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The granulation of ternary mixtures: the effect of the solubility of the excipients

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The importance of excipient solubility in wet granulation has been shown using mixtures of lactose and boric acid containing third components of differing solubility characteristics. Sucrose dissolved in the binder solution and increased the amount of liquid available to form liquid bridges between other solid particles and therefore increased the number of solid bridges when the damp mass was dried. Thus, stronger, larger granules were formed. The results obtained with Sta-Rx 1500 and magnesium carbonate powders were also dependent upon the extent of solubility of these powders in the granulating solution.

The granulation of ternary mixtures containing lactose, boric acid and various starches has been reported (Jaiyeoba & Spring 1979). The presence of starch resulted in the formation of smaller and weaker granules. Starches normally have an equilibrium moisture content of about 16% w/w. Therefore, dried starches will absorb water. This will leave less liquid available to form the bonds that contain dissolved materials which are deposited on drying to give the solid bridges holding the granules together. As a result less, or weaker bonds form giving smaller and possibly weaker granules.

In contrast to starch, an excipient of high solubility will dissolve in the binder solution and produce an increase in binder volume, a decrease of surface area of powder to be wetted and give more solids in the bridges which form on subsequent drying.

In this report, the effect of the solubility of a third component during granulation is considered. For this purpose powders of differing solubilities, in mixtures with lactose and boric acid powders were used.

MATERIALS AND METHODS

The mean particle sizes and true densities of materials, determined as described previously were: lactose B.P. (BDH) 20 μm, 1·55 g cm^{-3}; boric acid B.P. (BDH) 12·6 μm, 1·51 g cm^{-3}; sucrose (Goldex Icing Sugar, Goldrei, London) 16·5 μm, 1·60 g cm^{-3}; heavy magnesium carbonate B.P. (BDH) 4·3 μm, 2·31 g cm^{-3}; Sta-Rx 1500 (Colorcon Ltd., Kent, England) 17·0 μm, 1·49 g cm^{-3}.

Granules were prepared from 1 kg of blended powders using a 5% w/v aqueous solution of polyvinylpyrrolidone (Plasdone K29–32, GAF, U.K. Ltd) as binder. Blends contained 2·5, 5 or 10% of the third component and the remaining weight was made up with a mixture of lactose: boric acid in one of the ratios 90: 10, 75: 25, 50: 50 or 10: 90. Binder volumes as % w/w refer to the weight of the three blended powders. This was 1 kg for all granulations. The granulation process used and the methods of determination of granule properties have been described earlier (Jaiyeoba & Spring 1979).

RESULTS AND DISCUSSION

The determined properties of granules prepared from ternary blends of powders containing lactose and boric acid in various proportions with 10% of either sucrose, Sta-Rx 1500 or heavy magnesium carbonate, are given in Tables 1 and 2.

The effect of sucrose as third component

Sucrose is soluble (2 in 1) in the binder solution and its addition to blends of lactose and boric acid powders considerably reduces the amount of binder liquid necessary to granulate the resulting powder mixture (Table 1). An increase in the weight of binder solution from 5 to 10% w/w also gave an increase in the mean granule size.

Granules prepared from ternary mixtures containing 5% sucrose using 10% binder were observed to have similar mean sizes to those produced from the same blends, without sucrose, but using 15% binder. (Tables 1 & 3). From this observation, it would appear that the sucrose dissolved in the binder during massing to produce a total quantity of binder approximately equal to 15% w/w. Dissolution of 50 g sucrose in 100 g 5% w/w PVP solution gave 132 cm³ of solution. Assuming therefore a total sucrose dissolution, this would represent 13·9% v/w when

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Table 1. Mean sizes of granules produced from blends of lactose and boric acid containing 10% of different third components using various binder concentrations.

	Mean granule size (μm)									
Third component:	Control*	Sucrose			Magnesium carbonate			Sta-Rx 1500		
% w/w binder:	15	5	7·5	10	10	12·5	15	15	17·5	20
Lactose: boric acid										
90:10	1050	710	1200	1280	550	1050	1120	740	1120	1200
75:25	1180	490	1150	1250	550	1100	1200	290	1050	1200
50:50	980	360	1100	1280	430	860	1180	300	1150	1300
10:90	410	210	920	1140	—	400	1000	205	700	1200

* Control—Binary blends of lactose: boric acid.

Table 2. Mean granule strength of blends containing lactose, boric acid and 10% of different third components.

		Mean work required to crush granules (× 10^4 J)					
Third component:	*Control	Sucrose		Magnesium carbonate		Sta-Rx 1500	
% w/w binder:	15	7·5	10	12·5	15	15	17·5
Lactose: boric acid							
90:10	6·27 ± 1·22	12·6 ± 2·12	10·5 ± 2·04	3·79 ± 0·40	6·25 ± 0·92	14·61 ± 7·94	15·0 ± 4·70
75:25	6·20 ± 0·80	8·19 ± 1·49	13·6 ± 1·66	5·64 ± 0·71	9·57 ± 0·77	10·90 ± 4·48	14·8 ± 5·60
50:50	4·47 ± 0·61	9·66 ± 1·64	8·75 ± 0·88	5·76 ± 0·72	10·14 ± 0·78	9·30 ± 4·27	14·2 ± 6·67
10:90	3·30 ± 0·36	6·47 ± 0·89	3·96 ± 0·59	—	7·24 ± 0·86	6·68 ± 3·20	10·2 ± 5·08

* Control—Binary blends of lactose: boric acid.

Table 3. The effect of dissolved sucrose on the size of granules of 75:25 lactose: boric acid blends.

Sucrose %	Binder soln %	Percentage retained on sieves 1·2	1·0	710	500	355	250	180	90	<90	Mean size
2·5	10	16·8	30·1	18·6	7·0	6·4	6·5	5·6	6·8	2·4	980
2·5	10*	7·6	25·1	24·3	9·3	7·7	7·5	7·3	8·7	2·7	820
5	7·5	7·2	24·4	22·1	8·7	7·5	8·4	8·8	10·2	2·9	760
5	7·5*	4·4	18·2	20·8	9·6	8·5	9·8	11·6	14·1	3·6	540
5	10	47·0	24·8	10·6	4·2	3·8	3·2	2·1	2·2	2·1	1180
5	10*	32·0	26·5	14·5	6·3	5·9	5·0	3·9	4·5	1·8	1100
10	5	12·1	18·1	11·8	6·6	8·9	13·7	13·4	12·8	3·0	490
10	5*	3·4	14·7	13·8	7·6	9·4	13·5	17·6	16·7	3·4	340

* Sucrose dissolved in binder solution.

referred to the remaining powders. A similar calculation including the saturation dissolution of lactose and boric acid gives 11·6% v/w without sucrose and 15·7% v/w with sucrose in the blend.

Hence, if the algebraic sum of percentage binder and percentage sucrose is taken to represent approximately the effective binder quantity for granulations containing 2·5–10% sucrose, approximately linear relations can be shown between the mean sizes of granules and the effective binder quantity (Fig. 1). Significant deviations are obtained only in those cases where 100 g sucrose is calculated to dissolve in 50 or 75 g of binder solution (Table 3, Fig. 1). Granulations were therefore carried out to investigate the effect of the sucrose being in solution in the binder liquid before massing. The solutions obtained are relatively viscous and this can affect granule growth if the massing time is not altered. However, the same massing time was used to avoid the introduction of a further, significant, variable.

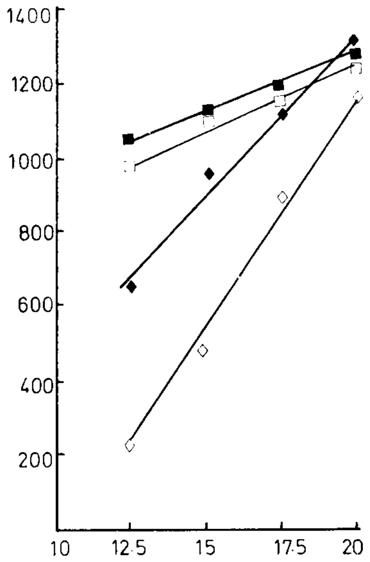

FIG. 1. Relationship between the mean granule size and the algebraic sum of % w/w binder and % sucrose in lactose, boric acid and sucrose blends. Lactose: boric acid ratio: ■ 90:10, □ 75:25, ◆ 50:50, ◇ 10:90. Abscissa: % w/w binder + % w/w sucrose. Ordinate: mean granule size (μm).

The mean sizes of granule batches shown in Table 3 are of the same order whether the sucrose was added as a dry powder or dissolved in the binder solution, in each case the mean size was larger if the sucrose was present as a powder. The blends granulated with a less viscous solution (as shown by the ratio of sucrose to binder weight) produce larger granules even though the total volumes of liquid available for massing were similar. These results can be explained in terms of the spreading of liquid through the powder bed. More viscous solutions spread less rapidly, even with forced massing, and as a result coalescence of granules is slower and so smaller granules are produced. Thus, with sucrose present as a dry powder the binder fluid can spread throughout the mass before a significant increase in its viscosity occurs. Increased viscosity causes a reduction in the weight of the finer fractions (Table 3). Sucrose, therefore, increases the mean granule size by increasing the total volume of binder liquid, except when the binder liquid which is produced has a high viscosity, then poorer mixing leads to the formation of smaller granules.

The effect of sucrose can also be seen in the work required to crush granules containing it (Table 2). Granules containing 10% prepared with 7·5 or 10% binder were much stronger than those containing none but using 15% binder. Increasing the binder concentration from 7·5 to 10% does not result in any significant change in granule strength. This is because there is no increase in dissolution of sucrose, as it is all soluble in the lower binder volume, the additional PVP, lactose and boric acid which dissolve have only a minor effect.

Sucrose alone acts as a good binder contributing to granule strength by dissolving readily in the binder fluid and then forming strong bridges when the binder solvent is removed.

The effect of Sta-Rx 1500 as third component

Sta-Rx 1500 (referred to subsequently as Sta-Rx) is a modified corn starch which has been used in the pharmaceutical industry as a direct compression tablet base. The starch is steam-treated and is partly gelatinized, there is about 20% cold water-soluble fraction present in the commercial material. In addition Sta-Rx has a normal moisture content of about 15% w/w. It thus represents an excipient with a partial solubility in water combined with a high equilibrium moisture content. Its affinity for water, after drying, will therefore be similar to that of starch.

The mean granule sizes of lactose: boric acid blends containing 10% of Sta-Rx, granulated with 15, 17·5, and 20% binder liquid are given in Table 1. Sta-Rx blends granulated with 15% w/w binder gave granules significantly smaller than those from blends without Sta-Rx. This result is similar to those found using untreated starches (Jaiyeoba & Spring 1979). The high affinity for moisture of dried Sta-Rx will result in less liquid being available for granulation and hence smaller granules.

Investigations using an apparatus similar to that described by Jehl (1977) indicated the volume of binder solution required to saturate Sta-Rx was 36% and for potato starch 38% w/w.

However, with an increase in binder concentration to 17·5 w/w the granules produced from the ternary mixture are similar to those produced from the corresponding binary mixture using 15% binder. A further increase in binder to 20% then gave the maximum granule sizes that were obtained for the various ternary blends examined. The increased size results from increased dissolution of the component powders and increase in the total free liquid available for massing.

The untreated starches are insoluble in water and can be recovered from granules with little or no damage to their structure by dissolving the lactose and boric acid and leaving the starch grains in suspension. This is not so with Sta-Rx as it interacts with water during massing and when dried forms a hard mass giving strength to the dry granules. All the granules containing Sta-Rx had a much greater resistance to crushing than those without it (Table 2). Further increase in Sta-Rx content had little effect on granule strength, whereas the mean granule size decreases.

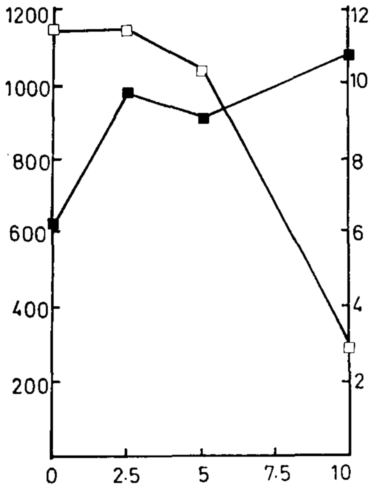

FIG. 2. The effect of Sta-Rx concentration on the size and strength of granules produced from 75:25 lactose: boric acid and Sta-Rz mixtures using 15% w/w of binder solution. ■ Granule strength. □ Mean granule size. Abscissa: % w/w Sta-Rx. Ordinates: Left: mean granule size (μm). Right: work done ($\times 10^4$ J).

Although an increase in the amount of PVP binder solution produced an increase in the size and strength of the granules, the contribution to strength due to the Sta-Rx was sufficiently great to make the effects due to increased PVP and excipient content of the solution of little significance. Granules obtained from two blends using 17·5% w/w binder solution or water as binder gave mean sizes and mean work to crush granules of 1050 μm and 14·8 ± 2·6 × 10^{-4}J and 1050 μm and 15·3 ± 2·8 × 10^{-4}J respectively.

With Sta-Rz therefore there is a major contribution to dry bond strength from the soluble component coupled with an affinity for water that reduces the amont available for forming wet masses and hence increase in Sta-Rx content produced a decrease in mean granule size.

The effect of magnesium, carbonate as third component

Magnesium carbonate powder is readily wetted, practically insoluble in water, but its solubility is enhanced in the presence of acids.

Blends containing different proportions of lactose: boric acid and 10% magnesium carbonate, granulated with increasing binder volumes (10–15% w/w) showed a progressive increase in mean granule size (Table 1). Granules prepared with 15% w/w binder are also found to be bigger than the corresponding ones without magnesium carbonate. A similar effect is seen on the work required to crush granules containing magnesium carbonate, with greater significance for blends containing higher boric acid concentrations (Table 2).

Blends containing higher proportions of boric acid appear to be more sensitive to the presence of magnesium carbonate as seen in their measured properties. This is due to the dissolution of magnesium carbonate in the binder solution when boric acid is present to give an acidic medium for dissolution.

Two tests were performed to examine the possibility of enhanced solubility of magnesium carbonate in boric acid solutions. In the first magnesium carbonate (10 g) was shaken intermittently with water (100 cm^{-3}) containing boric acid (0·5 g) for 2h. The solutions/suspensions were left for 24 h, filtered and washed with water. The residues were dried at 50 °C and weighed, the results, as dry weights of residue, were:— with no boric acid—9·75 g; 1%—9·56 g; 2%—9·38 g; 3%—9·14 g; 5%—8·60 g.

In the second test, approximately 2 g granules, accurately weighed, were subjected to a similar treatment. The results were:— with granules originally containing 10% boric acid—28% dissolved; 25% acid-37% dissolved; 50% acid-44% dissolved; 90% acid-60% dissolved.

These results indicate clearly that the solubility of magnesium carbonate is significantly increased in the presence of boric acid.

CONCLUSIONS

In wet granulation, granule growth is initiated by the formation of liquid bridges between primary particles. The number of such bridges depends on the total quantity of binder liquid available to wet the powder. Sucrose will dissolve in the binder solution to increase the liquid volume available for wet granulation and thus give mainly large damp granules, these will retain their size on drying due the presence of the dissolved components of the granulating liquid giving solid bridges of sufficient strength to withstand subsequent handling. In a previous study, starch in granulations caused a decrease in granule size and this was attributed to the absorption of water by the starch reducing the volume of liquid available to form damp granules.

A similar effect on granule size is found using Sta-Rx 1500 but with this material granule strength increases as Sta-Rx 1500 concentration increases. This results from dissolution of the water-soluble component of the Sta-Rx 1500 to give an increase in the amount of material in the solid bonds which form on drying the granules. Magnesium carbonate also produces results which are dependent in the solubility of the basic powder in the binder liquid.

The results given above indicate that the solubility of a component in the binder liquid can significantly influence the properties of the final granule. This is the result of two related effects, firstly dissolution will result in an increase in the binder liquid: solid ratio giving bigger damp granules and secondly this extra solid in the binder liquid will often result in stronger bridges when the granules are dried. If one of the components of the granule absorbs water, as does dried starch and Sta-Rx 1500 then this will reduce the volume of binder liquid available to form wet granules and so smaller granules will result.

As described previously (Jaiyeoba & Spring 1979) granule size data were fitted to the polynomial:—

$$Gd = P_0 + P_1x_1 + P_2x_2 + P_3x_1x_2 + P_4(x_2)^2 + P_5(x_1)^2x_2 + P_6x_1(x_2)^2 + P_7(x_2)^3$$

where Gd = mean granule size (μm), x_1 = binder concentration, x_2 = fractional percentage of lactose, $P_0 - P_7$ = variable parameters.

The values of parameters $P_0 - P_7$ and the corresponding coefficient (r) are given in Table 4. The values of r indicate that granule size can be related to the proportion of components in the mixture and the amount of binder liquid used for granulation.

The factors that favour the growth of wet granules may also contribute to the physical strength of these granules. This will occur if dissolution increases the volume of the binder liquid and also gives material that contributes significantly to the strength of the solid bridges that form when the granules are dried.

Table 4. Calculated values of parameters for a polynomial relating mean granule size to binder concentration and lactose concentration for blends of lactose: boric acid and various third components.

	Sucrose	Sta-Rx 1500	Magnesium	carbonate
	10%	10%	10%	2·5%
P	1·08	1·04	0·85	1·01
P_1	0·46	0·53	0·38	0·33
P_2	0·04	−0·21	0·58	0·52
P_3	−0·11	−0·15	−0·11	−0·43
P_4	−0·01	−0·09	−0·18	−0·41
P_5	0·01	−0·12	−0·25	0·19
P_6	−0·18	−0·25	−0·01	0·19
P_7	0·23	0·76	−0·26	−0·17
r	1·0	0·98	1·0	1·0

r = correlation coefficient.

A component present in a granulation at a concentration of 10% or less can thus affect the size and strength of the dry granules in a number of different ways. Change in formulation should, therefore, always take into account possible changes due to alteration in the amount of the granulation likely to dissolve in the binder liquid or the amount of liquid likely to be absorbed by a new component.

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