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COMPARISON OF MOISTURE-ACTIVATED DRY GRANULATION PROCESS WITH CONVENTIONAL GRANULATION METHODS FOR SEMATILIDE HYDROCHLORIDE TABLETS

Chih-Ming Chen*, Dhananjaya Alli,
Michael R. Igga, and Jeffrey L. Czeisler§

Berlex Laboratories, Inc.
Pharmacy R&D Department
Cedar Knolls, New Jersey 07927

ABSTRACT

During the development of a tablet formulation of a cohesive, fluffy investigational drug, a novel moisture-activated dry granulation (MADG) process was studied in comparison with two conventional granulation methods, i.e., wet granulation and dry granulation with a roller compactor, as well as with a direct compression formulation method. The MADG method produced granules with excellent flowability which were equivalent in a number of ways to those produced by either

§ Correspondence
* Current address: IVAX Labs., Product Development Department, Miami, Florida 33166

conventional wet granulation or dry granulation methods and which were much better than the powder blend from the direct compression formulation. The tablets prepared using the MADG method had better content uniformity than those made using material from wet and dry granulation processes. Other tablet properties, such as weight variation, friability and dissolution, were similar among the tablets produced by the four processes.

INTRODUCTION

Granulation is a commonly used process to improve the flow of powdered materials. In a tabletting process, the resulting flowable granules are essential for the continuous and rapid transport of materials through the hopper, into and through the feed frame, and into the dies of the tablet press. The many aspects of conventional granulation methods (e.g., dry granulation and wet granulation) have been reviewed by several authors.[1-3]

Sematilide hydrochloride, N-[2-(diethylamino)ethyl]-4-[(methyl sulfonyl)amino]-benzamide hydrochloride, is a new Class III antiarrhythmic agent. The initial solid dosage form for our studies is a capsule filled with material prepared using a wet granulation process because the bulk sematilide hydrochloride, which consists of fine needle-like crystals, is cohesive, is of low bulk density and is poorly flowable. However, there are two reasons for avoiding the use of a wet granulation process to prepare a tablet dosage form which will be a prototype for the final product: (1) drying a wet granulation is a time-consuming and costly process, and (2) case hardening, caused by

the high aqueous solubility of sematilide hydrochloride[4], can occur if drying conditions are not well-controlled. Therefore, other granulation methods were investigated. A novel moisture-activated dry granulation (MADG), prepared by the technique recently reported by I. Ullah, et. al.[5], was studied in addition to evaluating 1) an aqueous wet granulation, 2) a dry granulation prepared using a roller compactor, and 3) a direct compression formulation. All four formulations had very similar compositions.

In this paper, we report the comparative evaluation of the above four granulation methods based on the physical properties of the granules and the performance of the resulting tablets.

MATERIALS

Sematilide hydrochloride was supplied by our parent company. Excipients used in the experiments were: hydrous lactose, N.F. (Sheffield Products, Norwich, New York); Fast-Flo lactose, N.F. (Foremost Whey Products, Baraboo, Wisconsin); povidone, USP (K-29/31) and crospovidone, N.F. (GAF Corporation, New York, New York); microcrystalline cellulose, N.F. (Avicel PH-101 and 102, FMC Corporation, Philadelphia, Pennsylvania); colloidal silicon dioxide, N.F. (Cab-O-Sil, M-5, Cabot Corporation, Tuscola, Illinois); and magnesium stearate, N.F. (Mallinckrodt, Inc., St. Louis, Missouri).

METHODS

1. Preparation of Formulations

The respective compositions of sematilide hydrochloride tablets which were prepared using the various processes is shown in Table 1. The size of the batches was 1.5 kg.

TABLE 1
Composition Of Tablet Formulations For Various Granulation Processes

Ingredients	Percent Of Ingredient			
	MADG	Dry Granulation	Direct Compression	Wet Granulation
Active	25.0	25.0	25.0	25.0
Lactose	41.5[b]	44.5[b]	44.5[b]	45.0[a]
Povidone	3.0	2.0	2.0	2.0
Purified Water	2.0[c]	--	--	8.5[c]
Microcrystalline Cellulose	25.0[e]	25.0[e]	25.0[e]	25.0[d]
Crospovidone	2.0	2.0	2.0	2.0
Colloidal Silicon Dioxide	0.5	0.5	0.5	--
Magnesium Stearate	1.0	1.0	1.0	1.0

[a] [d]hydrous; [b] Fast-Flo; [c] partially removed during drying; Avicel PH-101; [e] Avicel PH-102

Moisture-Activated Dry Granulation

The bulk material of the active drug substance was first passed through a milling machine (Homolloid Machines, Model J; The Fitzpatrick Company, Elmhurst, Illinois) using a 0.063 inch screen and knives forward. The milled active ingredient was blended with Fast-Flo lactose and povidone in a planetary mixer for 5 minutes. The mixture was then passed through a #14-mesh screen. Using an ultrasonic atomizing nozzle (MicroSpray, Sono-Tek Corporation, Poughkeepsie, New York), deionized water (2%) was sprayed on the above mixture in a running planetary mixer. The rate of addition of water (3.5 mL/minute) was controlled by a peristaltic pump (Masterflex Model 7520, Barnant Company, Barrington, Illinois). Mixing was continued

for 3 minutes after completion of water addition (which required approximately 9 minutes) to ensure that moisture equilibration was achieved. The moistened granules were then passed through a #14-mesh screen to break a small amount of lumpy granules. The above steps were regarded as the agglomeration stage of MADG. The next stage of MADG involved the following blending. Avicel PH-102 was added to the moistened granules in the planetary mixer, and mixed for 10 minutes to sorb the previously added moisture. This was followed by the sequential addition of crospovidone, Cab-O-Sil and magnesium stearate with blending times of 3, 3 and 5 minutes, respectively.

Wet Granulation

The unmilled active ingredient was blended with hydrous lactose, povidone, and Avicel PH-101, in a planetary mixer (Hobart N-50, The Hobart Manufacturing Company, Troy, Ohio) for 5 minutes. The mixture was then passed through a #14-mesh screen, and granulated with water (approximately 8.5%) in the planetary mixer. The granulated wet mass was then passed through a #10-mesh screen and dried at 40°C in a forced-air oven for approximately 18 hours. The dried granules were passed through a #16-mesh screen and were then blended with crospovidone and magnesium stearate in the planetary mixer for 3 and 5 minutes, respectively.

Dry Granulation

The bulk active ingredient was densified using a roller compactor/granulator (Alexanderwerk AG, Model WP50 N/75, D-5630 Remscheid, West Germany). Since the compacted active material had a wide particle size distribution after subjecting it to

roller compaction, the dry granules of particle sizes smaller than #20-mesh and larger than #100-mesh were collected by a sieve shaker (Ro-Tap, W.S. Tyler Company, Cleveland, Ohio). The active material of the selected particle size range was then blended with other ingredients and processed as the direct compression formulation.

Direct Compression Formulation

The procedure for preparation of the direct compression formulation was the same as that described above for the preparation of the MADG formulation, except that water was not added to the formulation. Consequently, there was no need to pass the formulation through a screen to remove lumps.

2. Measurements of Physical Properties of Granules

Sieve Analyses

Sieve analyses were done with a Sonic Sifter (ATM Corporation, Milwaukee, Wisconsin). In order to properly compare the granules and to see the direct results of the MADG process the granules used for the sieve analysis were obtained from different stages of the respective processes as follows: (1) dry-sized granules, prior to blending with crospovidone and magnesium stearate, for the wet granulation process; (2) granules prior to blending with Avicel PH-102 for the other three processes.

Flow Properties

Measurements of the flow rate and of the angle of repose were conducted in duplicate or triplicate for the final blends

using a flow tester (Pharm Test, Type PTG, Appartebau GMBH, Hainburg, West Germany) with a 10mm orifice. This tester was equipped with a solenoid-operated gate valve that controlled the discharging orifice at the funnel throat and an LED display for the elapsed time (seconds) of flow of 100 mL granules. An optional stirrer device was used for the direct compression formulation because that formulation would not flow at all without using such a device. In addition to measuring the dynamic powder flow rate, this tester also gave the repose angle by measuring the exact height of the granule pile (formed on a small circular platform of fixed diameter) from the flow rate study.

Bulk and Tapped Densities

The compressibility[6] (%) is defined as $(D_T - D_B)/D_T$, where D_T is the tapped density and D_B is the bulk density. Both were determined using a Powder Characteristics Tester (Type PT-E, Hosokawa Micromeritic Labs., Osaka, Japan).

Scanning Electron Microscopy

The scanning electron microscopy (SEM) analysis was done on an Amray Scanning Electron Microscope (Model 1000B, Amray, Inc., Bedford, Massachusetts).

3. Preparation and Evaluation of Tablets

Tablets (200 mg, 5/16 inch diameter, standard concave) of each formulation were compressed using a tablet press (Stokes, B-2, Pennwalt Corporation, Warminster, Pennsylvania) with the same compression force at approximately 25 rpm. Only four of the total sixteen stations were used. Content uniformity of the tablets was estimated by assaying ten tablets individually

TABLE 2

Comparison Of Flow Properties Of Final Blends From Various Granulation Processes

Properties	MADG	Dry Granulation	Direct Compression	Wet Granulation
Flow Rate (g/sec)	5.5	5.1	0.8[a]	5.5
Angle of Repose (deg)	30.0	31.9	43.4	30.8
Compressibility (%)	18.2	18.5	29.3	19.3

[a] with assistance of optional stirrer; otherwise, no flow.

using a stability-indicating HPLC method. Moisture content was determined by a Karl-Fischer titrator (Metrohm, Model 658, Brinkman Instruments, Westberg, New York) on the ground tablets. The hardness of ten tablets was measured from each formulation process were measured using a hardness tester (Schleuniger-2E, Vector Corporation, Marion, Iowa). Friability was done on a Roche-type friabilator (Vanderkamp, Van-Kel Industries, Chatham, New Jersey) using 10 tablets for 120 revolutions. Dissolution was conducted using the USP paddle method (50 RPM) with water as the dissolution medium at 37°C.

RESULTS AND DISCUSSION

Three flow-related properties, i.e., flow rate, angle of repose, and compressibility (%), of the final blends from various granulation processes were compared to help evaluate the performance of the granulation processes. As shown in

Table 2, the wet granulation, dry granulation and MADG had very similar flow rates, ranging from 5.1 to 5.5 g/sec. However, the direct compression formulation had a much lower flow rate (0.8 g/sec) which was only achievable when an optional stirrer was used. Consistent with its poor flow, the direct compression formulation had the highest angle of repose (43.4 degrees), while the other granules had repose angles of 30 to 32 degrees. The data on repose angles agrees with Pipel's finding[7] that powders or granules with repose angles $\leq 30°$ generally flow freely, while those with angles $\geq 40°$ flow poorly.

The data on compressibility in Table 2 shows that the direct compression formulation had the highest value (29.3%), again consistent with poor flow. In contrast, the results for the wet granulation, for the dry granulation and for the MADG were all less than 20%. It is generally recognized that the higher the percent compressibility of a material, the poorer its flowability is likely to be. However, opinions on the precise definition of the percent compressibility for a free-flowing material are varied.[8,9] Nevertheless, a compressibility of 29.3% for direct compression formulation strongly suggested a poorly flowing formulation while the other three granules had fair to good flowability. From the above three flow properties, it can be concluded that 1) the three flow-related properties are quite consistent with each other for the tested granules; and 2) the MADG method can produce a granulation with flow as good as that of either wet or dry granulations.

The MADG method has two distinctive stages, as noted earlier. The first stage is the actual granulation (agglomeration) step in which only a small amount (2%) of water

TABLE 3

Comparison of Sieve Analysis Data of Intermediate Granules at Equivalent Stages from Various Granulation Processes

Screen No.	MADG	Dry Granulation	Direct Compression	Wet Granulation
25	4.3	1.6	1.9	15.9
40	20.3	10.9	3.4	19.9
60	33.6	18.8	6.9	23.7
100	17.6	23.2	20.5	25.2
200	25.2	37.0	47.1	17.6
Fines	0.2	8.6	20.2	4.7

is used to moisten the formulation and promote the formulation of granules. The second stage is simply the mixing of the moistened granules with microcrystalline cellulose to sorb the moisture. These slightly moistened granules can then, without a separate drying step, be blended with disintegrant, glidant and lubricant in a standard final blending. In the conventional wet granulation, however, the amount of water which is added could be as high as 50% of the weight of the dried granules, depending upon the ingredients in the formulation. It is also known that there are two mechanisms of granule growth[3] in the wet granulation process: (1) nucleation of particles, and (2) coalescence between agglomerates. Since, generally, only a small amount of water[5] (1-4%) is added in the MADG method, it appears that the mechanism of "nucleation of particles" plays the major role of granule growth in MADG, rather than "coalescence between agglomerates" or "ball

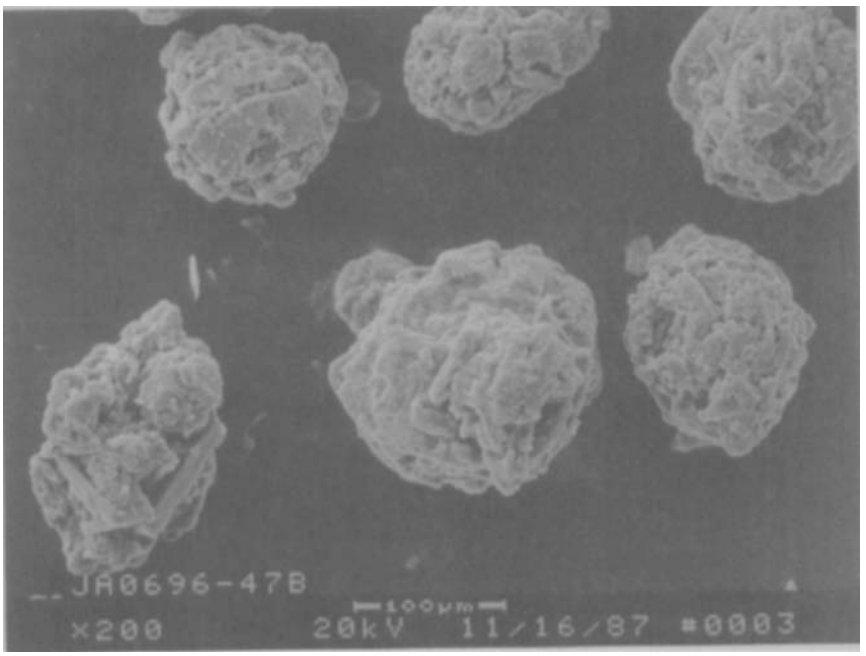

Figure 1: SEM Photomicrograph of the granules from the first stage of MADG process.

growth." This is supported by the results of the sieve analysis of the granules from the first stage of MADG and of the equivalent intermediate granules from the other processes (Table 3). As shown in Table 3, the MADG method gave almost no fines (only 0.2% by weight) while the direct compression formulation had approximately 20% by weight of fines which probably was the main cause of the latter formulation's poor flow as shown in Table 2. The indication that the mechanism of granule growth in the MADG process is particle nucleation is also supported by the scanning electron microscopy (SEM) analysis. As shown in Figure 1, the granules from the first stage of the MADG method were generally large and rounded, and

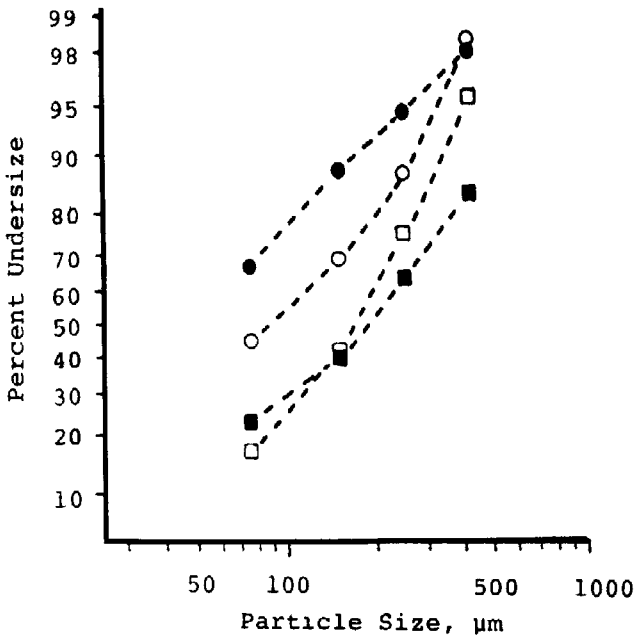

Figure 2: Particle size distribution of intermediate granules at equivalent stages of various granulation methods: (■) MADG; (□) Wet Granulation; (○) Dry Granulation; (●) Direct Compression.

the material contained very few fine particles. In other words, during the first stage of the MADG process, the fine particles of raw materials agglomerate to form bigger particles (granules).

The particle size distribution(s) of the respective intermediate granules were also compared using log-probability plots which are as shown in Figure 2. The sizes of these intermediate granules appear to follow nearly log-normal distributions based on the linearity or near-linearity of the plots in Figure 2. The geometric means of the diameters of the granules from

TABLE 4

Comparison Of Performance Characteristics Of Tablets From Various Granulation Processes

Test	Wet Granulation	Dry Granulation	Direct Compression	MADG
Weight Variation (% RSD)	0.91	0.66	0.84	0.81
Content Uniformity (% RSD)	4.5	4.1	0.91	1.02
Moisture Content, KF (%)	4.6	4.1	4.2	4.8
Hardness (kp)	10.5	12.6	13.2	10.9
Friability (% loss)	0.05	0.08	0.09	0.11
Dissolution % 15 min.	63.7	94.1	93.1	82.2
30 min.	100	100	100	100

wet granulation, MADG, dry granulation and direct compression are approximately 190, 170, 90 and 40 μm, respectively.

The characteristics of the tablets compressed from the four granulation processes were also determined. Results are shown in Table 4. Although the four formulations had substantially differing flow characteristics, as shown in Table 2, the tablets made from each of these granulations had a low relative standard deviation (RSD) of the weight variation. This is due to the fact that the compression process was maintained at conditions (e.g., low tablet press speed) which tolerated slow/poor-flowing formulations.

However, the content uniformity of the tablets showed significant differences among the processes (Table 4). The high RSD of the content uniformity for tablets from the wet granulation process can possibly be attributed to the uneven distribution of the drug in the granules due to migration of the very water-soluble sematilide hydrochloride in the granules during oven drying. As mentioned earlier in the METHODS Section, the active ingredient in the dry granulation formulation had particle sizes between #20 and #100 mesh, which is significantly larger than the milled active ingredient in the direct compression and MADG formulations. As a result of this coarser active ingredient, the dry granulation formulation had a higher RSD of tablet content uniformity.

Because the moisture content of the direct compression formulation was 4.2% (Table 4) and an additional 2% of water was added in the MADG process, the moisture content of the MADG formulation should have had a theoretical value of 6.2%. However, the moisture content of the MADG formulation was actually found to be only 4.8%, or 1.4% less than the theoretical value. A lower-than-theoretical moisture content was also noted by Ullah, et al[5], who reported a final moisture level which was 1.7% lower than the theoretical value. This indicates that most of the 2% water added in the MADG method may have been lost during the processes prior to tabletting, such as granulation in the open planetary mixer and sieving granules in the open environment. If other granulation/milling equipment with well-closed chamber(s) were to be used, then the moisture loss due to processes might be much less. The effect of the equipment changes on the tablet characteristics (such as hardness) needs further investigation. There was little difference in friability for the tablets made from the

different granulations. However, the higher moisture content of the tablets from the wet granulation and MADG appeared to result in tablets of slightly lower hardness (Table 4). Although there was some difference in the percent dissolved at 15 minutes for the tablets from the four processes, all tablets dissolved completely within 30 minutes.

In conclusion, the MADG process appears to have advantages as a granulation method for highly soluble active drugs such as sematilide hydrochloride tablets because it can: (1) yield granules of excellent flow, (2) produce granules which compress into good quality tablets, (3) eliminate the cost of drying wet granulations while producing materials which have similar desirable properties, and (4) save the investment in specialized equipment for dry granulation.

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