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Short Communication

The effects of some process variables on the concentration of minor components in tablet granules

M.S. SPRING

Pharmacy Department, Manchester University, Manchester M13 9PL (England)

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Variations in the proportions of minor components in different size fractions of granules have been reported (Ridgway and Rubenstein, 1971; Nishimura and Yui, 1978a and b; Travers and Patel, 1979). These variations have been attributed to the effects of solvent migration. In a previous study, (Whitaker and Spring, 1977), the variations in the minor component to the <75 μm-size fraction appeared to be concentration-dependent, irrespective of the solubility of the minor component in the binder fluid. This observation has been studied in detail using two batch sizes, two drugs of different solubilities at each of 5 concentrations and with 5 binder volumes using a central composite, rotatable, second-order design (Cochran and Cox, 1957).

Sulphanilamide (ICI), 14.8 μm, or sulphacetamide sodium (Ward Blenkinsop), 145 μm was blended with lactose (BDH) 29.6 μm to give 25 g of mix containing the required weight of minor component. This blend was added to either 175 g or 975 g lactose in a Z-blade mixer and pre-mixed for 4 min. The 200 g batches were made using a Winkworth mixer and the 1000 g batches using a Morton mixer. Half the required weight of binder solution, 5% (w/v) Plasdone K29-32 (GAF, U.K.), was then added and massed for 2 min, the second portion of the binder was then added and the whole massed for a further 13 min. The damp mass that was obtained was forced through a 1.4 mm screen using an oscillating granulator and then dried at 50°C for 105 min in an oven using one (200 g) or 5 (1000 g) rectangular trays. The dried granules were re-screened, 1.4 mm, and fractionated with sieves. A sample from each size fraction was weighed and dissolved in 0.05 M sodium bicarbonate solution to give 100 cm^3 of solution. Samples were taken to give a minor component concentration in the range 5–25 $\mu g \cdot cm^{-3}$, the solutions were assayed using a spectrophotometer at 259 nm or 256 nm for sulphacetamide sodium and sulphanilamide respectively.

Within each batch size the order of the granulations were randomized. The results are summarized in Tables 1 and 2 showing the average of 5 replicate granulations prepared using 0.5% minor component and 12% (w/w) binder solution.

A clear difference can be seen between the two minor components. With the very soluble (1 in 1.5) sulphacetamide sodium the finest fraction, <75 μm, has the lowest minor component concentration and there is some 20% of the total granule with a

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.ELATIVE CONCENTRATIONS OF SULPHACETAMIDE SODIUM IN VARIOUS SIZE FRACTIONS OF GRANULES, AND MEAN GRANULE SIZE OR EACH BATCH

ranule size	Weight (%)	200 g batch								
	Drug (%)	0.5	0.02	0.14	0.14	0.5	0.5	0.86	0.86	1
	Binder weight (%)	12 (±S.D.)	12	9.9	14.1	9	15	9.9	14.1	12
1.4– 1.0	37	1.00 ± 0.017	0.99	1.03	1.03	1.03	1.03	1.04	1.02	1.01
1.0–710	18	1.04 ± 0.019	1.00	1.02	1.04	1.01	1.04	1.02	1.03	1.04
10 –500	10	1.04 ± 0.009	1.03	1.03	1.08	1.03	1.05	1.03	1.06	1.03
00 –355	8	1.06 ± 0.011	1.03	1.01$^-$	1.08	1.02$^-$	1.06	1.02$^-$	1.06	1.04
55 –250	8	1.05 ± 0.011	1.06	1.04	1.07	1.01$^-$	1.04	1.02	1.06	1.04
50 –180	6	1.01 ± 0.008	1.06$^+$	1.01	1.00	1.01	0.99	0.99	1.02	1.00
80 – 75	10	0.88 ± 0.024	0.93	0.94	0.82	0.99$^+$	0.82	0.91	0.89	0.90
<75	3	0.70 ± 0.018	0.83$^+$	0.76$^+$	0.58$^-$	0.75	0.63$^-$	0.72	0.71	0.72
ean size (μm)		735 ± 9	714	601	792	517	796	641	770	719
		1000 g batch								
1.4– 1.0	43	1.05 ± 0.019	1.02	1.07	1.08	1.02	0.98$^-$	1.03	0.99$^-$	1.00
1.0–710	14	1.08 ± 0.025	1.07	1.04	1.08	1.02	1.12	1.01	1.17$^+$	1.05
10 –500	7	1.14 ± 0.040	1.15	1.09	1.23	1.11	1.21	1.07	1.14	1.13
00 –355	7	1.11 ± 0.013	1.13	1.09	1.16$^+$	2.20	1.19$^+$	1.05$^-$	1.13	1.13
55 –250	6	1.06 ± 0.026	1.08	1.04	1.06	1.10	1.18	1.04	1.20	1.20
50 –180	6	0.95 ± 0.037	0.97	0.94	0.90	1.02	1.03	0.98	0.96	1.00
80 – 75	12	0.72 ± 0.005	0.72	0.75$^+$	0.63$^-$	0.85$^+$	0.73	0.84$^+$	0.73	0.82$^+$
<75	5	0.57 ± 0.026	0.63	0.60	0.49$^-$	0.69$^+$	0.63	0.70$^+$	0.53	0.62
ean size (μm)		746 ± 8.5	798	697	765	616	812	740	809	767

:terminations carried out in 5 replicates. + or – indicate a result significantly (95%) different from that obtained using 0.5% drug and 12% (w/w) nder. +, greater; –, less.

TABLE 2

RELATIVE CONCENTRATIONS OF SULPHANILAMIDE IN VARIOUS SIZE FRACTIONS OF GRANULES AND MEAN GRANULE SIZE FOR EACH BATCH

Granule size	Weight (%)	200 g batch								
	Drug (%)	0.5	0.02	0.14	0.14	0.5	0.5	0.86	0.86	1.0
	Binder weight (%)	12 (±S.D.)	12	9.9	14.1	9	15	9.9	14.1	12
1.4– 1.0	47	1.06 ± 0.023	1.02	1.03	1.10	1.04	1.06	1.05	1.08	1.10
1.0–710	14	1.11 ± 0.042	1.04	1.03	1.07	1.05	1.17	1.08	1.09	1.10
710 –500	10	1.12 ± 0.013	1.13	1.06^{-}	1.64^{-}	1.07	1.12	1.07^{-}	1.11	1.04^{-}
500 –355	8	1.03 ± 0.123	1.13	1.09	0.89	1.06	0.93	1.03	1.00	0.98
355 –250	6	0.84 ± 0.646	0.98^{+}	1.00^{+}	0.91	1.02^{+}	0.97	1.00^{+}	0.91	0.88
250 –180	6	0.74 ± 0.027	0.85^{+}	0.88^{+}	0.87^{+}	0.89^{+}	0.65^{-}	0.84^{+}	0.69	0.68
180 – 75	8	0.61 ± 0.018	0.65	0.66	0.57	0.75	0.54	0.73	0.57	0.61
<75	1	0.90 ± 0.137	1.14	0.68	0.65	0.99	0.72	0.95	0.99	0.89
mean size (μm)		798 ± 9	775	757	835	625	850	702	816	796
		1000 g batch								
1.4– 1.0	45	1.07 ± 0.012	1.06	1.01^{-}	1.10	1.04	1.11^{+}	1.05	1.08	1.05
1.0–710	13	1.08 ± 0.014	1.08	1.07	1.12	1.05	1.11	1.11	1.11	1.07
710 –500	10	1.08 ± 0.625	1.12	1.12	1.18^{+}	1.10	1.07	1.08	1.09	1.08
500 –355	7	1.04 ± 0.012	1.10^{+}	1.10^{+}	1.08^{+}	1.10^{+}	1.00^{-}	1.03	1.05	1.05
355 –250	6.5	0.95 ± 0.024	0.99	1.03	0.94	0.98	0.89	0.99	0.92	0.94
250 –180	6.5	0.81 ± 0.043	0.82	0.89	0.72	0.88	0.73	0.89	0.76	0.81
180 – 75	7.5	0.65 ± 0.019	0.63	0.073^{+}	0.55^{-}	0.75^{+}	0.56^{-}	0.69	0.58^{-}	0.66
<75	2.5	0.83 ± 0.073	0.79	0.74	0.66	0.82	0.77	0.74	0.89	0.43
mean size (μm)		778 ± 7	784	742	781	654	794	724	780	793

Determinations carried out in 5 replicates. + or – indicate a result significantly (95%) different from that obtained using 0.5% drug and 12% (w/w) binder. +, greater; –, less.

reduced minor component concentration. The less soluble, sulphanilamide (1 in 170) has a minimum concentration in the 75–180 μm fraction, about 25% granule below the nominal drug content and significantly lower relative concentrations of minor component in the 75–355 μm size range. An enhanced concentration in the coarser size fractions, with peak values in the 500–710 μm fraction is common to nearly all batches.

The effect of batch size changing from 200 g to 1000 g was to produce much greater deviations from nominal composition when granules were made using sulphacetamide sodium. With sulphanilamide no significant differences were found.

The experimental design of Cochran and Cox (1957) made it possible to calculate the coefficients of a quadratic equation of the form:

$$y = b_0 + b_1x_1 + b_2x_2 + b_{12}x_1x_2 + b_{11}x_1^2 + b_{22}x_2^2$$

where b_0, b_1, b_2 etc. are the coefficients and x_1 and x_2 are the minor component concentration and the binder amount respectively; y is the relative concentration of minor component in any given size fraction. The data for the statistics of the fit for the <75 μm and the 75–180 μm fractions are given in Table 3.

These data show the poor fit achieved, and the large variations found, with the <75 μm fractions. However, the 75–180 μm fractions fit an equation of the form:

$$y = b_0 + b_1x_1 + b_2x_2$$

the calculated values for the coefficients b_0, b_1 and b_3 are given in Table 4 for the 75–180 μm size fractions. These results indicate that binder volume has the greatest effect on minor component concentration in this size fraction. The effect of absolute minor component concentration is small, except with the 1000 g batches of sulphacetamide sodium.

TABLE 3

MEAN SQUARES CALCULATED FOR THE FITTING OF THE DATA OBTAINED FROM THE QUADRATIC EQUATIONS FOR THE TWO FINEST SIZE FRACTIONS

Granule size		Mean squares × 10^4			
		Sulphacetamide sodium		Sulphanilamide	
		200 g	1000 g	200 g	1000 g
<75 μm	First-order terms	87	94	123	115
	Second-order terms	37	13	131	70
	Lack of fit	43	4.7	27	71
	Error	14	34	410	39
75–180 μm	First-order terms	93	169	194	204
	Second-order terms	6	17	11	3
	Lack of fit	14	12	9	3
	Error	4	3	3	11

TABLE 4

COEFFICIENTS RELATING TO A LINEAR EQUATION IN MEAN DRUG CONTENT (b_1) AND BINDER VOLUME (b_2) FOR THE 75–180 μm SIZE FRACTION

	Sulphacetamide sodium		Sulphanilamide	
Batch size	200 g	1000 g	200 g	1000 g
b_0	0.880	0.722	0.610	0.645
b_2	−0.001	0.041	0.001	0.005
b_3	−0.048	−0.050	−0.070	−0.071

It follows that the effect of binder amount is of major importance with a poorly soluble drug, but with a very soluble drug the concentration of that drug is also of significance in determining the concentration of drug in the finer size fraction.

The lower solubility of the sulphanilamide should restrict the migration and give more uniform granules as seen using water-soluble and lake dyes (Nishimura and Yui, 1978a and b). This does not occur even at 1% sulphanilamide, a concentration high enough to mask the effects of small amounts of drug in solution. It is possible, therefore, that the presence of the minor component affects the strength of the agglomerates so that the larger granules contain an excess of this compound and as a result the finer granules are depleted. This aspect is under further investigation, together with studies using an insoluble major component.

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