J. Pharm. Pharmac., 1976, **28**, 806–809 *Received July* 19, 1976

The granulation of binary mixtures: the effects of the composition of the granulating solution and the initial particle size of one component on granule properties

W. O. OPAKUNLE* AND M. S. SPRING†

*Department of Pharmacy, University of Manchester, Manchester M*13 9*PL, U.K.*

The effect of total solvent volume and the presence of dissolved material (other than binder) in the granulating solution, on the properties of granules prepared from lactose: boric acid mixtures has been studied. The total volume of binder solution available to powder mixtures during massing determines the ultimate average size of granules produced. Part-dissolution of powders being granulated contributes significantly to the average granule size by increasing the total solution volume and reducing the amount of powder to be wetted. Although the amount of PVP (binder) dissolved in the granulating solution contributed very little to granule size at the concentration examined, the combined effect of total volume of solution and amount of PVP present in the granulating solution determines granule strength and porosity. The effect of the initial particle size of lactose in a binary mixture with boric acid differs from its effect reported for single component systems.

Previously data were presented on the granulation of mixtures of lactose and boric acid to show the effect of (1) the proportion of components in the binary mixture, (2) the volume of the granulating solution, (3) the massing time and (4) the premixing time on the properties of granules prepared from lactose: boric acid mixtures (Opakunle & Spring, 1976).

No systematic study has been made of the role of the components of the granulating solution (solvent and solute) on the properties of granules made from binary mixtures. We have therefore assessed to what extent the total amount of solvent and solute (available to powders during granulation) affect granule formation and their respective contributions to the properties of granules prepared from such mixtures.

Part dissolution of components of a powder mixture being granulated may be a factor affecting granule properties. The effect of the presence of dissolved materials in the granulating solution (other than the binder) on granule properties has therefore been examined. An investigation into the effect of the initial particle size of one of the components of the binary mixture on the properties of granules prepared from such mixtures was also undertaken.

* Present address: School of Pharmacy, University of Ife, Ile-Ife, Nigeria.
† Correspondence.

MATERIALS AND METHODS

The physical properties of materials and the methods of preparation of the granules have been reported by Opakunle & Spring (1976). For the investigation into the contribution of the components of the granulating solution to granule properties, solutions containing varying quantities of binder (PVP) and solvent (distilled water) were prepared as shown in Table 1. Where the amount of solvent was increased, the additional quantity of solvent was always added as the last item before massing was completed.

To study the role of dissolution in granule formation, two modifications were made to the standard granulating solution. One was to dissolve the PVP in a saturated aqueous solution of lactose and boric acid and the other was to dissolve the same weight of PVP in a saturated aqueous solution of lactose. The two PVP solutions so obtained were then used to granulate a selected binary mixture of lactose and and boric acid.

To study the effect of the initial particle size of lactose on granule properties, two fractions of the original lactose batch were obtained by sieving this batch through a 63 μm aperture sieve on an Alpine Air Jet sifter (Alpine Machinery, Uxbridge, Middlesex). The two fractions were designated L240F (finer than 63 μm) and L240G (coarser than 63 μm) respectively. The mean particle diameter of L240F was determined using the Fisher Subsieve Sizer. The two lactose fractions each in combination with boric acid (lactose 25%: boric acid 75%) were then granulated as before. Two massing times, 5 and 15 min, were used. Analysis of the properties of the granules prepared was as described earlier (Opakunle & Spring, 1976). Granule properties investigated included size distribution, strength, porosity and micropore size distribution.

RESULTS AND DISCUSSION

The effect of the quantity of solute and solvent, in the granulating solution, on granule properties

The amounts of PVP and water in the granulating solutions were varied, as shown in Table 1, and used to granulate two blends of lactose: boric acid (75:25 and 25:75).

Similar results were obtained for both lactose: boric acid mixtures. A reduction in the total amount of solvent used but with the quantity of solute (PVP) kept constant resulted in a reduction in the average granule size and granule strength and an increase in granule porosity. The contribution of dissolved PVP was not significant (at the concentrations used) in the determination of granule size. The influence of PVP was seen more significantly in the determination of granule strength. The effect on granule size is clearly shown by the granule size distribution of the batches prepared using lactose 25%: boric acid 75% (Fig. 1). Increase in massing time led to the formation of stronger and less porous granules and granules of greater mean size. It seems, therefore, that the total volume of liquid available to lactose: boric acid mixtures controls the size of the granules produced from such mixtures. Although the contribution of PVP to granule size was not significant it may become so at higher concentrations. However, the granule strength and porosity are a function of both the total volume and the concentration of the binder solution used. This may be owing to the fact that in the systems studied, the major requirement for satisfactory granule formation is either the solubility of the components in the aqueous binder solution or their wettability or both of these two properties.

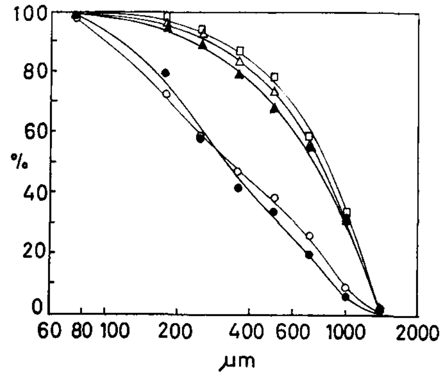

FIG. 1. The effect of varying the total volume and PVP content of the granulating solution, on the size distribution (µm) of granule batches prepared from lactose 25%: boric acid 75% mixtures. y axis—cumulative weight % oversize.

	Total binder volume (cm³)	PVP content (g)	Massing time (min)
○	120·0	6·0	15
△	150·0	7·5	15
▲	150·0	6·0	5
□	150·0	6·0	15
●	120·0	7·5	15

Table 1. *The effect of varying the quantities of solute and solvent on the properties of granules prepared from selected binary mixtures of lactose and boric acid.*

Lactose: boric acid %	Massing time (min)	Vol. of PVP (cm³)	% v/w of PVP solution	Vol. of extra water added (cm³)	Total wt PVP added (g)	Mean gran. size (µm)	Intragran. porosity %	Granule strength (× 10⁴ J)
25:75	5	120	5	0	6	375	46·1	4·8 ± 0·5
25:75	15	120	5	0	6	310	44·1	5·3 ± 0·4
25:75	5	120	5	30	6	740	44·9	7·0 ± 0·9
25:75	15	120	5	30	6	780	44·1	7·3 ± 1·0
25:75	15	150	5	0	7·5	750	44·2	7·5 ± 0·9
25:75	15	120	6·25	0	7·5	300	46·1	5·9 ± 0·9
75:25	5	120	5	0	6	900	46·3	7·4 ± 1·0
75:25	15	120	5	0	6	1100	43·5	8·2 ± 1·5
75:25	5	90	5	30	4·5	920	42·1	7·0 ± 0·9
75:25	15	90	5	30	4·5	1120	41·2	7·5 ± 1·0
75:25	15	90	6·67	0	6	290	49·0	5·1 ± 0·9

The effect of the presence of dissolved solid (other than the binder) in the granulating solution, on granule properties

The results obtained are shown in Table 2. Some lactose and boric acid will dissolve in the granulating liquid during massing. The contribution of this dissolution to granule formation was investigated using granulating solutions already saturated with lactose and boric acid. It was found that part-dissolution of the starting materials in the granulating solution had a profound influence on the mean size of granules prepared from binary mixtures. Granule strength was not significantly ($P = 0{\cdot}05$) affected by the presence of previously dissolved lactose and boric acid in the granulating solution but granules of lower porosities than the standard granules (made with 5% PVP in distilled water) were produced. The micropore size distributions were also affected as there was a change in mean pore radius (Table 2). The results show the influence of total solvent volume on granule growth. This in turn indicates the profound effect of the solubility of components in the granulating solution on granule formation in the systems examined. Since the granulating solutions were already saturated with lactose the amount of solid lactose in the mixture remained almost constant throughout the massing period as none could dissolve in the granulating solution. There was therefore more powder surface to be wetted in these cases than when the binder solution was made with distilled water. The standard granulating solution still had the capacity to dissolve part of the lactose present in the blend and so increase its own volume, while decreasing the amount of powder to be wetted.

Table 2. *The effect of the quantities of dissolved solute in a granulating solution on the properties of granules prepared from a selected binary mixture of lactose and boric acid. Mixture: Lactose 75%, boric acid 25%. Massing time = 15 min.*

Gran. sol.	Mean gran. size (μm)	Gran. stgth ($\times 10^4$ J)	Intra-gran. porosity (%)	Mean pore radius (μm)
A	1100	8·22 ± 1·26	43·5	1·23
B	460	8·75 ± 0·79	42·3	2·29
C	520	8·04 ± 0·67	43·1	3·06

Granulating solutions: A = 5% w/v PVP solution made in distilled water. B = 5% w/v PVP solution made in a saturated solution of lactose and boric acid. C = 5% w/v PVP solution made in a saturated solution of lactose (5% w/v PVP = 12% w/v).

Although the granule strengths were not affected by the presence of previously dissolved lactose and boric acid, lower intragranular porosities were obtained for these batches of granules. This may be due to the recrystallization of the solutes, on drying, leading to some of the pores being filled with crystals of these materials which were not part of the initial powder system. The lower porosity may also be due to the retention of more of the finer particles which would be preferentially removed by dissolution when using a non-saturated solution as binder.

The effect of initial particle size of lactose on the properties of granules prepared from lactose: boric acid mixtures

The results obtained using the two lactose fractions in blends with boric acid (Table 3) differ from those reported by Hunter & Ganderton (1972) for single component systems. They reported that an increase in initial particle size of lactose produced granules of reduced strength and porosity. Our results indicate that for a binary mixture, increasing the initial particle size of one of the components (in this case, lactose) leads to increased granule strength and reduced mean pore size, for pores finer than 14 μm.

Table 3. *The effect of initial particle size of a component on the properties of granules prepared from a binary mixture.*

Lactose: boric acid (%)	Mean part. diam. of lactose (μm)	Mass. time (min)	Gran. stgth ($\times 10^4$ J)	Intra gran. poros. (%)	Mean pore radius (μm)
25:75 (F)	15·23	5	4·25 ± 0·45	47·5	2·63
25:75 (G)	>63·0	5	5·46 ± 0·41	48·0	1·79
25:75 (F)	15·23	15	5·84 ± 0·47	45·6	2·29
25:75 (G)	>63·0	15	7·05 ± 0·45	45·5	1·47

Amount of granulating solution = 12% v/w PVP in distilled water. F = Lactose fraction finer than 63 μm. G = Lactose fraction coarser than 63 μm.

This relation is independent of massing time, as shown by our results from the 5 and 15 min massing times. The micropore sizes for these granules indicate the presence of a greater number of larger pores in the granules containing the finer lactose fraction than those containing the coarser fraction. This is in accordance with the granule strength results. It seems, therefore, that the blend containing the coarser lactose fraction packs more effectively and more closely in the presence of a second component (boric acid, mean particle diameter 10·5 μm), the particles of which presumably fill the spaces between the lactose agglomerates more effectively, yielding smaller pores in the final product.

CONCLUSIONS

It can be concluded from these investigations that the total volume of solvent (or liquid) available to powder mixtures determines the ultimate average size of the granules produced. Part-dissolution of [illegible]ers being granulated makes a significant con- [illegible]tion to the final mean granule size because the [illegible] reduction of the capacity of the granulating solution to dissolve some of the starting materials leads to the production of weaker granules and granules of smaller mean size. The combined effect of total volume and the total amount of binder present in the granulating solution determines granule strength and porosity. The effect of the initial particle size of a component of a binary mixture, on granule strength, was found to differ from that reported for single component systems.

REFERENCES

HUNTER, P. M. & GANDERTON, D. (1972). *J. Pharm. Pharmac.*, **14**, *Suppl.*, 17P–24P.
OPAKUNLE, W. O. & SPRING, M. S. (1976). *Ibid.*, **28**, 508–511.