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The granulation of binary mixtures

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Granules have been prepared from blends of lactose and boric acid by the massing and screening method and their properties have been compared with those of granules from the individual materials, granulated separately. Increasing the volume of binder solution used produced granules stronger and of greater mean size in all blends studied. The largest and strongest granules, for any given binder solution volume and massing time, were obtained from a blend, as were the granules with the minimum pore size. The effect of massing time on granule properties was generally similar to those already reported for single component systems; prolonged massing in some blends led to a reduction in mean granule size. Variation in pre-mixing time produced no significant change in the physical properties of granules prepared from a lactose: boric acid blend.

There has been no systematic study of the granulation of multi-component powder systems with a view to understanding the mechanisms involved in granule growth in such systems and also possibly predicting the properties of the granules obtained from them. The work reported here deals with the granulation of mixtures of lactose and boric acid using an aqueous solution of polyvinylpyrrolidone (PVP) as binder. Lactose was chosen as the common diluent in tablet formulations and boric acid as a poorly water soluble, non-readily wetted, finely divided solid of similar density to lactose.

MATERIAL AND METHODS

Lactose B.P. (Whey Products Ltd): 3 batches having specific surface areas of 1·39, 1·32 and 1·32 $\times 10^3$ cm^3 g^{-1} and true densities of 1·5438, 1·5522 and 1·5432 g cm^{-3} respectively were used. Boric acid (BDH Chemicals Ltd) 2 batches having specific surface areas of 3·64 and 3·81 $\times 10^3$ cm^3 g^{-1} and true densities of 1·5048 and 1·5049 g cm^{-3} respectively were used. Polyvinylpyrrolidone (PVP) mol wt $\sim$700 000 (BDH Chemicals Ltd). All water used had been distilled in an all glass still.

Granulation. In a typical granulation, a mixture of lactose and boric acid (1 kg total) was dry blended for 4 min in a Z-blade mixer at 1·01 rev s^{-1}. Aliquots (30 cm^3) of freshly prepared 5% w/v aqueous PVP solution were added and massing continued for 60 s between each addition of binder solution and up to the total massing time. The mass was then forced through a 1·0 mm screen using an oscillating granulator. The resultant granules were dried for 24 min at 60°, screened through a 1·7 mm sieve and stored in glass jars. The moisture content of the granules so obtained was <0·5% w/w, as determined by loss of weight *in vacuo* at 50°.

Granule size distribution. A 50 g sample was subjected to sieve analysis using BS 4101, 4 inch test sieves.

Maximum tapped density. An unfractionated sample of granules was used to obtain the value of maximum tapped density according to Neumann (1953). The values were corrected for the effect of true densities of the components to calculate the fraction of space occupied by the granules.

Granule strength. A series of single granules, dried at 50° for 24 h, from a 1·18–1·0 mm sieve fraction were used to determine granule strength using the method of Ganderton & Hunter (1971).

Intragranular porosity and pore size distribution. Measurements were made on samples (1 g) from a 1·4–1·0 mm sieve fraction. The granules were dried at 50° for 24 h before the porosities were determined using mercury intrusion (Carlo Erba, Model 820) assuming a surface tension of 0·48 MN m^{-1} and a contact angle of 140° for mercury.

Reproducibility of the granulation method. Six batches of granules were made with lactose 75% w/w: boric acid 25% w/w using a fixed procedure. Premixing was for 4 min, PVP solution 5% (120 cm^3) was added in four equal aliquots with 60 s mixing between each addition and 2 min mixing after the final aliquot had been added. Details of the six batches are given in Table 1. This shows that the granulation gave reproducible results within the quoted limits.

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Table 1. *Details of six batches of granules made by the same procedure.*

Sieve size	1·4	1·0	710	500	355	250	180	75	<75
Mean weight (retained, %)	0·70	44·2	20·9	7·95	8·84	7·9	5·3	3·9	0·37
s.d.	0·21	3·03	2·28	1·65	1·12	1·00	0·81	1·05	0·16

Intragranular porosity % mean 42·45 (s.d. 0·36). Fraction of volume occupied by granules mean 0·346 (s.d. 0·0033). Granule strength (× 10⁴J) mean 9·06 (s.d. 0·27).

Effect of pre-mixing time. Variation of pre-mix time from 2–16 min did not produce any significant ($P > 0{\cdot}05$) changes in the properties of granules prepared from 50% lactose: boric acid mixtures.

Effect of the volume of binder solution used and of the proportion of each component of the granules. Lactose, boric acid and mixtures of both all showed an increase in mean granule size and granule strength with increasing volume of binder solution (Fig. 1). These increases are similar to those reported for single component systems (Hunter & Ganderton, 1972). There is also a blend of lactose and boric acid that produces granules of maximum size and strength when using 12% v/w or 15% v/w binder solutions. Student's *t*-tests showed significant ($P > 0{\cdot}95$) differences between the granule strength values of the strongest granules and of granules made from other proportions of lactose and boric acid, using the same granulation conditions.

For lactose: boric acid blends, the blend that gave the strongest granules usually had the highest mean granule size. Typical granule size distributions of granules prepared from lactose: boric acid blends for a single set of granulating conditions are shown in Fig. 2.

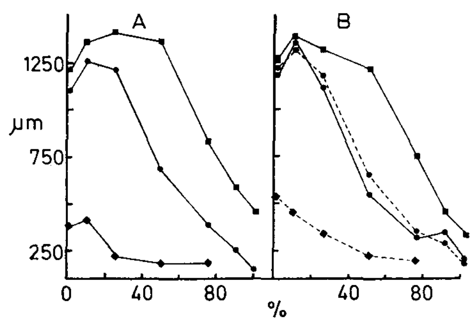

FIG. 1. The effect of varying the proportion of boric acid and the volume of granulating solution used on the mean size of granules (µm) prepared from lactose: boric acid mixtures. Vol. of granulating solution (% v/w) ◆9, ●12, ■ 15. Massing times A 5 min for 9% and 12%, 6 min for 15%. B——— 15 min; - - - 60 min. x-axis-Percentage w/w boric acid in mixture.

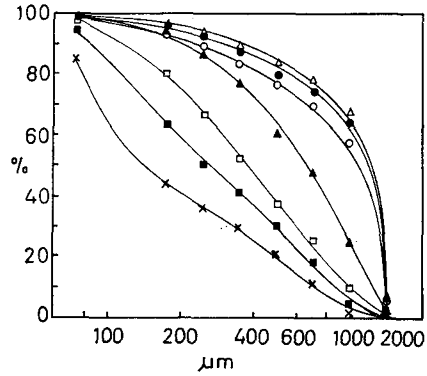

FIG. 2. Granule size distribution (µm) of batches of granules prepared from lactose: boric acid mixtures by massing and screening. Volume of granulating solution used = 12% v/w. Massing time = 5 min. Lactose: boric acid mixtures ○ 100:0. △ 90:10. ● 75:25. ▲ 50:50. □ 25:75. ■ 10:90. × 0:100. y-axis-Cumulative weight % oversize.

The values obtained for intragranular porosities (Table 2) showed a minimum corresponding to the maximum granule strength. The mean pore size (below 14 µm) of mixtures also had a minimum value (Fig. 3). Increasing the volume of binder solutions resulted in an increase of mean pore size with blends containing 25% or less boric acid and a decrease with blends containing more than 25% boric acid. With 12% binder solution the minimum mean pore size (below 14 µm) was obtained for a 25% boric acid: 75% lactose blend. With 15% binder solution the minimum was obtained for a 50:50% blend.

The relation between proportion of components in the blend, massing time and volume of binder solution used on granule packing properties are

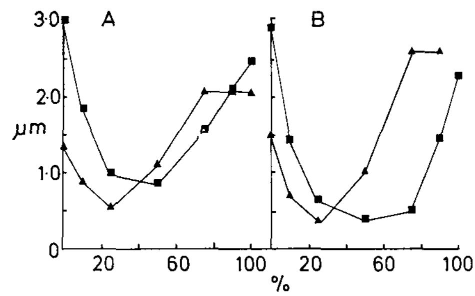

FIG. 3. The effect of varying the proportion of boric acid on the size of pores (smaller than 14 µm in diameter) of granules prepared from lactose: boric acid mixtures. Amount of granulating solution used: ▲ = 12% v/w. ■ = 15% v/w. Massing time (min) A = 5 for ▲ and 6 for ■ B = 15. y-axis-Mean pore radius (µm). x-axis-Percentage w/w boric acid in mixture.

Table 2. *Mean granule strength of 1·18–1·0 mm granules, and intragranular porosity of 1·4–1·0 mm granules prepared from mixtures of lactose and boric acid.* P = % v/w of 5% w/v PVP solution used as binder solution.

% lactose: boric acid	Mean granule strength (× 10^4J)								Intragranular Porosity (%)							
	P9 massing time (min)		P12 massing time (min)			P15 massing time (min)			P9 massing time (min)		P12 massing time (min)			P15 massing time (min)		
	5	60	5	15	60	6	15	60	5	60	5	15	60	6	15	60
100:0	6·5	6·7	6·8	10·3	11·3	8·2	12·8	12·7	51·6	48·8	45·2	44·1	44·2	44·9	36·8	34·7
90:10	6·2	7·1	8·7	12·5	14·4	10·0	12·9	—	46·5	44·2	43·4	36·1	29·4	40·8	33·1	—
75:25	5·3	7·3	9·1	10·2	12·5	11·0	15·2	—	45·0	44·7	36·5	39·1	37·7	42·7	29·4	—
50:50	4·6	5·8	7·0	9·9	11·4	9·0	12·5	—	46·8	47·9	43·8	40·5	39·0	43·2	32·3	—
25:75	4·2	4·5	6·2	6·5	8·3	8·3	11·4	10·8	48·5	49·1	46·1	44·4	44·6	42·2	42·1	39·0
10:90	—	—	5·5	6·2	7·9	7·9	8·2	8·9	—	—	47·5	48·4	44·3	42·2	42·9	43·2
0:100	—	—	5·0	5·6	6·8	6·8	6·0	6·1	—	—	48·5	49·4	47·6	48·5	47·1	45·5

given in Table 3. After 5 min total massing the effect of increased binder volume is to produce denser granules with all the blends examined. With further massing, this increase in density with different volumes of binder solution is not seen. Prolonged massing (60 min) with 9% v/w binder solution produces less dense granules in all the blends examined.

DISCUSSION

Increased volume of binder solution led to the production of stronger granules, this is due to a number of factors. Firstly, more binder will be added to the powders and hence there will be more PVP available to form bonds. Secondly, as the volume of liquid increases, so will the amounts of lactose and boric acid that will dissolve during massing, this will also contribute to the crystal bridges formed between particles in the dry granule. Thirdly, as more solids go into solution, the smaller particles will be dissolved preferentially, thus reducing the surface area of solid to be wetted during massing.

It would thus be expected that lactose being more soluble would produce stronger, bigger granules alone than in admixture with boric acid. Boric acid is more difficult to wet than lactose and also produces weaker granules for the same granulation condition, more binder liquid is therefore required to adequately wet the boric acid and in mixed granulations the lactose will be preferentially wetted A 12% w/v binder solution is insufficient to adequately wet a 25% boric acid blend and it gives a maximum strength and mean size with 10% boric acid. Increased binder is needed to move the maxima to the 25% boric acid granules. Increased strength with massing time is presumably due to increased packing and we find the decrease in mean pore size in agreement with this.

Table 3. *The effect of amount of granulating solution used and massing time, on the packing property of batches of granules made from lactose: boric acid mixtures.* P = % v/w granulating solution. Granulating solution 5% w/v PVP in distilled water.

% lactose: boric acid	Fraction of space occupied by granules after tapping (cm^{-3}) after massing for:							
	5 min			15 min		60 min		
	P9	P12	P15	P12	P15	P9	P12	P15
100:0	0·364	0·325	0·331	0·348	0·373	0·386	0·361	0·369
90:10	0·360	0·355	0·344	0·348	0·387	0·380	0·365	—
75:25	0·388	0·374	0·344	0·374	0·395	0·427	0·395	—
50:50	0·408	0·362	0·344	0·391	0·402	0·454	0·402	—
25:75	0·423	0·395	0·356	0·396	0·368	0·472	0·402	0·405
10:90	—	0·406	0·379	0·406	0·380	—	0·432	0·412
0:100	—	0·405	0·411	0·446	0·380	—	0·446	0·439

Relation between average granule size and the volume of binder solution used

The model proposed by Butensky & Hyman (1971) for the relation between average granule size and the amount of granulating solution used was applied to lactose : boric acid mixtures. Butensky & Hyman used glass beads as the starting material and proposed a linear relation between the logarithm of the relative mean granule sizes (RMGS, see Fig. 4 for definition) and the volumes of binder solution used.

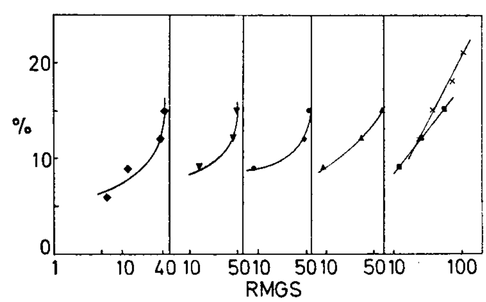

FIG. 4. Relation between volume of binder solution used and the relative mean granule size (RMGS) of granules prepared from lactose: boric acid mixtures. RMGS = (mean granule size)/(average particle diameter of powder blend). ◆ = Lactose 100%. ▲ Lactose 90%, boric acid 10%. ● Lactose 75%, boric acid 25%. ▼ Lactose 50%, boric acid 50%. ■ Lactose 25%, boric acid 75%. × Lactose 0%, boric acid 100%. y-axis-Percentage v/w granulating solution used.

Fig. 4 indicates the relations obtained using mixtures containing lactose and boric aicd in varying proportions. It seems that the proposed model is solubility-dependent as the relation holds quite well for boric acid and less well for lactose. Increasing the proportion of boric acid in the mixture gave progressively better correlation with the proposed model.

Effect of massing time on granule properties

The results obtained using a selected blend of lactose: boric acid (Table 4) were in agreement with published data for single component systems (Hunter & Ganderton, 1972) in that increased massing time resulted in larger, stronger, more compact granules. However, for other blends of lactose : boric acid the relation between mean granule size and massing time for binary mixtures is dependent on the proportions of the components in the mixture and on the volume of the binder solutions used (Fig. 1).

Increase in massing time results in an increase in granule strength and a decrease in intragranular porosity (Table 4). Prolonged massing times at the highest binder volumes with blends containing more than 50% lactose produce pasty masses difficult to granulate. Generally, increased massing time produced more compact granules having reduced intragranular porosities and increased mean granules size for blends of lactose and boric acid. However, because of the variation in average bond strengths (which later determine granule strengths) in the various blends, and also because blends reach maximum granule size after different massing times, differences must occur in the observed effects of increasing massing time on mean granule size. Where massing has taken place for much longer than necessary for maximum mean granule size to be achieved, breakdown of the larger agglomerates into smaller ones can occur especially where the agglomerates are held together by relatively weak bonds (e.g. in blends with high proportions of boric acid).

Despite a possibility of reduced mean granule size, consolidation and compaction of the granules still take place with increased massing time leading to reduced granule porosity.

Table 4. *The effect of massing time on the properties of granules prepared from a selected mixture of lactose: boric acid (75:25%).* A = Mixture granulated with 9% v/w of PVP solution (5% w/v). B = Mixture granulated with 12% v/w of PVP solution (5% w/v).

	Massing time (min)	Mean granule size (μm)	Intra-granular porosity (%)	Mean pore radius (μm)	Granule strength (× 10⁴J)
A	5	215	49·7	7·0	4·13 ± 0·53
	15	215	48·1	2·2	5·08 ± 0·59
	60	335	44·7	1·08	5·68 ± 0·50
	90	360	46·1	0·89	6·44 ± 1·02
B	5	900	46·8	1·56	7·42 ± 1·07
	15	1100	43·5	1·23	8·22 ± 1·26
	60	1150	36·6	0·47	10·19 ± 0·98

CONCLUSIONS

The results for mixtures of lactose and boric acid indicate that the properties of mixed granules are not the result of addition of the properties of their components.

For any particular volume of binder and, to a lesser extent, massing time, one blend exhibits maximum mean granule size and strength.

Blends reach maximum granule size after different massing times due to variations in the rate of achieving equilibrium wetting. Prolonged massing can result in the breakdown of the larger aggregates to give a reduced mean granule size. This effect is not large and may well be due to the loss of excess water from a wet, and therefore, large aggregate.

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