size	1 kg	5 kg	10 kg	1 kg	5 kg	10 kg
Trials (as in Tables 1 and 3A)	4	12	13	7	14	15
Plate Size	12"	19"	19"	12"	19"	19"
% Yield	85.40 ± 6.65	87.16 ± 7.13	83.97 ± 2.33	91.2 ± 32.24	96.35 ± 5.5	87.84 ± 11.47
% LOD	2.71 ± 1.70	1.85 ± 0.35	2.46 ± 0.64	6.85 ± 2.34	11.21 ± 7.62	10.65 ± 11.10
% Drug Content	94.47 ± 0.65	99.2 ± 4.90	90.52 ± 4.71	91.44 ± 1.64	98.23 ± 1.89	98.65 ± 4.37
Geometric Mean Diameter (μm)	455 ± 1.57	483 ± 1.61	545 ± 1.67	417 ± 1.80	553 ± 1.54	603 ± 1.79
Sphericity	0.88 ± 0.09	0.90 ± 0.01	0.90 ± 0.01	0.91 ± 0.00	0.89 ± 0.01	0.88 ± 0.02
Flowability (deg)	23.36 ± 0.75	19.54 ± 1.08	24.11 ± 5.39	22.49 ± 0.83	19.29 ± 0.73	25.17 ± 7.59
Carr's index (%)	8.92 ± 3.97	6.71 ± 1.23	6.21 ± 4.3	8.92 ± 0.53	5.33 ± 0.19	7.84 ± 2.75
True density (g/cm^2)	1.30 ± 0.00	1.283 ± 0.01	1.284 ± 0.02	1.31 ± 0.01	1.281 ± 0.01	1.272 ± 0.01
Bulk density (g/cm^2)	0.64 ± 0.08	0.65 ± 0.03	0.64 ± 0.004	0.66 ± 0.01	0.67 ± 0.01	0.63 ± 0.00
Q20 (%)	83.27 ± 5.02	82.95 ± 12.66	85.53 ± 5.08	91.75 ± 2.10	79.47 ± 12.88	86.76 ± 13.00
Friability (%)	1.5 ± 1.66	1.50 ± 1.65	1.50 ± 1.17	0.33 ± 0.71	1.00 ± 0.00	4.0 ± 4.71

LOD: % Loss on drying. Two replicate batches used for all trials.

presented in Table 3B ($P < 0.05$). Nevertheless, some measures will be taken in further processing to ensure that the LOD of all future batches would be = 5% at the drying end point. There is statistically no difference between 10 kg, 5 kg, or 1 kg of the teflon batches' LOD.

Drying time

The time it took for the product made with similar plates to reach 50°C increased as percentage yield and batch size increased. For the batches made with stainless steel smooth plates, the times were 29 to 40 minutes for the 1 kg batches and 36 to 79 minutes for the scale-up batches. For waffle teflon plate batches, the drying times were 47 to 64 minutes for the 1-kg batches and 47 to 90 minutes for the scale-up batches. Not only are these results in agreement with previous reports that drying efficiency decreases with increased batch size [18,19], but, as mentioned earlier, the data also confirmed that the heat conductivity of the stainless steel disk added to the overall drying efficiency of the process, while teflon had an insulating effect.

Moreover, it has been shown that at any given time, the moisture content of the granules depends on wettability and evaporation, which in turn are controlled by liquid flow rate and inlet temperatures, respectively [20]. Equilibrium liquid flow rate has been defined as one at which liquid supply is balanced by evaporation, and critical liquid flow rate as one above which fluidization is impossible due to cohesion in the bed [21]. Though the liquid flow rate is the same in both plate types used, the insulating nature of the teflon material could hinder the achievement of equilibrium during processing, thereby affecting the balance between liquid supply and evaporation, which in turn might have adversely affected the drying efficiency of these batches.

Carr's index, flowability and true density

The low values of Carr's index (less than 15%) signify good flowability of the spheroids for all batches, since the angle of repose of all the formulations was less than or equal to 30° (± 0.13° to 7.59°) [22], (Tables 3A and B). As shown in Table 3A, the flowability was decreased by the use of HPMC (trial 6) and high rotor speed (trials 5 and 8) that could have resulted from the higher level of nonspherical and smaller geometric mean size of spheroids obtained from these variables,

respectively. Use of HPMC (trial 6) and high speed (trials 5 and 8) also increased the tap density and consequently increased the percent compressibility of the spheroids, thereby confirming the poor flowability of the products.

The results (means and standard deviations of 10 replicates from 2 batches) of the true densities before and after purging were practically similar, and almost identical results were obtained for all the batches (Tables 3A and B). From these results, it could be inferred that the samples have similar moisture content, indicating that the LOD (apart from influencing the yield that was measured immediately after production) might not have affected other product characteristics determined during storage at ambient conditions. Scaling up of batches did not affect the quality of the spheroids.

Drug content

With the exception of the batch without SLS (Tables 3A and B), the formulations contained 90.52% ± 4.71% to 98.65% ± 4.37% ibuprofen.

Friability

The percentage weight loss from the batches was generally less than 5% (± 0.00 to 4.71) as shown in Table 3A. However, increased rotor speed (trials 5 vs 1 and 8 vs 7), use of HPMC (trial 6 vs 1), and use of different plate contours (trial 4 vs 1) increased the friability due to attrition and weakly agglomerated particles.

Sphericity and morphology of the spheroids

The sphericity of the microparticulates was in the range of 0.84 ± 0.01 to 0.92 ± 0.01, which is close to 1.0, the optimal value for sphericity. In the 1-kg batches, the sphericity was reduced by the use of the binder HPMC (Table 3A), which, being a polymer, could cause more agglomeration of the particles during spheronization. Sphericity was not affected by the use of SLS, although SLS is supposed to enhance the wetting, which would enhance the formation of spherical particles [16].

Batch or process scale-up did not affect the sphericity of the spheroids (Table 3B). The results represented in Tables 3A and B are the means of sphericity of 30 to 60 randomly selected spheroids from replicate batches. Figures 3A-D showed typical morphology of 1-kg, 5-kg, and 10-kg batches of both plate material types, and the 1 kg produced with HPMC as binder (x 30 magnification). The magnified morphology of the produced microparticulates (x 200 magnification) are shown in Figures 4A-C.

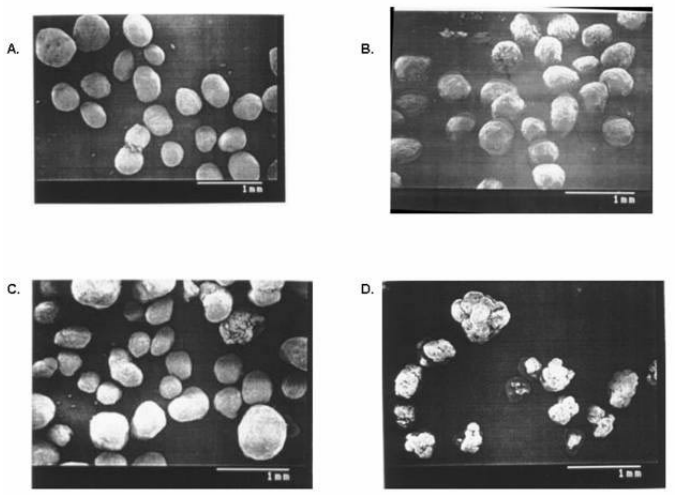

Figure 3-Typical scanning electron micrographs (x 30) of ibuprofen spheroids made with smooth stainless steel or waffle teflon plates: 1-kg (A), 5-kg (B), 10-kg (C), and 1-kg batch made with HPMC as binder (D).

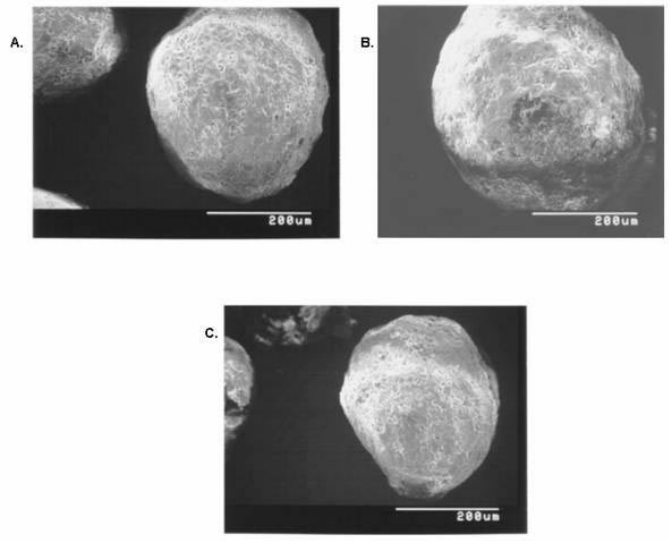

Figure 4 - Typical scanning electron micrographs (x 200) of ibuprofen spheroids, 1 kg (A), 5 kg (B), 10 kg (C).

Size distribution of spheroids

Size distributions for most of the batches depicted log normal distribution (results not shown), with the values of the 20/60 mesh products (usable fraction) ranging between 88% and 96%, except for the 1-kg batch made with stainless steel waffle plate at 650 rpm (trial 5) and that containing HPMC as binder (trial 6). The presence of surfactant (SLS; trial 1 vs 2) and binder (trial 6 vs 1) decreased particle size, as did the use of water (in the standard) as binder. Type of Avicel® hydrocolloid (trial 1 vs 3), and disk contour type (trial 4 vs 1) did not affect the distribution. Rotor speed (650 rpm) decreased the particle size of the products made with stainless steel plate compared to the 500 rpm used in the standard (trial 5 vs 1), while plate type slightly increased the particle size at higher speed (formulations 8 vs 5). The geometric mean diameters of the spheroids together with the geometric standard deviations are shown in Tables 3A and B. The particle size increased slightly with increase in batch size. The error bars did not show because of the very low geometric standard deviation (1.43-1.95).

The difference in size distribution between the batches could be attributed mainly to the formulation components and process variables, because the size distribution of the starting raw materials was kept uniform by sieving the powders through a 16-mesh size prior to blending and spheronization. The decrease in the mean diameter with increased rotor speed (trial 1 vs 5), could be due to surface defects on the pellets by the high speed, thereby producing more fines [2,23].

In the scale-up batches, the particle size, especially of the teflon plate batches, appeared to increase with larger batch size (Table 3B). This is due to greater attrition by the smaller -sized batches that are lighter, are more readily fluidized, and fall from higher heights during drying. The stainless steel batches had less attrition presumably because the spheroids dried up more easily than the products of equivalent batch sizes made with the teflon plate. Mean particle size also increased in the absence of SLS, probably due to decreased wettability that made these spheroids less vulnerable to attrition during drying. However, the 20/60 mesh sizes' yield in each of the scale-up batches was up to 85%, thereby meeting the set acceptance criteria. These observations, however, did not correlate with the report that the granule size is inversely related to the batch size [18], and the observations will therefore be further investigated.

Ibuprofen release from spheroids

The Q20 for all the formulations was 80%, which meets the Food and Drug Administration dissolution release specification for an immediate release product. The exceptions were the batches containing HPMC and that without SLS, which released 75% and 74% ibuprofen, respectively, at the same time -20 minutes (Tables 3A and B, and Figures 5A and B). The variability between the replicate batches was generally around 5%. The slower release from spheroids made with HPMC as binder or in the absence of SLS could be attributed to densification, larger particle size and reduced surface area of the spheroids that consequently retarded diffusion. There was no difference in drug release in batches made with Avicel® RC and CL cellulose types, contrary to previous reports in which extrusion spheronization technique was used [24, 25, Table 3A]. There were also no changes in drug release beyond 60 minutes.

Generally, the batch size appeared not to affect the characteristics of 5-kg and 10-kg batches using the 19-inch plate. In a previous report involving traditional extrusion/spheronization [18], it was shown that undesirable product qualities could result if inappropriate plate size was used relative to batch size. This is because at too low a load, there are relatively insufficient granules to interact with each other, thereby leading to poor particle/particle interaction, while the opposite is true at high loads.

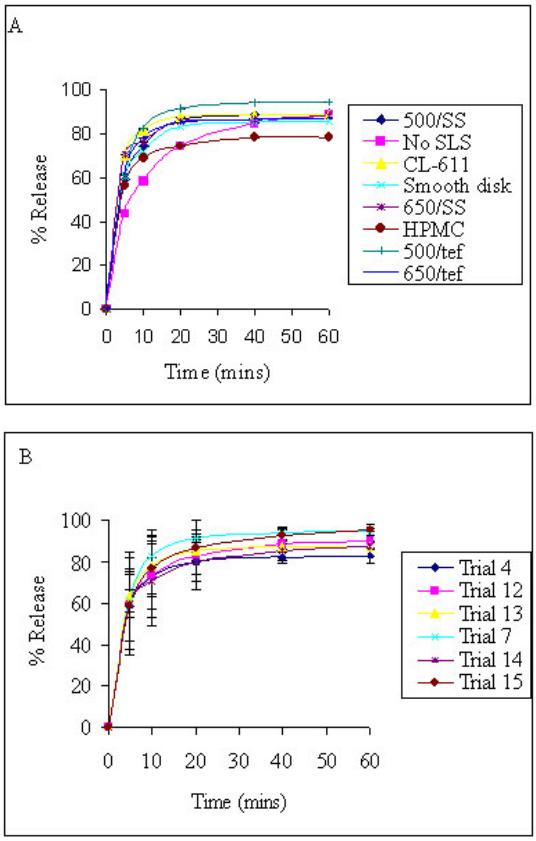

Figure 5 - Profiles of 1-kg replicated batches (A); profiles of scale-up batches (B). Trial 4: SS/1 kg; trial 12: SS/5 kg; trial 13: SS/10 kg; trial 7: Tef/1 kg; trial 14: Tef/5 kg; trial 15: Tef/10 kg. HPMC indicates hydroxypropylmethyl cellulose; SLS, sodium lauryl sulfate; SS: stainless steel/ smooth; Tef: waffle teflon.

CONCLUSION

Ibuprofen spheres with very good physical characteristics were developed using the rotor disk fluid-bed technology, a 1-step closed process that did not require additional unit processes. Based on plate radius and centrifugal force used as similarity factors for scale-up, the batch size and process could be scaled up to 5 x and 10 x.

An attempt to simultaneously characterize spheronized ibuprofen granules, investigate process parameters and scale-up the batch has been made. Further efforts will be centered on experimental design for critical study of important process variables and formulation on scale-up and coating for slow release properties.

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