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COMPARISON OF MILLING PROCESSES: BALL MILL VERSUS AIR CLASSIFYING MILL

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ABSTRACT

A study was initiated to compare the milling process and equivalence of mills for milling a fibrous material. In this study, milling processes using either a ball mill (Abbe Model Number 2) or an air classifying mill (Mikro ACM 10) were compared. Samples from both processes were evaluated by appropriate physical and chemical analyses such as particle size, surface area, densities, and potency. The particle size distribution and surface area analysis showed equivalence between the two milling processes. Scanning electron micrographs (SEM) showed that the samples had similar morphology. The potency of samples obtained from either of the milling processes was not affected by differences in the milling processes. In

addition, results of milled samples that were subsequently granulated and compressed into tablets showed no difference in assay, content uniformity or disintegration time. Based on these results, it is concluded that the ball mill and the air classifying mill produce material that is equivalent in terms of physical and chemical properties, and therefore the processes of milling are interchangeable.

INTRODUCTION

This study was initiated to compare the milling process of the ball mill with an air classifying mill. A low dose, high potency fibrous material was chosen as the model compound. Ball mills are not used extensively in the pharmaceutical industry, but from a theoretical point of view they exemplify the principle of particle diminution (1). Most of the size reduction methods rely on mechanical forces to produce stresses within particles leading to breakage (2). The ball mill is a cylindrical or conical shell usually filled to about half its volume with balls of various composition. The shell rotates and the balls are made to climb the shell walls as a result of rotation, and drop from their elevated position to the bed of media, resulting in the primary means of particle fracture by impact. The ball mill is designed for batch milling. In ball mill technology, it is not single particles that are stressed, but beds of particles (3). Though a basic assumption of first-order kinetics in ball mills can be made, the experimental results from breakage in a laboratory ball mill shows abnormal, significantly non-first order breakage when particle size becomes sufficiently large with respect to ball and mill (4). The wear in a ball mill occurs to the balls and to a lesser extent, to the grinding chamber wall. If these mills are lined with ceramic, and the same material is used for the balls, an iron-contamination-free grinding can be carried out.

In contrast to the principle means of ball mill technology, size reduction machines which have an air classifier integrated into them are known as classifying mills. Classifying mills operate with an internal grinding - classifying circuit with continuous discharge, during grinding, of the ground product which has already reached the desired particle size. These mills are used for the range of medium-fine to fine size reduction (5). The classifier initially classifies the feed material and sends the coarse particles to the pulverizer. The pulverizer uses large volumes of air to disperse the pulverized particles before they re-enter the classifier, thus only coarse particles stay in the pulverizer. As a result, the grinding efficiency is improved and requires less energy than a pulverizer system (6), whereas in ball mills, the bed of particles is impacted constantly at the expense of more energy. Air classifying mills have the flexibility of producing various particle sizes of powders, and are easy to clean and maintain from a current Good Manufacturing Practices (cGMPs) standpoint.

The purpose of this study is to compare the performance of a ball mill and an air classifying mill using a low dose fibrous material as a model compound. The model compound will be compared using the parameters of particle size, surface area, densities and morphology for the bulk drug substance, and the of assay, content uniformity, disintegration time and physical properties (e.g. hardness and thickness) for tablets composed of the milled model compound.

MATERIALS AND METHODS

A 400 Kg portion of the model compound was loaded into a ball mill (Abbe, Model Number 2 BM, Paul O. Abbe Inc., Little Falls, New Jersey), with circulation of water through the jacket of the ball mill. The material was milled until all of the sample passed through a number 60 U.S. mesh screen. This milling process took approximately 10 hours. The ball milled material was passed through a Fitzmill equipped with a #1 screen and operated at high speed, impact forward to de-lump the milled material. The milled material was then sampled for particle size, surface area, densities, morphology and chemical analysis for potency.

The air classifying mill (Mikro ACM 10, Micron Powder System, Summit, New Jersey) was used to mill a batch size of 70 Kg composed of the same lot of model compound used in the ball mill experiment. The material was charged into the grinding chamber of the mill at a constant rate. The material was milled to the desired particle size by controlling air supply and speed of the rotor and classifier. The throughput was approximately 40 kg/hour. During this milling process, the temperature of the product bed was maintained at 55°C as compared to a temperature of 35°C in the ball mill. This difference in temperature did not affect the stability of the model material. The milled material was collected in a bag collector (Model Number 36-1-130, Mikro Pulsaire, Summit, New Jersey). The milled material was then sampled for particle size, surface area, densities, morphology and chemical analysis for potency.

Particle size measurements were determined using a Malvern Laser Particle Size Analyzer (Model Number 2600 C, Malvern Instruments, Malvern, England). Surface area measurements were obtained using Brunauer-Emmett-Teller (BET) surface area analysis (Quantasorb Jr., Quantachrome Corporation, Syosset, N.Y.). The bulk and tap densities were also determined on all samples. The morphology of the particles were studied using scanning electron microscopy (Amray Model Number 1100 Amray Inc., Cambridge, Massachusetts). The chemical analysis for potency was carried out by digestion and assay by high performance liquid chromatography (HPLC).

Tablets were prepared using a wet granulation method produced by a high shear/low shear granulator. The tablets from both processes were monitored for physical parameters such as weight variation, hardness, thickness, friability and disintegration. The potency and content uniformity of the tablets were also determined.

RESULTS AND DISCUSSION

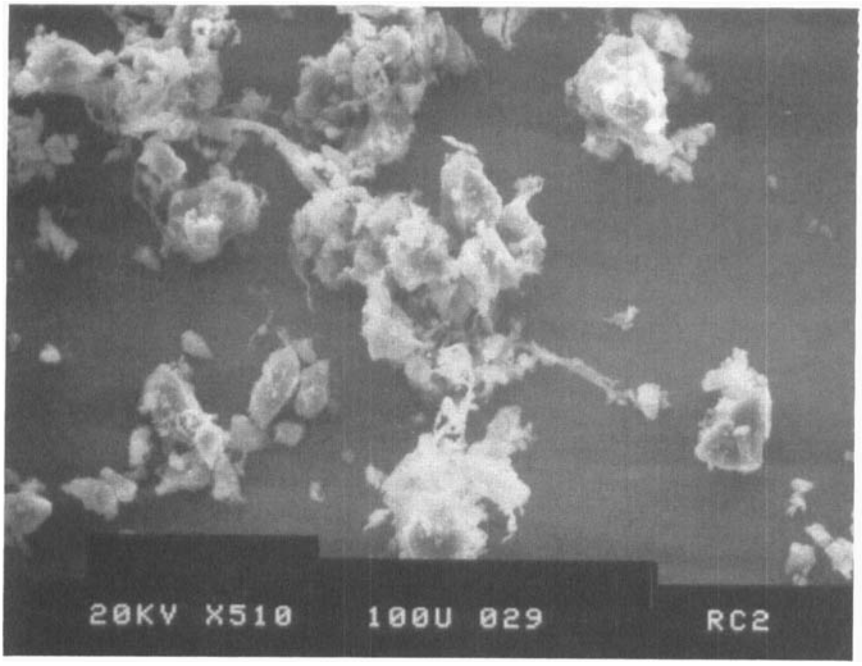
The results of the experiments indicate that the milled material from the air classifying mill has similar physical properties such as particle size, and surface area when compared to the material produced by the ball mill as shown in Table I. The target average particle size (M50) of 20 microns was chosen based on the reference sample material obtained from the ball mill. The milled material from the air classifying mill has an average particle size of 22 microns (M50) and 56 microns (M90) as compared to an average particle size of 14 microns (M50) and 43 microns (M90). This particle size was obtained in the air classifying mill using parameters of 400 CFM on the inlet air, 7000 rpm

TABLE I

Results of Milled Fibrous Material Processed by the Ball Mill and the Air Classifying Mill.

	Ball Mill	AIR CLASSIFYING Mill
Raw Material Lot Numbe	A	A
BULK MATERIAL		
Particle Size (micron)		
M 50	14	22
M 90	43	56
B E T surface Area (m^2/g)	2.13	1.73
Bulk Density (g/ml)	0.31	0.25
Tap Density (g/ml)	0.52	0.44
Assay (µg/mg)	2.9820	3.0481
TABLET		
Assay (µg)	8.55	8.15
Disintegration Time	9 minutes	7 minutes
Content Uniformity		
Average:	92.5%	91.3 %
RSD:	3.1%	3.0%

rotor speed and 2500 rpm of classifier speed. BET also indicates a surface area of 1.73 m^2/g for the material from the air classifying mill as compared to a surface area of 2.13 m^2/g for the material from the ball mill. These differences are not significant as they have not affected the distribution of this low dose, high



FIGURES 1(a-c)

Scanning Electron Micrograph: (a) Air classifying Mill Milled Sample at 510x Magnification; (b) Ball Mill Milled Sample at 480x Magnification; and (c) Unmilled Sample at 900x Magnification.

(continued)

potency model compound as shown by the content uniformity of the final tablets.

The bulk density of 0.25 g/ml and tap density of 0.44 g/ml for the material from the air classifying mill were slightly different when compared with the bulk density of 0.31 g/ml and tap density of 0.52 g/ml for the material from ball mill. Again these differences in densities did not affect any mixing conditions or parameters, and a uniform distribution of

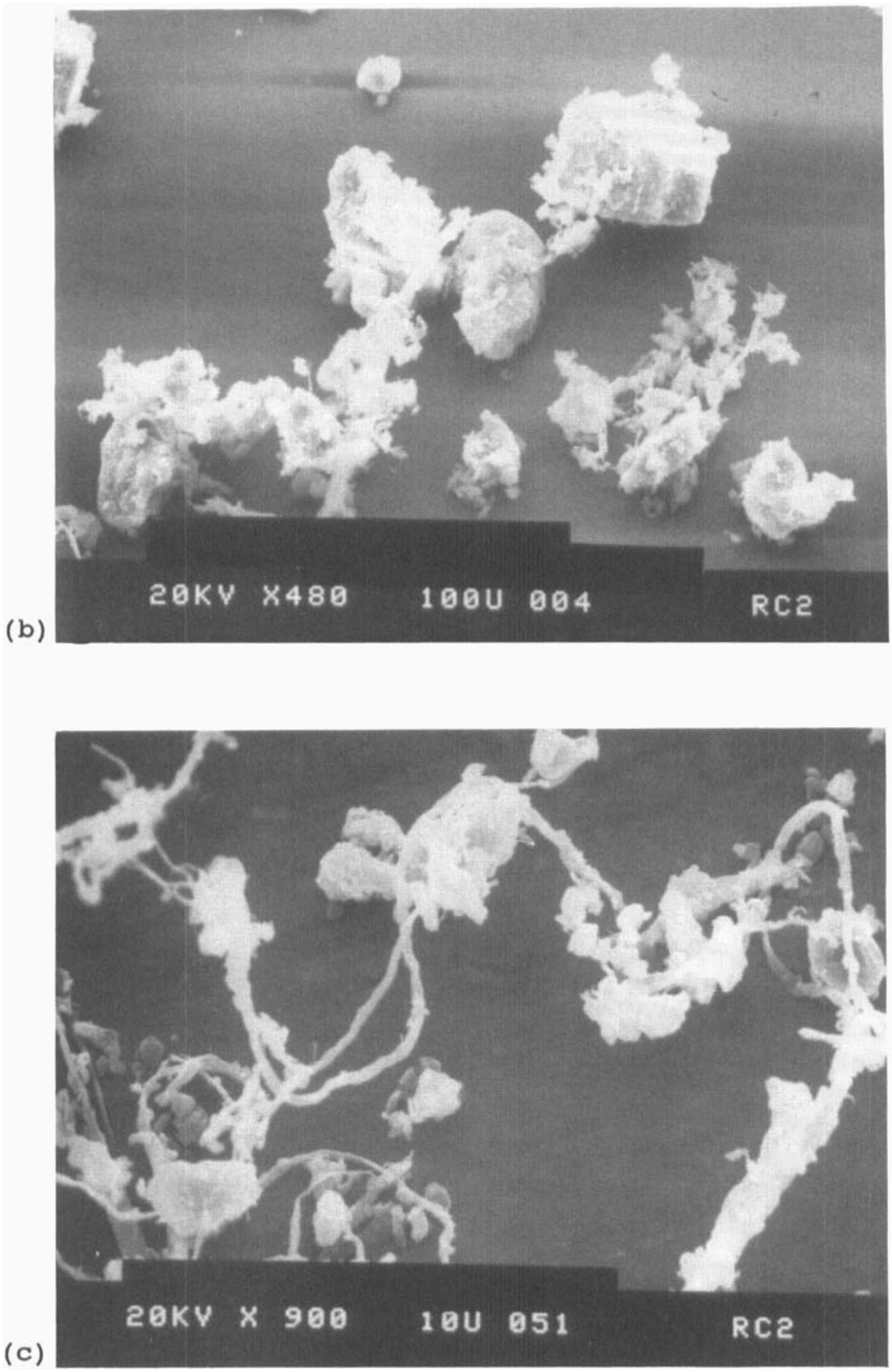


FIGURE 1. Continued

the active material during processing was achieved. SEM photographs at high magnification (480-510x) shown in Figures 1(a-c) demonstrate that the particles obtained from the air classifying mill have a similar morphology (Figure a) as compared to samples obtained from the ball mill (Figure b). SEM photograph (Figure c) of the unmilled sample material shows the fibrous nature of the model compound. In general, the particles from the two milled samples display a similar appearance and being a fibrous material, the physical similarities between the samples appear to be very close by microscopic examination.

The assay of 3.0481 µg/mg for potency for the material from the air classifying mill compares well with an assay result of 2.9820 µg/ml for the material from the ball mill taking into consideration that it is a low dose, high potency compound. The results of the assay for potency of both milled samples, as shown by the results in Table I, indicate that the change from the ball mill to the air classifying mill did not significantly affect the physical or chemical properties of the milled material even though the model material is most difficult to process because of its fibrous nature and its low dose . These attributes make it difficult to distribute the compound uniformly in the blend. It should be emphasized that this is a worst case study because the model compound is present in a fibrous matrix and present only approximately 8 µg per tablet. The tablets made using both milled materials were within specification for the typically measured parameters of assay, content uniformity and disintegration time as shown in Table I. The assay of 8.15 µg per tablet, a content uniformity of 91.3% (RSD ± 3.0%) and 7 minutes disintegration time for tablets processed using the material milled in the air classifying mill compares well with an assay of 8.55 μg per tablet, a content uniformity of 92.5% (RSD ± 3.1%) and 9 minutes disintegration time for tablets made with material from the ball mill. The assay, content uniformity and the disintegration time results of the tablets were very similar considering the low dose, high potency of the product. Improved pharmaceutical elegance and uniform color distribution were also noted for the tablets manufactured using the material from the air classifier mill.

Based on these results, it is concluded that the air classifying mill and the ball mill produce material that is equivalent in terms of physical and chemical properties, and therefore the processes of milling are interchangeable under these experimental conditions.

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