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The granulation of ternary mixtures containing lactose and boric acid with different starches

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Ternary mixtures of lactose, boric acid and starch have been granulated by massing and screening. The properties of the granules have been compared with those resulting from granulation of blends of lactose and boric acid without starch. Potato, maize and rice starches have been studied as the third component at concentrations similar to those employed in tablet formulations. The starches caused a reduction in both mean granule size and granule strength. The effect is dependent on the proportions of the excipients. Increasing the amount of binder solution used gave bigger, stronger granules but did not compensate for the effects produced by the starches.

The work reported here is an extension of that dealing with the granulation of binary mixtures (Opakunle & Spring 1976). The lactose/boric acid blend has been used with the addition of three starches in order to examine the effect of granule components on granules in a state more closely related to that found in normal tablet granules.

MATERIALS AND METHODS

The excipients used had the following mean particle sizes and true densities: lactose B.P. (BDH) 31 μm, 1·5386 g cm^{-3}; boric acid B.P. (BDH) 14 μm, 1·5071 g cm^{-3}; potato starch (BDH) 32 μm, 1·520 g cm^{-3}; maize starch (BDH) 14·5 μm, 1·5424 g cm^{-3}; rice starch (BDH) 6·4 μm, 1·5302 g cm^{-3}. The materials were oven dried before granulation. The binder was an aqueous 5% w/v solution of polyvinylpyrrolidone (Plasdone K 29–32 GAF, U.K. Ltd.). The densities were determined with an air compression pycnometer (Beckman Instruments Ltd.), and the mean particle sizes were obtained using a Fisher Sub-Sieve Sizer.

Granulation

Granules were prepared using a massing and screening technique from 1 kg of blended powders. The weighed powders were pre-mixed for 4 min in a 'Z'-blade mixer at 1·01 rev s^{-1}, the required weight of freshly prepared 5% polyvinylpyrrolidone (PVP) solution was added in two equal portions. After the addition of the first portion, massing was carried out for 1 min and after the addition of the second portion massing was continued for 4 min. The resultant damp mass was forced through a 1·0 mm screen using an oscillating granulator. The damp granules were dried in a fluid bed drier with an inlet air temperaure of 50 °C for 30 min and then cooled and passed through a 1·4 mm screen before being stored in screw capped glass jars.

Analysis of granules

The size distribution was determined using a 100 g sample of granules and a set of 8 inch BS 4101 test sieves. The cumulative weight per cent retained was plotted against sieve aperture. The mean granule size was taken as the size corresponding to 50% cumulative weight oversize.

The work done in crushing single granules from the 1·18–1·0 mm sieve fraction was determined using the method of Ganderton & Hunter (1971). The mean of 20 determinations was taken as a measure of the mean granule strength for each batch.

Flow of unfractionated granule batches through a 1 cm circular orifice was measured using a perpendicular Perspex tube 6·3 cm internal diameter. The orifice was situated in the centre of the base of the tube. The weight of granules flowing and the time for the flow were recorded for the middle third of the total granule flow. The tube was initially filled to a level 25 cm above the base.

RESULTS

Reproducibility of the method of granulation

Four batches of the granules were prepared from blends of lactose: boric acid: potato starch, 71:24:5 using 15% w/v of PVP binder solution using the standard granulation technique described above. The calculated mean granule sizes were 960 ± 5 μm and

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* Correspondence.

mean work required to crush single granules was $3{\cdot}06 \pm 0{\cdot}13 \times 10^{-4}$ J.

Effect of the type of starch

Typical size distributions of granules prepared from blends of lactose, boric acid with and without starch are shown in Fig. 1. In each case the ratio of lactose to boric acid is 75:25. The results for mean granule size of all batches prepared are given in Table 1. From this it can be seen that the effect produced by the three starches used depend not only on the starch but also on the ratio of lactose to boric acid in the blend, and the amount of binder fluid used. In general, potato starch gave the biggest granules and rice starch the smallest ones. These differences were much less at lower lactose concentrations. Increasing the binder volume produced a general increase in size as expected with maximum values in the region of 1000–1100 μm due to the mesh screens used during granule preparation. There was also a general trend for granules of maximum size to be produced at 75% lactose in the lactose/boric acid blend.

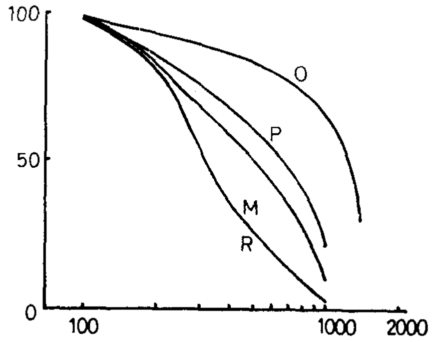

FIG. 1. Effect of starch on the size distribution of granules. O, no starch; P, potato starch; M, maize starch; R, rice starch; lactose 75: boric acid 25, binder 15% w/w of PVP solution. Abscissa: Log size μm. Ordinate: Cumulative % over size.

Table 1. Mean sizes of granules produced from blends of lactose, boric acid and starch using various binder volumes.

% w/w PVP binder (5% w/v solution)	Lactose: boric acid ratio	Mean granule sizes (μm)					
				Maize starch		Potato starch	Rice starch
		0	2·5%	5%	10%	10%	10%
15	90:10	1050	980	820	350	580	350
	75:25	1150	1050	900	480	635	300
	50:50	1020	780	500	400	370	240
	10:90	380	400	210	310	220	230
17·5	90:10		1050	950	600	940	700
	75:25		1180	1000	750	1000	650
	50:50		1180	1000	550	780	355
	10:90		520	280	420	350	300
20	90:10		1080	1050	840	1000	740
	75:25		1120	1150	1070	1000	760
	50:50		1300	1150	1050	1050	800
	10:90		1050	940	470	750	480

Granule strength results are given in Table 2. In all cases the presence of starch produced a significant fall in granule strength, potato and maize starches produced the greatest fall and rice starch rather less.

Table 2. Mean granule strength of blends of lactose, boric acid and starch.

% w/w PVP binder	Lactose: boric acid ratio	Mean work required to crush granules ($\times 10^{4}$J)					
			Maize starch			Potato starch	Rice starch
		No starch	2·5	5·0	10%	10%	10%
15%	90:10	6·27	3·99	2·57	2·25	2·82	4·50
	75:25	6·20	3·84	2·81	2·31	2·50	3·84
	50:50	4·47	3·04	2·95	2·29	1·92	4·13
	10:90	3·30	3·18	1·93	2·04	2·06	2·78
17·5%	75:25	—	5·31	4·02	3·35	3·39	5·04
20%	75:25	—	9·08	5·83	4·38	4·40	5·71

Effect of binder volume

Increasing binder volume to 17·5% w/w led to an increase in the mean granule size and strength for all blends investigated. A further increase to 20% w/w produced masses that were nearly overwet for the blends containing the higher proportions of lactose and gave granules of similar size to the lactose and boric acid granules with 15% w/w PVP. Increasing the binder volume in blends containing 10:90 lactose: boric acid however resulted in increasing granule size and strength (Tables 1 and 2).

Effect of starch concentration

The effect of varying the quantities of starch in the granules was studied using maize starch in different concentrations. For all blends of lactose and boric acid an increase in the starch content led to a decrease in granule size except the 10:90 blend which gave the smallest granules with 5% starch at 15% and 17·5% w/w binder volume (Table 1).

With 90:10 and 10:90 lactose: boric acid blends, 2·5% w/v starch has no detectable effect on the size distribution of the granules.

Effect of particle size of starch

To determine the extent of the influence of the particle size of starch on the growth of granules a batch of potato starch was fractionated on an Alpine jet sifter using a 45 μm sieve. The size distributions of granules containing up to 10% of these fractions were similar and also not significantly different from those of the batches prepared with 10% of the unfractionated batch of potato starch.

DISCUSSION

The mean granule size (G_d) of a batch of granules is the resultant of a large number of factors, many of them interacting.

These can be summarized by

$$G_d = f(C_i, D, V, E)$$

when C_i = fractional concentration of the ith component ($i = 1, 2$, etc.), D = packing density of particles in the granules; V = binder volume. This volume will vary with massing time if any or all of the components are soluble in the binder solution. E = energy transmitted to the damp mass. This will vary with mixer, mixer speed and possibly with V.

In addition, post-massing screening will affect size and could well contribute to both E and D. Finally, the dried granules may decrease in size if they are not sufficiently strong to withstand handling.

The aim of this work has been to treat each batch in a similar manner and to investigate the result of changing C_i and V.

If we further assume that D is a function of V, E and C_i we can fit the data to a polynomial of the form:

$$G_d = P_0 + \Sigma p_i C_i + \Sigma p_{ij} C_i C_j + \Sigma p_{ijj} C_i C_j^2$$
$$i,j = 1,2$$

For our system we assume that the final granule size is dependent on binder volume and the fractional lactose concentration and so the polynomial reduces to:

$$G_d = P_0X_0 + P_1X_1 + P_2X_2 + P_3X_1X_2 + P_4X_1^2 + P_5X_2^2 + P_6X_1^2X_2 + P_7X_1X_2^2 + P_8X_1^3 + P_9X_2^3$$

where X_1 = binder concentration; X_2 = fractional percentage of lactose; X_0 = dummy variable; P_0–P_9 = variable parameters.

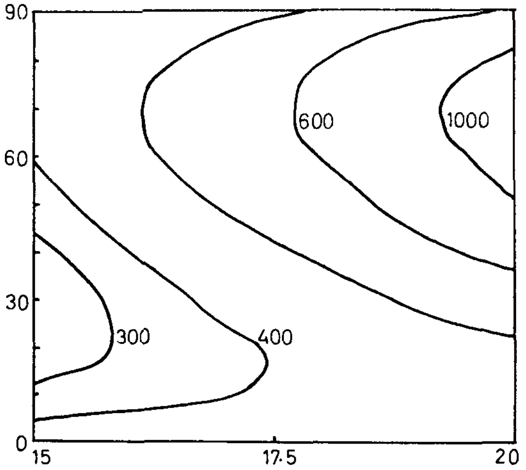

FIG. 2. Contour drawing to show the calculated relations between binder volume, lactose content and mean granule size of granules prepared using 10% w/w maize starch. Abscissa: Percentage w/w binder fluid added. Ordinate: Percentage w/w lactose in granules.

Using this equation and a non-linear curve fitting computer program we were able to find values of P_i and the corresponding values for the correlation coefficient. These values were found using binder concentration coded 15% ≡ −1, 20% ≡ +1 and fractional percentage of lactose coded 0 ≡ −1, 100% ≡ +1 and G_d as mean granule size in millimetres. The results are given in Table 3. We can thus draw contour diagrams for mean granule size with varying binder concentration and percentage lactose (Fig. 2). The inclusion of the X_1^2 and X_1^3 terms did not affect the value of the correlation coefficient and so these were excluded.

From Fig. 2 the presence of a maximum granule size and a minimum granule size can be clearly seen. Similar contour diagrams can be drawn for each data set.

The value of P_0 can be taken as an indication of mean granule size as we consider each data set. It can be seen from Table 3 that the effect of increasing starch is to reduce the mean granule size. In addition, reduction in the mean particle size of the starches from potato, through maize to rice also results in a further fall in mean granules size.

Table 3. Calculated values of parameters for a polynomial equation relating mean granule size to binder volume and lactose concentration. r = correlation coefficient.

	Starch conc. % w/w	P_0	P_1	P_2	P_3	P_5	P_6	P_7	P_9	r
Maize	2·5	1·09	0·22	0·35	−0·20	−0·38	−0·15	−0·07	−0·03	0·98
Maize	5	0·88	0·22	0·35	−0·18	−0·27	−0·15	−0·10	−0·29	0·97
Maize	10	0·67	0·32	0·45	0·10	−0·26	−0·02	−0·25	−0·53	0·99
Rice	10	0·47	0·27	0·34	0·04	0·003	−0·15	−0·17	−0·12	0·98
Potato	10	0·73	0·30	0·57	−0·05	−0·15	−0·21	−0·12	−0·29	0·99

The presence of starch as the third component with blends of lactose and boric acid is seen therefore to produce smaller, weaker granules. This effect can be explained partly by the high affinity of starch for water. Shotton & Harb (1965) have reported equilibrium moisture contents of 35·6% and 27·4% at 100% R.H. for potato and maize starches respectively. This means that a significant proportion of binder water is required to saturate the starch particles thus removing it from the interparticulate spaces in the powder bed. To compensate for this in a blend with 100 g (10%) potato starch approximately a further 35 cm^3 of binder would be required. However, a further 50 cm^3 (15 to 20%) failed to fully compensate for the size and strength lost due to the starch. It seems probable therefore that the presence of the starch also affects the strength of the granules by reducing the strength of intragranular bonds. This could either be an intrinsic effect or due to alteration in the packing density within the dry granules.

All three starches produce a significant weakening of the granules as measured by the work required to crush single granules. At the 10% w/w level, rice starch produced less weakening than either potato or maize starch. The rice starch has much smaller grains and so it is likely that closer packing is achieved and hence stronger granules result.

Generally all granules containing starches exhibited higher flow rates than those without starch and this is related to the reduced size of the granules containing starch. The type of starch used had no significant effect on flow rates (Fig. 3). The implication of this observation is that the flow rate is related chiefly to the granule size and once incorporated into the granules different types of starch do not alter flow rates significantly.

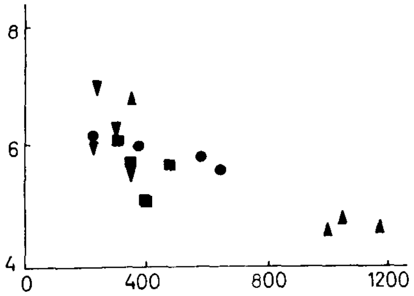

FIG. 3. Flow rates of granule batches as a function of mean granule size of the batch. ● 10% Potato starch. ▼ 10% Rice starch. ■ 10% Maize starch. ▲ no starch. Abscissa: mean granule size, μm. Ordinate: Flow rate g s^{-1}.

It follows from the above results that alterations in formulation by changing the proportion of dry component or by substitution of one starch for another could well significantly affect the size and strength of the subsequent granules.

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