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The distribution of components in the different size fractions of granules prepared from binary mixtures

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Boric acid, sulphanilamide and citric acid have been mixed separately with lactose and then granulated by massing and screening. The granules have been fractionated by sieving and each fraction has been analysed for lactose content. The effect of premixing time, massing time, binder volume and ratio of components on the distribution of lactose between size fractions of granules prepared from lactose:boric acid mixtures has been investigated. Uneven distribution of lactose has been found for all blends examined. There is a premixing time and massing time that gives the optimum distribution of lactose for any given blend and binder volume. Increased binder volume in some cases improves granule uniformity. The proportion of lactose in the blend has a major effect on the distribution of this component in the granules, as does the particle size of the lactose. Granules prepared from blends of lactose with sulphanilamide and with citric acid were also examined for lactose distribution.

Published results (Lachman & Sylwestrowicz, 1964; Cox, Ambaum & Wijnand, 1968; Nicholson & Enever, 1974) indicate significant variations in drug content with granule size. The highest drug concentrations have been found in the largest granules. Selkirk (1974) reported a similar result using borax 2% in lactose and noted that the distribution was dependent upon the time for which the damp mass was mixed before screening. Selkirk (1976) has also found a decrease in borax content in the finer granules when a planetary mixer was used to prepare granules of borax and lactose. It has been suggested by the workers previously mentioned that solvent migration could account for the results reported.

The migration of components present in excess of 5% has not been considered. We have examined the uniformity of granules prepared from mixtures of lactose with boric acid, citric acid or sulphanilamide, with the lactose content varying from 10–90% w/w.

MATERIALS AND METHODS

The relevant physical properties of the materials used and the method of preparing the granules have already been reported (Opakunle & Spring, 1976a,b).

The sieve fractions obtained from a 50 g sample of granules during the determination of granule size distributions were assayed for lactose content using an Autoanalyer II (Technicon Instruments Co.) set to analyse lactose by Industrial Method 81–71E. Sample size varied depending upon the concentration of lactose in the granule, for 90 and 75% lactose the sample size was 200 mg, for 50 and 25% lactose the sample size was 400 mg and for 10% lactose the sample size was 500 mg.

Results quoted, unless otherwise stated, are the mean of two assays of a solution prepared from a single sample from the size fraction. The Auto analyser assays of samples from the same granule fraction had a coefficient of variation dependant upon lactose concentrations, values were 90, 75 and 50, 1; 25, 1·3; 10, 3·2% for the mean of two results from replicate samples.

RESULTS

The effect of pre-mixing time. The results obtained for a lactose:boric acid, 50:50 blend are given in Table 1. None of the pre-mixing times gave a uniform lactose content in the granules, however, as no improvement was discernable after 4 min pre-mixing this period was used for all subsequent batches.

Reproducibility of the lactose distribution. Six batches of granules, each with 75% lactose:25% boric acid were prepared as described previously (Opakunle & Spring, 1976a) massing time 15 min, binder volume 120 cm^3, and assayed for lactose content. The results expressed as mean percentage followed by the standard deviation for granules retained on the various sieves were: sieve 1·0, 75·4 (0·39); 710, 74·9 (0·76); 500, 74·5 (0·45); 355, 73·7 (0·70); 250,

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Table 1. *The effect of pre-mixing time on the distribution of lactose in the different size fractions of granules prepared from a lactose 50%: boric acid 50% mixture.* Granulating solution 12% v/w of 5% PVP solution. Massing time 5 min.

Pre-mixing time min	% lactose in granules retained on sieve number 1·0	710	500	355	250	180	75	Finer than 75
2	48	51	51·5	54·5	57·7	55·5	47	48
4	50	50	50	51	54	54	50	43
8	49	49·5	50	51	53	52	47	35
16	50	51	51	53	54	54·5	49	44

74 (0·59); 180, 75·2 (1·15); 75, 77·2 (1·38); finer than 75 μm 83·6 (1·89).

Student's *t*-tests of the mean concentration for each size against the overall mean (75·2%, s.d. 0·75) indicated that the lactose content of the granules retained in the 500, 355, 250 and 75 μm sieves and the powder finer than 75 μm differed significantly ($P = 0{\cdot}95$) from the overall mean.

The effect of the volume of binder used. Batches of granules were prepared using differing volumes of binder, proportions of components and massing times, the results of the granule assays are given in Table 2. Increase in the volume of binder solution from 9–15% v/w produced major differences only in certain blends. These were the 75% lactose blend after 5 and 15 min massing and the 50% lactose blend after 5 min massing in which the <75 μm fractions were deficient in lactose only when 9% v/w binder was used; with 12 and 15% v/w binder solution the fines had an excess of lactose (Fig. 1). A similar difference was found for the 50% blend after 60 min massing. The other effect noted was an improvement in uniformity with 15% v/w binder in most batches analysed. The exceptions were the blends with 90% lactose in which the amounts of material <75 m were very small.

The effect of massing time. Massing was carried out for 5, 15 or 60 min. Increasing the time of massing generally resulted in an increased lactose content of the <75 μm fraction. This resulted in an improvement in the uniformity of granules containing less than 50% lactose and a deterioration in those granules containing 50% or more lactose in the original blend.

The effect of initial particle size of the lactose. The lactose used for other granulations was sieved into two size fractions, that retained and that which passed a 63 μm sieve. Granulation was as previous described and the assay results are given in Table 3.

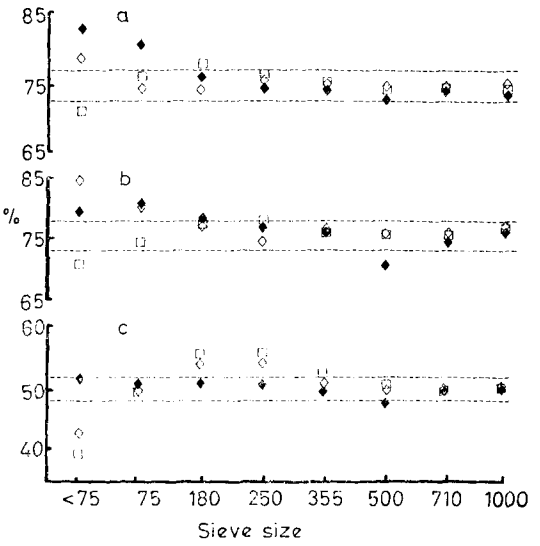

FIG. 1. Concentration (%) of lactose in granules retained on various sieves. □ 9, ◇ 12, ◆ 15% v/w binder solution. Dotted lines indicate extreme significance ranges ($P = 0{\cdot}95$) for the three batches allowing for differences in means. a—5 min massing time, b—15 min massing time, c—5 min massing time (6 min for 15% v/w binder solution).

The finer lactose gave granules more uniform than those from the unfractionated lactose and the coarser lactose gave less uniform lactose content in the granules. Decrease in the amount of binder used produced granules of much poorer uniformity when the coarse lactose fraction was used.

The distribution of lactose in the various size fractions of granules prepared from lactose mixed with sulphanilamide

A better distribution of lactose in the granule size fractions was observed in mixtures with sulphanilamide (Table 4) than in mixtures with boric acid (Table 2). The former showed maximum lactose content in the 180–250 μm granules with reduced lactose concentration in the <75 μm fraction, thus reduction being most marked in granules containing 50% or less of lactose in the original mixture. The increased lactose contents found in the <75 μm fractions of mixtures of boric acid and lactose, containing 75 and 90% lactose, were not present in the equivalent sulphanilamide: lactose mixtures.

The mean particle size of the boric acid powder (14·8 μm) and the sulphanilamide (10·4 μm) were similar. However, sulphanilamide differs from boric acid in solubility, cohesiveness and wettability.

Table 2. *The distribution of lactose in sieved fractions of granules prepared from blends of lactose with boric acid.*

Vol % v/w binder	Mass. time min	% lactose in granule retained on sieve nos. 1·4	1·0	710	500	355	250	180	75	<75
Lactose 90%										
9	5	91	93	92	92	93	94	91·5	94	88·5*
	60	—	91·5	91	90·5	90·5	93·5	94*	94*	94·5
12	5	91	91·5	91·5	94*	91	91	92	91·5	94*
	15	91·5	91	91	90	91	92	93	94*	92
	60	92·5	92	93	92	95	94	95*	96*	94
15	6	90	90	90	91	90	90	96·5*	93	—
	15	91	90	89	89	89	89	91	91	83·5*
Lactose 75%										
9	5	—	76·1	75	75	75	77	78·5	76	71*
	15	—	76·5	75·5	75·5	75·2	78	77·5	74·5	71*
	60	—	77	76·4	76	74*	75·6	78	82·5*	84·4*
	90	—	76·8	76	76	71·5*	73·5*	81·5*	83·5*	84*
12	5	—	75	74	74	75	76	74	74	79*
	15	—	77·5	76	75·5	76	74·5	77	80*	84·5*
	60	—	74	75·5	72·5*	77·5	80*	82*	87*	91*
15	6	75	73	73	72	74	74	75·5*	81·5*	84*
	15	76	76	74	70	76	77	78·5	80·5*	79*
Lactose 50%										
9	5	—	50·5	50	50·5	52*	56*	56*	50·5	40*
	60	—	50	50	48·5	51·5	53·5	53	51	43*
12	5	—	50	50	50	51	54*	54·5*	50	43*
	15	—	50	51	49	51·5	53*	51·5	53*	61*
	60	—	51	50	48·5	49	56*	59*	61·5*	62*
15	6	50	50	50	48*	50	51	51	52*	53*
	15	50	50·5	48	49·5	51	56*	61*	63*	63*
Lactose 25%										
9	5	—	25	25	25	26·5*	32·5*	34*	25	13*
	60	—	26	25	24	28*	31*	29·5*	26	22*
12	5	—	25	24	25	28*	25	32*	18·5*	10
	15	—	25	25	25	25	27*	29	24	18·5*
	60	—	25	25	25	28·5*	29*	24·5	22*	12·5*
15	6	—	25	25·5	25·5	28*	28·5*	26	28*	16*
	15	—	24	26	24·5	24·5	26	23	24·5	23·5*
	60	—	26	25·5	26	26·5*	28*	28*	26·5*	25·5
Lactose 10%										
12	5	—	10	10	11*	11·5*	16·5*	17*	9*	7*
	15	—	11·5	11	12*	11·5	12*	16·5*	12·5*	8*
	60	—	10·5	10·5	11	12·5*	16*	12·5*	7·5*	3*
15	6	—	9	9	10	12*	12*	9	7*	4*
	15	—	10·5	10·5	11	11	13*	12*	5·8*	5*
	60	—	10	10	10	10·5	10·5	10	10·5	8·5*

* Results that differ significantly ($P = 0.95$) from the mean.

Table 3. *The distribution of lactose in sieved fractions of granules prepared from blends of lactose and boric acid (25 : 75).*

Vol % binder	Mass. time (min)	% lactose in granule retained on sieves nos. 1·0	710	500	355	250	180	75	<75
Lactose >63 μm									
9	5	23	23·5	24	29*	43*	53·5*	25	1*
12	5	25·5	25	25	27*	36·9*	39*	20*	8·5*
	15	25	25	25	29*	34·5*	33*	20*	12·5*
Lactose <63 μm									
12	5	24·5	25·5	25·5	25·5	24	26	26·5*	21*
	15	25	25	25	25	24	26	26·5*	24

* Results that differ significantly ($p = 0.95$) from the mean.

Table 4. *The distribution of lactose in sieved fractions of granules prepared from blends of lactose and either sulphanilamide or citric acid.* Massing time 5 min, volume of binder used 12% v/w for sulphanilamide: lactose and 6% v/w for citric acid: lactose.

% lactose	% lactose in granule retained on sieves nos.								
	1·4	1·0	710	500	355	250	180	75	<75
Sulphanilamide									
90	88·5	91	91	91	91·5	92·5	92·5	93*	91
75	76	75	77	76	76	79	80	78·5*	75
50	—	50	50	49·5	51	52	52	47*	42*
25	—	25·5	27	27	28·5	31*	30*	24	18*
10	—	10·5	11	11	12	15	15	10	6·5*
Citric acid									
95	95	97	94·5	94	95·5	97	97	96	96
92·5	92·5	95	94	93	94	93	92·5	94	94·5
90	87·5	88	88·5	87·5	88	88·5	89	90	90
75	77	74	73·5	75	74	75	73·5	74·5	71*
50	50·5	50·5	50·5	51·5	51·5	54*	54*	54*	52
25	25·5	26	25·5	26	26	26·5	27*	26	23
10	10	11	10·5	10·5	11	11	11	10·5*	6·5*

* Results that differ significantly ($p = 0{\cdot}95$) from the mean.

The distribution of lactose in the various size fractions of granules prepared from lactose mixed with citric acid

Lactose: citric acid blends produced the best distributions of lactose of all the three systems studied (Table 4). The increased lactose content observed in the 180–250 μm granules for most blends of lactose with boric acid and with sulphanilamide, was much reduced or absent from blends with citric acid.

The mean particle size of the citric acid powder (22·7 μm) was closer to that of the lactose (29·4 μm) and in addition citric acid is readily wetted and is very soluble (3 in 5) in water. Any or all of these properties may have contributed to the better mixes obtained. The <75 μm fraction had reduced lactose content in the blends containing less than 50% lactose, this effect is similar to, though less marked than, the reduction seen in the blends with sulphanilamide and with boric acid.

DISCUSSION

In each of the three mixtures studied the larger granules (greater than 500 μm) contained the same proportions of ingredients as the original mixtures. Earlier work (Lachman & Sylwestrowicz, 1964; Cox & others, 1968, Nicholson & Enever, 1974) have reported an excess of minor component in the coarser granules. Selkirk (1976) using 2% borax in lactose reported that granules greater than 500 μm contained about 2% borax whereas those finer than 500 μm were deficient in borax. This difference could be due either to differences in drying methods or to the smaller proportion of minor component used in the earlier studies. Granule fractions finer than 500 μm showed variations in lactose content for mixtures with boric acid and with sulphanilamide, but not with citric acid.

The general pattern of variation below 500 μm with boric acid or with sulphanilamide mixed with lactose was an increase in lactose content of the granules in the region 250–180 μm. If the mixtures contained 50% or less of lactose there was a decrease in lactose content to below the theoretical content in granules finer than 180 μm. With more than 50% lactose the lactose content increased, in mixtures with boric acid, as the granules became finer. Changes in massing time and binder volume affected these variations only slightly.

The use of a lactose fraction (finer than 63 μm, mean diameter 15·3 μm) mixed with boric acid eliminated the variations in lactose content: a coarse fraction (greater than 63 μm) produced much greater variations than those found using the unfractionated lactose.

Uniform granules have been obtained in two sets of granulations. Firstly, with citric acid: lactose and secondly, with a fine sieve fraction of lactose with boric acid.

The chief significance of this is that in both cases the two components of the mixtures were of similar particle size. It therefore follows, from these limited data, that uniform granules can only be prepared from materials of similar particle size. It is, however, not possible to define clearly the function of the solubility of the components on uniformity.

With small amounts of soluble materials solvent migration can produce non-uniform granules (Ridgway & Rubinstein, 1971).

A second significant observation is that the larger granules contained the correct proportion of each ingredient. This may be a result of differential wetting of the powders, the large granules will arise from the wetter regions of the damp mass. Addition of binder solution will cause overwetting of some regions and thus 'lock' the proportions of ingredients in those regions. Subsequent massing will spread the binder liquid to drier regions and during this stage the lactose will wet more readily than boric acid or sulphanilamide. This will result in intermediate sized granules with a higher lactose content and the finest material will be lactose deficient. This is the result obtained in all cases except in granules with 75 and 90% lactose mixed with boric acid. In these cases the lactose content is so high that some remains unwetted or that on the surface of formed granules is abraided during subsequent dry screening. In the granules with greater than 50% lactose content the proportion of material finer than 53 μm was low and so abrasion could produce a significant amount of fine powder.

The use of powders of similar particle size eliminates the excess lactose in the 180–250 μm granules. This could be due to the reduction of the mean particle size of the lactose making it less easily wetted and so reducing the spread of binder through the powder bed. It may also be a result of the greater cohesiveness of the finer powder causing stronger adhesion between lactose and boric acid particles thus maintaining their relative proportions in the mixture.

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