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MOISTURE-ACTIVATED DRY GRANULATION IN A HIGH SHEAR MIXER

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ABSTRACT

The applicability of a 25 litre high shear mixer for moisture-activated dry granulation was examined. Microcrystalline cellulose, potato starch or a mixture of 50% m/m of each was used as moisture absorbing material. The effects of water content, wet massing time, moisture absorbing material and dry mixing time on the size distribution, and the compressibility of the granulations were investigated. Tablets were compressed on a single punch press from all the granulations and on a rotary press from a few of the granulations.

It was shown that the physical properties of the tablets were primarily affected by the water content, the moisture absorbing material, and the compression force. Tablets with low mass variation, high crushing strength, low friability, and short disintegration time were achieved with both tablet presses by using a mixture of microcrystalline cellulose and potato starch as moisture absorbing material.

INTRODUCTION

Wet granulation is the granulation method, which is used most commonly in the pharmaceutical industry. A disadvantage of this method is, however, that a time-consuming and costly drying step is required. If dry granulation or direct compression is used instead in order to avoid the addition of water, other disadvantages such as poor flowability, insufficient compression properties, and poor content uniformity might occur.

Moisture-activated dry granulation (MADG) is a process which implies the advantages of wet granulation without requiring a drying step (1,2). The MADG process consists of two distinctive stages, an agglomeration stage and a moisture absorption stage. Agglomeration occurs during the first stage by adding a small amount of water to a mixture of the drug substance, a binder and possibly a filler. In the next stage, a moisture absorbing material is mixed with the moistened agglomerates in order to absorb any excessive moisture. After addition of a lubricant, and if necessary a disintegrant, the granulation is suitable for compression of tablets without drying.

The quantity of water used for MADG is equal to 1% to 4% of the final formula weight dependent on the actual formulation (1). In the experiments described in the literature (1,2), microcrystalline cellulose was used

as moisture absorbing material, and the process was carried out in a planetary mixer. The MADG method was found to produce granules with characteristics which were equivalent to those of granules produced by either conventional wet granulation (1,2) or dry granulation methods (2) and which were superior to those of a direct compression formulation (2).

In the previous experiments (1,2), the formulation and the process variables were kept constant. The purpose of the present investigation is to elucidate the effects of product and process variables on the properties of granules and tablets prepared by a MADG process in a high shear mixer.

MATERIALS

Phenobarbitale (Alkaloida, Hungary) (41 μm), lactose (Pharmatose 200 mesh, De Melkindustrie Veghel BV, the Netherlands) (42 μm), polyvidone (Plasdone K 29-32, ISP, USA) (140 μm), microcrystalline cellulose (105 μm), potato starch (Pharma M 20, Kartoffelmelcentralen, Denmark) (34 μm), magnesium stearate (MF-2, Breyer Chemie B.V., the Netherlands) (11 μm) and talc ("Extra Superiore dec", Talco Val Chisone, Italy) (21 μm) - all of Ph. Eur. grade - were used as starting materials. The values in the parentheses are the geometric mean particle sizes of the distribution by volume, determined by a Malvern 2601Lc laser diffraction particle sizer (Malvern Instruments, UK).

METHODS

Granulation

A 25 litre vertical high shear mixer (Fielder PMA.T. 25-2G, T.K. Fielder Ltd., UK) was used for the MADG

process. The water was added through a two component nozzle (1/4 J SS, Fluid Cap 60100, Air Cap 120, Spraying Systems, USA) mounted in the lid of the mixing bowl close to the periphery of the lid.

The formulations used in the experiments are shown in Table 1.

Phenobarbitale, lactose, and polyvidone were dry mixed for 1 min. (impeller speed 250 rpm, chopper speed 1500 rpm). After that the water was added at a constant flow rate of 12.7 ml/min. at an air pressure of 6 ato. A water content of 1.0, 1.5, 2.0, 2.5 or 3.0 %m/m of the total formulation weight (exclusive of water) was used in the preliminary experiments. In the final experiments, a water content of either 1.5 (95 g) or 2.5 %m/m (159 g) was used. The mixing was continued for either 1, 3 or 5 min. after the end of the liquid addition. This additional mixing is called the wet massing time, and during this the impeller speed was increased to 495 rpm and the chopper speed to 3000 rpm.

During the subsequent moisture absorption stage either potato starch, microcrystalline cellulose or a mixture of 50 %m/m of each was added and mixed with the moistened mass at an impeller speed of 250 rpm and no chopper action. This mixing period is called the dry mixing time. The process was stopped at dry mixing times of 2, 4 and 8 min., respectively, and a sample of 380 g was drawn. These samples were sieved (1 mm) and were then manually mixed with 20 g of a mixture of magnesium stearate and talc, which was sieved (1 mm) immediately before.

The experiments mentioned above resulted in a total number of 54 different granulations, which were stored in air-tight bags of aluminium foil until tests (compressibility and sieve analysis) and compression of tablets were carried out.

TABLE 1
The formulations used in the MADG experiments.

Material	Mass	% of tablet mass
Phenobarbitale	956 g	15
Lactose	2360 g	37
Polyvidone	191 g	3
Purified water	varied	
Moisture absorbing material (either potato starch, microcrystalline cellulose or a mixture of 50 %m/m of each)	2546 g	40
Magnesium stearate	31.8 g	0.5
Talc	286.2 g	4.5
Total mass of granule (exclusive of water)	6371 g	100

Compressibility

The compressibility of the granulations was estimated by a Tap-Pak Volumeter (J. Engelsmann A.-G., Germany). Samples of 100 g and a 250 ml graduated cylinder were used for estimation of the poured volume (V_p) and the tapped (1250 taps) volume (V_t). The compressibility in per cent is defined as: $(V_p-V_t)*100/V_p$

Sieve analysis

Granule size and size distribution were estimated by sieve analysis (Retsch, type Vibro, Germany) of samples

of 50 g using a series of 12 standard sieves in the range of 75 - 1000 μm. The sieves were vibrated in three stages: all sieves for 2 min. at intensity 0, sieves finer than 710 μm for further 4 min. at intensity 50 and finally sieves finer than 300 μm for further 10 min. at intensity 85. The geometric-weight mean diameter ($\bar{d}_{gw}$) and the geometric standard deviation (S_g) were calculated, and the amount of fines was defined as the percentage passing through the 75 μm sieve.

Compression of tablets

Tablets (100 mg, 6 mm in diameter, flat-faced punches with bevelled edges) were compressed on a single punch press (Diaf TM special, Denmark) at a compression speed of 65 tablets/min. The compression force was varied at two levels in order to achieve tablets of crushing strengths of approximately 4 and 8 kP. A few complementary experiments were carried out on a rotary press (Korsch type PH 106, Germany), where only three of the six stations were used. The punches used in the rotary press were equal to the punch used in the single punch press and the compression speed was 100 tablets/min.

Mass variation

The mass variation of each formulation was determined by weighing 20 tablets individually and was expressed by the relative standard deviation in per cent.

Crushing strength

The crushing strength of the tablets was estimated by a hardness tester (Schleuniger 2E/205 serie 7410, Switzerland) as the mean value of ten individual measurements.

Friability

The friability of the tablets was estimated as the loss of weight in per cent after rotation of 30 tablets (4 min., 25 rpm) in a friability tester identical to the Roche friabilator.

Disintegration time

The disintegration time was measured on 6 tablets by a disintegration tester (Pharma Test PTZ 1, Germany) using the Ph. Eur method without discs, and the mean value of the six measurements was calculated.

RESULTS AND DISCUSSION

Preliminary experiments

Preliminary experiments were carried out with water contents of 1.0, 1.5, 2.0, 2.5 and 3.0 %. The selection of these water contents was based on former MADG-experiments (1,2) in which water contents of 2.0 and 2.7 %, respectively, were used.

In these preliminary experiments, the mixture of potato starch and microcrystalline cellulose was used as moisture absorbing material and wet massing time as well as dry mixing time were kept constant at 4 min. The water content 1.0 and 1.5 % resulted in granules which looked rather dry, whereas the higher water content gave rise to granules with a moist appearance. It was possible to make tablets from all the granulations. The mass variation of the tablets, however, was too high at a water content of 1.0 %. On the basis of these experiments, the levels of water contents were chosen to be 1.5 and 2.5 % in the final experiments.

Granule size and size distribution

The effects of wet massing time, formulation, and water content on mean granule size and content of fines are shown in Figures 1 and 2.

No significant effects of the dry mixing time were found. Since the first sample was drawn at 2 minutes of dry mixing, it can be concluded that no significant changes in granule size and size distribution occur after 2 minutes of dry mixing. On the basis of the results, it is not possible to decide, however, if agglomeration occurs simultaneously to mixing during the first 2 minutes of dry mixing.

Figure 1 shows that the mean granule sizes obtained from the MADG process are small compared to those obtained by ordinary wet granulation in a high shear mixer of the same type and size (3). This is partly due to the use of a lower amount of water for MADG. Water contents of 1.5 and 2.5% in the final product correspond to water contents of 2.7 and 4.5% in the agglomeration stage of the process. The sieve analyses were carried out on the final granulations in order to elucidate effects of mean granule size on tablet compression. The values of mean granule size, therefore, are further lowered due to addition of a large amount of ungranulated material during the moisture absorption stage.

The effects of wet massing time, formulation as well as water content on the mean granule size (Figure 1) were found to be significant ($p=0.000$) by analysis of variance (ANOVA). These three factors were found to interact ($p=0.000$).

As can be seen from Figure 1, prolonged wet massing results in a larger mean granule size at the high level of water content, whereas no effect of wet massing time

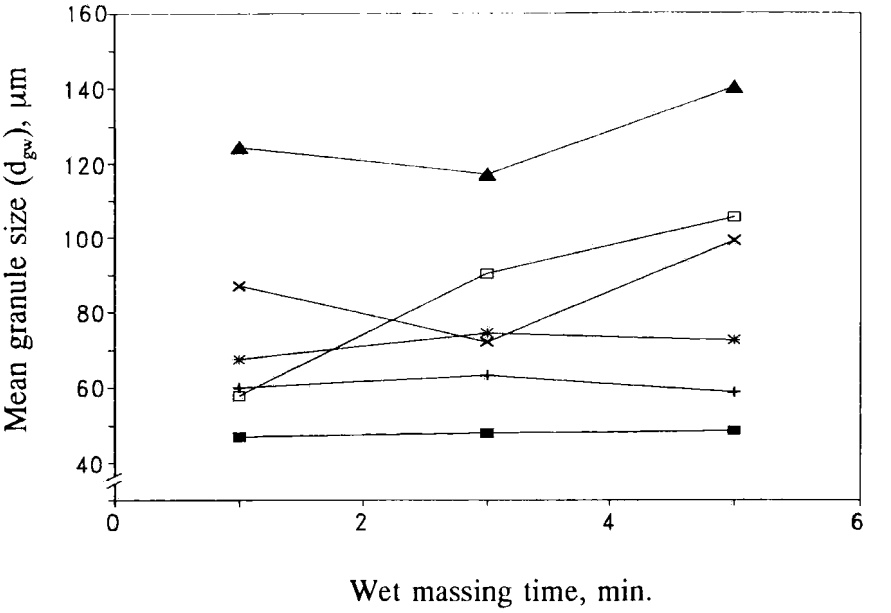

FIGURE 1
Effect of water content, moisture absorbing material and wet massing time on the mean granule size. Dry mixing time: 2 min. ■ : starch, 1.5% water; + : starch/micr. cellulose, 1.5% water; * : micr. cellulose, 1.5% water; □ : starch, 2.5% water; × : starch/micr. cellulose, 2.5% water; ▲ : micr. cellulose, 2.5% water.

is seen at the low water content. This interaction might be explained by the fact that a proper wetting of the surface of the particles is a prerequisite of granule formation and growth. At the low water content, the wetting of the particles is insufficient for formation of agglomerates by liquid bridges between the particles, and consequently the mean granule sizes are similar to the mean particle sizes of the starting materials.

The granule growth will further be affected by the fact that polyvidone as well as lactose will be partly dissolved in the water during the process. Dissolution of solid particles during a granulation process will

usually result in a larger granule size (4,5). Consequently, the effects of water content and wet massing time on granule size might be more pronounced, because an increased amount of lactose and polyvidone is assumed to be dissolved at higher water content and prolonged wet massing. At the high water content, the increase in product temperature during wet massing was found to be about 20°C, and this might further increase the amount of material dissolved.

The formulation is kept constant during wet massing, because the starch and/or the microcrystalline cellulose are not added until at the start of the subsequent dry mixing stage. The effect of formulation on granule size, is therefore, primarily ascribed to the difference in the initial particle size between the potato starch and the microcrystalline cellulose. Since the particle size of the starch is markedly lower than that of the microcrystalline cellulose, an increase in starch content will result in a smaller mean granule size.

However, significant interactions were found between formulation and wet massing time and between formulation and water content. These interactions indicate that granule growth might occur during the first two minutes of dry mixing. It is likely that the addition of moisture absorbing material gives rise to some granule growth by coalescence between the added particles and the moist particles or agglomerates.

The effects mentioned above are reflected in the content of fines. A marked increase in granule size during wet massing was only seen in the case of a high water content combined with the starch formulation. Figure 2 shows that this granule growth results in a decrease in the content of fines. The content of fines is nearly constant during wet massing with the other

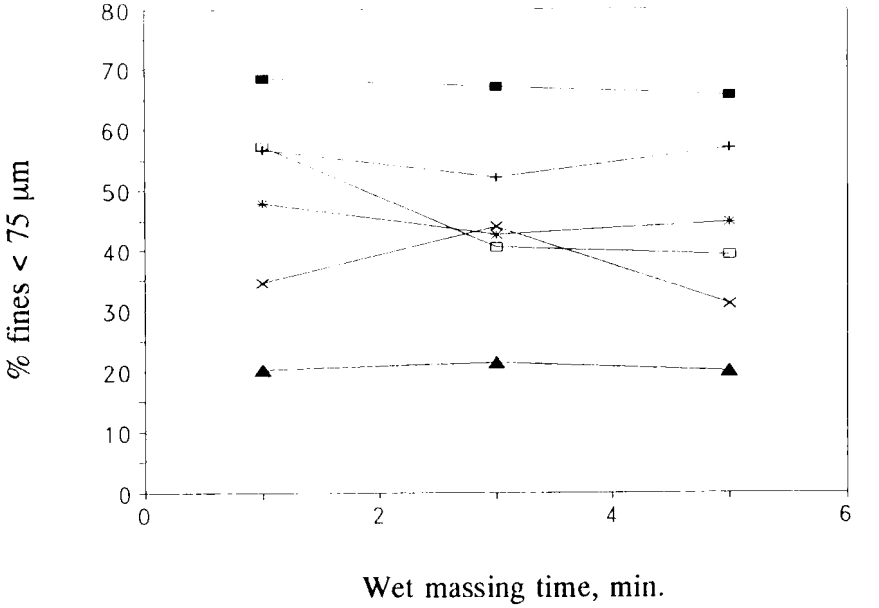

FIGURE 2
Effect of water content, moisture absorbing material and wet massing time on the amount of fines. Dry mixing time: 2 min. ■: starch, 1.5% water; + : starch/micr. cellulose, 1.5% water; *: micr. cellulose, 1.5% water; □ : starch, 2.5% water; × : starch/micr. cellulose, 2.5% water; ▲ : micr. cellulose, 2.5% water.

combinations of water content and formulation. The amount of fines in the granulations is seen to be very high. This is primarily due to the addition of ungranulated particles after the wet massing. The initial particles of starch, talc, and magnesium stearate are smaller than 75 µm, whereas most of the initial particles of microcrystalline cellulose are larger. The content of fines, is therefore, seen to be markedly higher with the starch formulations.

Compressibility

The compressibility was used as a measure of the flow properties of the granulations. The lower the compress-

ibility the better the flow properties. It was found by ANOVA that the compressibility was affected by all the variables: formulation ($p = 0.000$), water content ($p = 0.000$), wet massing time ($p = 0.039$), and dry mixing time ($p = 0.010$).

The effect of the formulation is primarily assumed to be due to a difference in particle shape. Potato starch particles are rounded, which resulted in a better compressibility (mean value (M) = 21.4%) than the irregular microcrystalline cellulose particles (M = 23.0%). The effect of the water content on compressibility is assumed to be due to the increase in granule size at a higher water content. Granulations containing 2.5% of water were found to have lower compressibilities (M = 21.4%) than granulations containing 1.5% of water (M = 23.4%), because larger granules have better flow properties.

The lowest compressibility (M = 19.7%) was found for the starch formulation containing 2.5% of water and the highest compressibility (M = 23.9%) for the microcrystalline cellulose formulation containing 1.5% of water. These values are a little higher than the one obtained in a previous MADG experiment (2).

The effects of wet massing time and dry mixing time were less pronounced. Prolonged dry mixing resulted in a slightly higher compressibility. The effect of wet massing time was complex due to interactions.

Mass variation of tablets

The mass variations were found to vary between 0.7 and 2.1% with a mean value of 1.3%. However, no significant effects of the variables on mass variation were found. Thus the differences in the flow properties of the granulations are not reflected in the mass variation of

the tablets. This is probably because the flowability of the granules is rather uncritical by compression of tablets on a single punch press.

Crushing strength of tablets

It was attempted to make tablets of crushing strengths of 4 and 8 kP. It was impossible, however, to make tablets containing starch as moisture absorbing material with a crushing strength of more than about 6 kP. The means of the crushing strengths obtained at the two levels were 4.1 and 7.9 kP (starch formulation not included at the high level) with a standard deviation of 0.3 kP. Even though the ANOVA showed slight differences between the crushing strengths obtained at the same level, these differences were so small that it is unlikely that differences in friability and disintegration time might be explained by variations in the crushing strength of the tablets.

Friability of tablets

The friability was found to be affected by the crushing strength of the tablets ($p = 0.000$) and the formulation ($p = 0.001$). A higher crushing strength and an increasing content of microcrystalline cellulose reduced the friability. At the high level of crushing strength, the friability varied between 0.1 and 0.4% with both the formulations containing microcrystalline cellulose. At the low level of crushing strength, the mean values of the formulations with microcrystalline cellulose, starch/microcrystalline cellulose and starch were 0.5, 0.6 and 0.8%, respectively. Microcrystalline cellulose gives rise to a lower friability than starch, because microcrystalline cellulose acts as a dry binder.

Disintegration time

ANOVA showed significant effects of crushing strength ($p = 0.000$), formulation ($p = 0.000$), water content ($p = 0.000$) and wet massing time ($p = 0.039$) on the disintegration time (Table 2).

As can be seen, an increase in crushing strength results in an increase in disintegration time. A significant interaction ($p = 0.000$) was found between crushing strength and formulation. At a crushing strength of 4 kP, the starch formulation shows a slightly longer disintegration time than the formulations containing microcrystalline cellulose. An increase in crushing strength from 4 to 8 kP results in a marked increase in disintegration time with the microcrystalline cellulose formulation, whereas a moderate increase is seen with the starch/microcrystalline cellulose formulation. The starch formulation compressed to a crushing strength of 6 kP showed disintegration times of about 1 min. at the low water content and between 2 and 4 min. at the high water content. These results are in accordance with previous findings, which showed that the disintegration properties of microcrystalline cellulose formulations were very pressure dependent (6,7), whereas the disintegration time of starch formulations was independent (8) or only slightly dependent (9) on the compression force.

A higher water content results in a longer disintegration time. Prolonged wet massing increases the disintegration time, but at the high level of water content only. These effects are ascribed to an increased strength of the granules, which is caused by the increased amount of lactose and polyvidone being dissolved at higher water content and prolonged wet massing as discussed above.

TABLE 2

Effects of product and process variables on disintegration time of tablets.

Disintegration time (sec)		water content (%)		1.5			2.5		
		wet massing time (min)		1	3	5	1	3	5
		Dry mixing (min)							
Crushing strength	4 kP	starch	2	26	20	30	62	139	149
			4	20	23	26	72	121	149
			8	27	27	21	48	93	153
		starch/ micr. cellulose	2	11	10	11	48	32	104
			4	10	12	10	31	32	92
			8	11	12	10	38	27	105
		micr. cellulose	2	8	11	8	48	38	72
			4	6	12	7	59	42	100
			8	10	9	9	46	56	96
	8 kP	starch/ micr. cellulose	2	91	187	110	359	292	418
			4	92	154	131	335	276	380
			8	102	183	93	327	311	428
		micr. cellulose	2	105	200	95	1380	1680	2640
			4	50	132	50	2340	1590	5100
			8	100	205	117	2580	1080	3060

Complementary experiments

The complementary experiments carried out on a rotary press were made with 6 of the 54 granulations. These 6 granulations had the wet massing time (1 min.) and the dry mixing time (2 min.) in common. Instead of making tablets of equal crushing strength, it was attempted to make tablets with equal compression force. The variables were the formulation and the water content. The results of the experiments are shown in Table 3.

The effects of the formulation and the water content on disintegration time and friability are similar to

TABLE 3

Results of the experiments on the rotary press. Wet massing time: 1 min., dry mixing time: 2 min.

Formulation	starch		starch/microcrystalline cellulose		microcrystalline cellulose	
Water content (%)	1.5	2.5	1.5	2.5	1.5	2.5
Compr. force (kN)	3.33	3.26	3.28	3.33	2.94	3.35
STD on compr. force (kN)	0.03	0.02	0.01	0.01	0.32	0.08
Mass variation (%)	1.9	2.9	1.4	0.9	13.8	6.7
Crushing str. (kP)	5.0	4.5	7.8	9.0	8.1	14.8
Disintegration time (sec)	36	130	80	308	1311	>1800
Friability (%)	0.4	0.5	0.2	0.2	0.2	0.2

those found with the single punch press. The rotary press, however, gives rise to differences in mass variation between the formulations contrary to the single punch press.

The differences found in the compressibility of the granulations are partly reflected in the mass variation, since the microcrystalline cellulose formulation, which had the poorest flowability, shows the highest mass variation. This confirms the assumptiom that the flowability of the granulations is more critical when using a rotary press. The uneven filling of the die with the microcrystalline cellulose formulation is reflected in the standard deviation on the compression force.

As can be seen, the starch/microcrystalline cellulose formulation gives rise to the lowest mass variation. The mass variation obtained with the starch formulation

is higher, and it was further observed that the small particle size of these granulations caused compression problems due to friction between the punches and the die.

CONCLUSIONS

The present experiments confirm that the MADG technique can be used in a high shear mixer for producing granulations, which are suitable for tablet compression.

The process variables showed to be of minor importance to the properties of the tablets. Increased wet massing time might result in a slight increase in disintegration time, whereas dry mixing time had no significant effect. The slight effect of these variables is ascribed to the high mixing intensity of the high shear mixer, which causes that the distribution of water and the dry mixing are finished within a very short time. However, the wet massing time might be more critical when using excipients which are more cohesive than lactose (3).

Tablets with satisfactory mass variation, crushing strength, friability, and disintegration time could be produced on a single punch press from MADG granulations with potato starch, microcrystalline cellulose as well as a mixture of 50% of each as moisture absorbing material. The disintegration time of tablets from a microcrystalline cellulose formulation, is however, very sensitive to variations in compression force.

The content of water has to be low in order to avoid drying. If the water content becomes too low, the flowability of the granules will be insufficient. An increase in water content might increase the strength as well as the disintegration time of the tablets, because more of the binder and the filler will be

dissolved. In the actual formulation, the optimum water content was found to be between 1.5 and 2.5%.

The physical properties of the MADG granulations were found to be more critical by compression on a rotary press. The formulations with potato starch as well as microcrystalline cellulose were found to be unsuitable for tablet compression, whereas the formulation with a mixture of 50% of each showed to be capable of giving tablets with high crushing strength, low friability, short disintegration time and low mass variation. These differences between formulations are primarily ascribed to differences in size and shape of the granules. If the granule size is too low or the shape of the granules is too irregular, the filling of the die will be uneven and give rise to a high mass variation.

It is assumed that it will be possible to produce MADG granulations suitable for compression of tablets on a rotary press with potato starch as well as microcrystalline cellulose as moisture absorbing material by optimization of the formulation. In order to obtain tablets with a high strength combined with a low disintegration time, it seems to be favourable to use a mixture of starch and microcrystalline cellulose.

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