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COMMUNICATION

Evaluation and Comparison of a Moist Granulation Technique to Conventional Methods

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ABSTRACT

In the moist granulation technique (MGT), a minimum amount of liquid is used to activate a binder in a planetary mixer. Then, any excess moisture is absorbed by the addition of a moisture-absorbing substance. In the experiments described below, acetaminophen (APAP) was the model drug; polyvinylpyrrolidone (PVP) and microcrystalline cellulose (MCC) served as the binder and moisture-absorbing material, respectively. Water was used as the granulating fluid. Comparison of the MGT with direct compression (DC) and wet granulation (WG) methods was accomplished by sieve analysis (particle size) and density measurements. Moist granulation yielded an increase in particle size compared to direct compression; these results are comparable to those from the traditional wet granulation after drying and screening. Based only on the particle size, moist granulation appears comparable to conventional wet granulation for this formula. The moist granulation technique appears to have potential for the development of controlled-release formulations.

Key Words: *Granulation; Tablets.*

INTRODUCTION

Conventional tablet formulation development is carried out using direct compression, wet granulation, or dry granulation. Wet granulation is by far the most frequently used method. A novel granulation method called moisture-activated dry granulation (MADG) was developed and reported by Ullah et al. (1). Briefly, MADG uses a minimum amount of liquid to activate a binder added as a dry powder, which in turn facilitates particle growth. This is the agglomeration step. Finally, a water-insoluble material such as microcrystalline cellulose (MCC) is then added to absorb any excess moisture so that the resultant granulation does not require a drying step. This is the

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stated advantage of MADG over wet granulation. True dry granulation is a granulation obtained using either slugging or roller compaction to achieve densification. Since slugging and roller compaction are not used in the method in the literature, a more appropriate name for this process is moist granulation. Since this process was first reported in 1987, two other groups have used it successfully (2,3). To evaluate the feasibility of this method, our laboratory also tried to reproduce the results of Ullah et al. Our objectives were threefold: to obtain results similar to those reported in the literature, to contribute to the sparse literature on this novel method, and eventually to apply this technique to develop controlled-release dosage forms.

EXPERIMENTAL

Materials

The batch size for the experiments was 540 gm. The formulation consisted of acetaminophen (APAP) USP (Hoechst Celanese, Bishop, TX); MCC (Avicel® PH-102, FMC Corp., Philadelphia, PA); polyvinylpyrrolidone (PVP) USP (Plasdone K 29-32 GAF/ISP, Wayne, NJ), croscarmellose sodium (Ac-Di-Sol®, FMC Corp.); magnesium stearate (Amend, Irvington, NJ). Water was used as the granulating fluid. For wet granulation, 280 ml (approximately 52% of the dry ingredient weight) of water was used. For moist granulation trials, the levels of water added were 1%, 3%, 5%, 7%, and 10% of the dry ingredient weight.

Methods

Moist Granulation

APAP was passed through no. 16 mesh screen and transferred into a Kitchenaid (Hobart, St. Joseph, MI) planetary mixer bowl. PVP and Ac-Di-Sol were added and then mixed at the lowest setting on the mixer for 5 min. Moisture was introduced with continued mixing and allowed to distribute. MCC was added and mixed for 5 min. The granulation was passed through a 16-mesh screen and then transferred to a 4-quart PK twin-shell blender (Patterson-Kelly, East Stroudsburg, PA). Magnesium stearate (passed through a 40-mesh screen) was added and blended for 5 min.

Direct Compression (Control Process)

All ingredients except magnesium stearate were blended in the Kitchenaid mixer for 5 min and then lubricated with magnesium stearate in the PK blender for 5 min.

Wet Granulation (Control Process)

All ingredients except magnesium stearate were blended in a Kitchenaid mixer for 5 min, water was added, and the granulation was dried in a 45°C oven for 24 hr. The dried granulation was passed through a 16-mesh screen, transferred to the PK blender, and then lubricated with magnesium stearate for 5 min.

Physical Characterization

Determination of particle size distribution for batches made by our procedure was carried out on a C. E. Tyler portable sieve shaker (Mentor, OH) using 16-, 30-, 50-, 100-, 200-, and 325-mesh screens after shaking for 5 min. For batches made according to the procedure of Ullah et al., 40-, 60-, 100-, and 200-mesh screens were used, and shaking was carried out for 10 min.

Bulk and tapped density were determined on a VanKel tap density tester (Chatham, NJ) for batches made by both procedures. The compressibility factor (%C) was calculated from the bulk and tapped density results using the formula (4)

$$\%C = [(\rho_t - \rho_b) \div \rho_t] \times 100$$

where ρ_t is the tapped density, and ρ_b is the bulk density. The flow rate was measured in grams/second. A 100-gm sample was poured into a stainless steel funnel with an aperture of 2.2 cm; the height of the fall was 13 cm. Measurements were made in triplicate. The loss on drying was determined on a CSC Cenco Moisture Balance (Fairfax, VA) at 90°C.

Tableting

Formulations were tested for tableting behavior. Each formulation was compressed on a Stokes F press (Warminster, PA) equipped with 1/2-inch, round, flat-face tooling. The target tablet weight was 540 mg, and the tablets were compressed to a hardness of 8–10 kp. Ten tablets were randomly selected for measurements of weight variation, thickness, and hardness. Formulations made with varying moisture levels were not compressed.

RESULTS AND DISCUSSION

A single formula processed by the three methods is shown in Table 1. The physical properties of those three batches are summarized in Table 2. For the direct compression process, 20% of the blend was in the 16/50-

Table 1

Formulation Table

Ingredient	% w/w	mg/tablet
Acetaminophen	60.0	325.0
Microcrystalline cellulose	35.0	189.6
Ac-Di-Sol	2.0	10.8
PVP	2.0	10.8
Magnesium stearate	1.0	5.4
Water	Variable	Variable
Total	100.0	541.6

mesh cut and 67% was in the 50/100 mesh cut (see Table 2). The moist granulation yielded an increase in particle size; these results are comparable to the traditional wet granulation.

The compressibility factor is a measure of the flow characteristics of a granulation. It is generally desirable to have values of 15% or lower, with values of 25% or higher indicating poor flow (5). The lower the value, the better the flow. The values of the compressibility factor for the batches are summarized in Table 2. Density measurement and the compressibility factor indicate that the moist granulation is closer to the direct compression process. Physical properties of the tablets are shown in Table 3.

Tablets made by the direct compression process showed considerable variation, an expectation based on the %*C* values. In other words, weight variation showed good correlation with %*C* values. Tablets made by the MGT process were similar to those made by the WG process, but this finding for MGT did not correlate with the compressibility factor value. It is possible that the vibration produced during the tableting operation was enough to initiate flow for the MGT batch, but not for the DC batch. Compared to DC, a lower compaction force was required to achieve the same hardness for the MGT and WG processes.

Moist granulation batches were also prepared at varying moisture levels; the results are summarized in Table 4. The particle size distribution for the 1% MGT batch (not shown) was almost the same as for the DC batch. An increase in added moisture resulted in an unexpected decrease in the 16/50-mesh cut (see Table 4). The increase in added moisture shows some decrease in percentage compressibility, but none is as low as that of the traditional wet granulation. As expected, the moisture content increased with added moisture, but some evaporation seemed to occur at all levels. Indeed, Ullah et al. (1) and Chen et al. (2) also observed a moisture content that was less than the theoretical one. The loss in moisture was probably due to the use of equipment in an open environment. If a closed mixer were used, moisture loss could be minimized. The results obtained by Ullah et al. showed that the MADG batch was very similar to the wet granulation batch with respect to particle size distribution, %*C*, and flow rate.

Table 2

Physical (Powder) Properties for the Three Processes

	Batch Type		
Property	Direct Compression	Moist Granulation	Wet Granulation
Sieve analysis		(3% w/w)	
Screen size (% retained)			
16	0.0	0.0	0.0
30	2.0	14.0	11.0
50	18.0	24.0	29.0
100	67.0	49.0	46.0
200	11.0	10.0	11.0
325	0.0	2.0	2.0
Pan	0.0	0.0	0.0
Total	98.0	99.0	99.0
Density (g/ml)			
Bulk	0.43	0.41	0.43
Tapped	0.65	0.60	0.51
Compressibility %	34.0	32.0	16.0
Flow rate (g/sec)	Did not flow	Did not flow	9.4 ± 0.4
Moisture (%)	1.6	3.0	1.6

Table 3

Characteristics of Tablets Made by the Three Processes

Tablet Characteristics	Direct Compression	Moist Granulation	Wet Granulation
Weight variation (% RSD)	3.6	0.6	0.7
Hardness (kp)	7.8	9.7	9.0

The procedures of this laboratory were slightly different from those of Ullah et al. Hence, another three batches were made following the exact procedures of Ullah et al. (1). The results in Table 5 show a comparison of the particle size distributions of the three batches made according to the procedure of Ullah et al. For reference, results obtained by Ullah et al. (1) are also included. It is obvious that the particle size distribution of the MGT batch is comparable to that of the DC batch rather than the WG batch. Another observation is the percentage of fines that were seen for the MGT and the WG. The granulations obtained from MGT and WG were rather difficult to pass through the respective screens. Hence, the granules had to be pulverized in a mortar and pestle to facilitate the screening process. On the other hand, if a high-shear mill, like a Fitzmill, were used, the percentage of fines could have been higher.

Although the %*C* value obtained for the moist granulation batch is comparable to the value obtained for the wet granulation batch, the flow characteristics of the three batches were poor (see Table 5). Physical properties of tablets obtained when these batches were compressed are shown in Table 6. Again, the tablets made by the direct compression process show more variability than those made by the corresponding moist and wet granulation batches. The DC tablet properties correlate with compressibility factor value. In this case, also the WG and MGT tablet properties do not correlate with compressibility factor values.

Moisture-activated dry granulation is a useful process because it is possible to reduce considerably the quantity of liquid used for granulating compared to the traditional wet granulation. The current work was not able to reproduce the results reported in the literature. The reason may involve differences in processing. In the current work, all dry ingredients except MCC and magnesium stearate were mixed before the addition of water. However, Ullah et al. (1) mixed APAP and PVP in a PK blender for 10 min and then screened the mixture through 30-mesh screen. These steps probably distribute PVP more evenly. Our initial formula contained 2% PVP, compared to 3.6% in the case of Ullah et al. We added disintegrant in the dry mix, while Ullah et al introduced disintegrant during the lubrication stage. Because disintegrants have a strong affinity for water, it is possible that the low levels of water used in this process are immediately sequestered by the disintegrant, leaving little or no water for the binder to be activated. This may result in a granulation that does not flow well. When the procedure of Ullah et al. was followed, we were expecting the moist granulation batch

Table 4

Particle Size Distribution of Moist Granulation Batches with Varying Moisture Contents

Property	Batch Type			
Sieve analysis	3% MGT	5% MGT	7% MGT	10% MGT
Screen size (% retained)				
16	0.0	0.0	0.0	0.0
30	11.0	4.0	6.0	6.0
50	29.0	6.0	7.0	15.0
100	46.0	32.0	52.0	60.0
200	11.0	38.0	23.0	16.0
325	2.0	7.0	9.0	1.0
Pan	0.0	11.0	2.0	0.0
Total	99.0	98.0	99.0	99.0
Density (g/ml)				
Bulk	0.41	0.35	0.38	0.37
Tapped	0.60	0.50	0.51	0.51
Compressibility %	32.0	30.0	26.0	27.0
Moisture (%)	3.0	4.8	6.8	9.8

Table 5

Particle Size Distribution of Batches Made According to the Procedure of Ullah et al. (1)

Property	Batch Type		
Sieve analysis	Direct compression	Moist granulation (3% w/w)	Wet granulation
	% Retained		
Screen size	USIP/Ullah	USIP/Ullah	USIP/Ullah
40	5.0/0.6	8.0/20.8	27.0/16.3
60	26.0/12.9	16.0/35.7	29.0/40.8
100	59.0/20.4	37.0/13.9	18.0/17.4
200	9.0/36.4	17.0/15.3	15.0/16.3
Pan	1.0/29.7	20.0/14.3	10.0/9.2
Total	100.0/100.0	98.0/100.0	99.0/100.0
Density (g/ml)			
Bulk	0.42/0.45	0.46/0.52	0.53/0.51
Tapped	0.65	0.62	0.69
Compressibility %	35.0	26.0	23.0
Flow rate (g/sec)	Did not flow	3.0 ± 0.1[a]	4.3 ± 0.2[a]
Moisture (%)	2.6	4.4	1.6

USIP = experimental batches, University of the Sciences, in Philadelphia; Ullah = literature results, Ref. 1.
[a]Indicates flow had to be initiated, but after initiation, powder flowed freely.

Table 6

Characteristics of Tablets from Batches Made According to the Procedure of Ullah et al. (1)

Tablet Characteristics	Direct Compression	Moist Granulation	Wet Granulation
Weight variation (% RSD)	1.9	0.6	0.6
Hardness (kp)	8.1	8.5	9.6

to be very comparable to the wet granulation batch, but as can be seen from the results in Table 5, that was not the case. However, based on results shown in Table 6, MGT was comparable to WG as far as tablet properties were concerned.

CONCLUSIONS

The experimental results with this immediate-release formulation demonstrate that it is possible to granulate with a reduced quantity of liquid. Although our results are slightly different from those of Ullah et al. (1), our conclusions were the same; that is, MGT is better than DC and comparable to WG. This technique has advantages, and further evaluation is warranted, specifically with respect to controlled-release formulations. Based on these results, work will be expanded to determine whether MGT can be applied to a controlled-release formulation.

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