J. Pharm. Pharmac., 1976, **28**, 915–918 *Received July* 19, 1976

The granulation of binary mixtures: the effects of the properties of the component powders on granules

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Sulphanilamide and citric acid individually and in various proportions with lactose, have been granulated by massing and screening. There was an optimum blend, that produced granules of maximum mean size and strength, for each binary system examined. The proportion of the components of this optimal blend was dependent on the physical properties of the second component in a mixture with lactose. Results from three systems, lactose : boric acid, lactose : sulphanilamide and lactose : citric acid indicate that although part dissolution of powder during granulation is a factor affecting granule properties, in some systems other physical properties of the second component may become dominant. It is suggested that the combined effect of cohesiveness and wettability of the powders may make the major contribution to granule strength with the sulphanilamide systems. The ultimate mean granule size produced is determined by the wettability or solubility of the powders, or both, in all cases examined. The great affinity of citric acid for aqueous binder solution was the dominant factor determining the properties of granules prepared from lactose : citric acid mixtures.

We have previously shown the effect of part-dissolution of powders, during granulation, on granule formation and on granule properties (Opakunle & Spring, 1976a,b). The dissolution of some of the lactose in lactose : boric acid mixtures during granulation was considered a major factor in determining certain properties of the granules formed from such mixtures. One of the binding mechanisms in the granulation process proposed by Rumpf (1958) was that involving solid bridge bonds. These bonds include those obtained by recrystallization of dissolved materials and the hardening of binder material after drying. Harwood & Pilpel (1968) and Hunter & Ganderton (1972) have linked the strength of granules, prepared from single component systems, with the solid bonds formed by recrystallization of dissolved material on drying the wet agglomerates.

The solubility of materials in the granulating solution seems to be a parameter affecting the physical properties of granules formed by massing. We now show the significance of the phenomenon of part-dissolution to granule formation by granulating sulphanilamide (solubility 1 in 250 in water) and citric acid (solubility 5 in 3 in water) separately and in mixtures with lactose.

MATERIALS AND METHODS

The physical properties of the materials used were determined as previously reported (Opakunle & Spring, 1976a). Sulphanilamide, B.P.C. (ICI Pharmaceuticals) mean diameter 14·8 μm, specific surface $2{\cdot}65 \times 10^3$ cm^2 g^{-1}, density 1·5285 g cm^{-3} and citric acid powder (BDH Chemicals), mean diameter 22.7 μm, specific surface $1{\cdot}688 \times 10^3$ cm^2 g^{-1}, density 1·568 g cm^{-3} were mixed with lactose (Whey Products, Crewe, England) mean diameter 29·4 μm, specific surface $1{\cdot}323 \times 10^3$ cm^2 g^{-1}, density 1·5432 g cm^{-3} and granulated as described by Opakunle & Spring (1976a). All blends were premixed for 4 min and massed for 5 min, 12% v/w binder solution was used for lactose : sulphanilamide blends while 6% v/w was sufficient to produce satisfactory wet masses from the lactose : citric acid blends. Granule properties were determined as before (Opakunle & Spring, 1976a).

RESULTS AND DISCUSSION

We have suggested that part-dissolution of powders, in a binary mixture, during granulation is a factor that determines granule size and strength. Stronger granules are obtained from at least one binary mixture than are obtained using either component separately. This has been shown to be true using blends of lactose with boric acid, with peak strengths at 75 : 25 and 90 : 10 lactose : boric acid (Opakunle & Spring, 1976a).

Lactose: sulphanilamide mixtures

Blends of lactose : sulphanilamide produced stronger granules and granules of greater mean size than either component granulated separately. Maximum strength was observed with the 50 : 50 blend while maximum mean size was observed with the 90 : 10

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lactose: sulphanilamide blend. The strongest granules had the lowest intragranular porosity (Table 1) linear regression for strength/porosity, r = 0·73.

The mean micropore sizes did not show any significant differences for batches containing up to 50% sulphanilamide, but mixtures containing more than this amount showed an increase in mean pore size with increase in sulphanilamide content until a maximum was reached at 100% sulphanilamide. Granules made from 90:10 lactose: sulphanilamide blend showed maximum packing, occupying the least fraction of space; this blend had the highest mean granule size (Table 1). With decreasing lactose content the mean granule size also decreased and the fraction of space occupied by the same mass of granules increased (Table 1).

Comparison of the granule strength results obtained for blends of lactose with sulphanilamide with those obtained previously from lactose: boric acid blends using the same granulation conditions (Fig. 1) shows the blend giving the strongest granules whilst being 90:10 for lactose: boric acid was 50:50 for lactose: sulphanilamide. This may be the result of sulphanilamide being less water-soluble (1 in 250) than boric acid (1 in 20), thus the binder will wet the lactose preferentially to produce a wetter granule which will dry to give stronger granules. Alternatively, the stronger granules with 50% sulphanilamide could be due to a difference in the particle shape of boric acid and sulphanilamide crystals, but the crystals are similar in shape, or to a difference in cohesiveness between boric acid and sulphanilamide.

Whilst with lactose: boric acid blends maximum granule strength occurred with the same blend as that producing the greatest amount of larger granules (Opakunle & Spring, 1976b), this was not so with lactose: sulphanilamide blends where maximum strength was observed with the 50:50 blend while maximum mean granule size was obtained with the 90:10 blend.

Lactose: citric acid mixtures

Lactose: citric acid mixtures required much less granulating solution than their lactose: sulphanilamide counterparts to produce mainly larger granules. Citric acid is more soluble (5 in 3) in an aqueous solution than lactose (1 in 6) and thus had a greater affinity of binder solution and produced stronger granules than lactose. In a lactose: citric acid mixture therefore, the lactose is the less readily wetted in contrast to the conditions found in lactose

Table 1. *The effects of varying the proportion of lactose on some properties of granules prepared from lactose: sulphanilamide and lactose: citric acid mixtures.*

% lactose: sulphanil. in mixture	Mean granule size (μm)	% gran. >355 μm	Mean pore size < 14 μm	Intragran. porosity %	Gran. strgth (× 10⁴ J)	Fraction of space occupied by granules after tapping
100:0	1100	83·8	1·3	45·2	6·8 ± 0·3	0·352
90:10	1250	90·8	1·35	42·9	8·3 ± 0·7	0·346
75:25	1190	89·6	1·35	40·9	10·2 ± 0·9	0·349
50:50	1050	85·5	1·4	39·9	12·3 ± 1·0	0·363
25:75	690	72·1	3·5	43·1	9·6 ± 0·9	0·373
10:90	570	65·5	3·1	44·5	10·0 ± 1·0	0·374
0:100	570	65·6	3·8	47·2	8·5 ± 1·0	0·372
% lactose: citric acid in mixture						
100:0	200	19·7	1·4	51·8	3·85 ± 0·4	0·432
95:5	620	69·8	3·1	44·5	7·4 ± 0·4	0·327
92·5:7·5	1075	87·4	0·7	43·4	12·7 ± 0·9	0·309
90:10	1130	93·9	0·6	33·8	21·5 ± 1·8	0·327
75:25	>1400	98·9	1·55	41·2	17·0 ± 1·3	0·374
50:50	1380	96·2	2·1	38·0	16·1 ± 1·0	0·370
25:75	1320	96·6	1·7	37·7	15·5 ± 1·6	0·366
10:90	1290	96·0	2·2	40·8	13·6 ± 1·2	0·361
0:100	1200	94·1	2·4	45·2	12·0 ± 1·2	0·358

Total massing time, 5 min.
Amount of granulating solution used = 12% v/w for sulphanilamide and 6% v/w for citric acid.

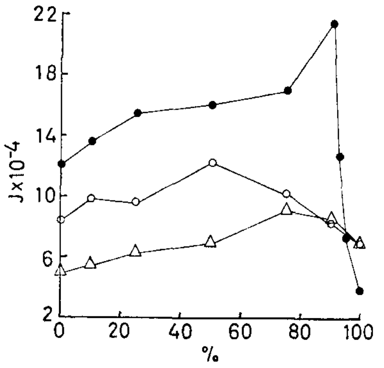

FIG. 1. The effect of type of powder on the strength of $-1 \cdot 18 + 1 \cdot 0$ mm granules prepared from binary mixtures. y axis—Work done ($J \times 10^{-4}$) x axis—Lactose (% w/w).

	Massing time (min)	Amount of granulating solution used (% v/w)
△ Boric acid	5	12
○ Sulphanilamide	5	12
● Citric acid	5	6

blends with boric acid and with sulphanilamide. In fact, citric acid had such a great affinity for the binder solution that only 10% was required in a mixture with lactose to produce granules much stronger than those made from 100% citric acid, despite the fact that citric acid produces much stronger granules than lactose when each is granulated separately. Maximum strength and packing were obtained at around the 90:10 lactose:citric acid blend (Table 1). The intragranular porosity results showed decreased porosity with increasing granule strength ($r = -0{\cdot}93$). The mean micropore size results did not follow any particular pattern but the smallest mean pore size was found with the 90:10 blend. Granules containing 50% or more of citric acid showed little change in mean granule size, granule porosity and packing volume. It also appears that blends containing 5 to 10% citric acid represent a point, after which, the citric acid becomes so dominant that the lactose plays little part in determining granule properties. The results indicate that the blend containing 10% citric acid is unique in some respects. Apart from the properties already mentioned, this batch was the most hygroscopic of all the blends with lactose (100 g of citric acid in 6% v/w binder solution, 60 cm^3, coincides with the solubility of citric acid in water). The 90:10 lactose: citric acid blend granulated with 6% v/w solution thus corresponds to a condition wherein the maximum quantity of citric acid may go into solution. This could account for the hygroscopicity of the granules as they become coated with a film of citric acid which recrystallized on drying.

Comparison of the binary systems studied

A fact that became apparent when comparing the strength of granules made from lactose: boric acid and lactose: sulphanilamide mixtures is that although boric acid is more water soluble (1 in 20) than sulphanilamide (1 in 250), sulphanilamide produced the stronger granules and granules of greater mean size. Thus part-dissolution of material in the granulating solution may not always be the most important factor in the production of granule strength and granule size. Consideration of the way in which boric acid and sulphanilamide behaved during granulation and the rate at which they were wetted (sinking times of 0·5 g in a thin layer, lactose 25 s; boric acid 23 min, by dissolution; sulphanilamide >2 h; citric acid, instant dissolution) show the considerable part played by the affinity for binder solution, wettability and cohesiveness in granule formation. An attempt to quantify the relative cohesiveness of the starting materials by plotting the reciprocal of the bulk density against the natural logarithm of the applied load and calculating the slopes of the resulting lines did not show any significant differences. However, from the way these powders behaved before wet granulation (i.e. sieving and premixing) it was possible to arrange them in the following order of cohesiveness: citric acid > sulphanilamide > lactose > boric acid. This is also the order of granule strengths of granules prepared from the powders separately.

CONCLUSIONS

Our results show that for each binary system examined, there is an optimum blend that gives granules of maximum size and strength. The proportion of components in this blend is a function of their solubility, wettability and cohesiveness. Although solubility in the granulating solution has been found to be a factor affecting granule formation and granule properties in lactose: boric acid and lactose: citric acid blends, other properties, such as cohesiveness become dominant in determining granule properties with lactose: sulphanilamide mixtures. It is, therefore, possible to speculate that the combined effect of cohesiveness and wettability of a powder is the major factor determining granule strength while part dissolution enhances and sometimes solely determines average granule size.

It has been found that 5% citric acid in a mixture with lactose greatly enhances granule build up, and greatly increases granule strength. This may be a characteristic of powders with high solubility in the granulating solution in which case it could be possible to take advantage of this property in formulation. Incorporating a powder of high solubility into a system with a poor affinity for binder solution and which does not readily form agglomerates can greatly enhance granule strength and build-up. The hygroscopicity which results from the use of citric acid may possibly be avoided using a compound which is not hygroscopic when in its anhydrous state.

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