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COMMUNICATIONS

The effect of solute migration on the distribution of borax throughout a batch of granules

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Dose variation in tablets generally arises either as a result of tablet weight variation or because the drug is heterogeneously distributed throughout the tablet mass. Lachman & Sylwestrowicz, (1964), studied the distribution of a hydrophobic drug throughout a batch of granules. They showed that the larger granules contained a disproportionately high concentration of drug at the expense of the smaller granules. However, they gave no experimental details of either the massing conditions or the drying conditions. Such variables have been shown to effect both the physical properties of granules, prepared by a wet granulation process (Ganderton & Hunter, 1971) and also the migration of soluble constituents to the periphery of such granules during the drying stage, (Rubenstein & Ridgway, 1974; Travers, 1975). I have examined the effect of binder concentration and massing time on the distribution of borax throughout a batch of granules. Borax has been chosen to represent a water soluble drug because of its low cost and ease of analysis.

Borax, of mean particle size 15·3 μm (Analar grade, BDH), and lactose B.P. (Hopkins and Williams), of mean particle size 5 μm were sieved to remove any particles greater than 50 μm. They were then mixed in a planetary mixer, (Hobart Manufacturing Company Ltd., London), for 2 min. The overall concentration of borax in the mixer was 2·0%. The contents of the mix were emptied onto a tile and subdivided into 16 portions. Each of these portions was assayed for its borax content by titrating 20 samples each approximately 1 g in weight with 0·01 N HCl. The mean borax concentration was 2·0% with a standard deviation of 0·01 indicating a satisfactory degree of mixing of the powders.

Similar proportions of lactose and borax were placed in the planetary mixer, mixed for 2 min and then massed with water. The mass was force screened on a reciprocating granulator, (Erweka, Germany), and the granules so formed, dried to a constant weight in a hot air oven at 70° and rescreened. Both massing water concentration and massing time was varied in the granulation process. Three massing water concentrations; 12, 14 and 16% v/w of dry powder, were used. At each of these concentrations, two batches of granules were prepared with massing times of 0·5 and 10 min respectively. The resultant granules were sieved and the sieve fractions; −8+16, −16+22, −22+30, −30+44, −44+60, −60+85, −85 mesh were collected for assay. The borax content of each sieve fraction was determined by titration with 0·01 N HCl, using an automatic titrimeter, (Radiometer, Copenhagen). The results presented in the paper are the average values of 20 assays for each sieve fraction.

The particle size distribution of all batches of granules was established by sampling and sieve analysis (B.S. 410 test sieves).

Figs 1 and 2 show the effect of massing water concentration on borax distribution throughout the granules. In both these figures there was a steady decrease in borax concentration with the finer granules. A peak concentration of borax was also found with the intermediate sized granules. This peak concentration differed significantly from the borax concentration in both the largest and smallest granules of the batch ($P < 0.01$). As the massing water concentration was increased, the variation in borax concentration throughout the granule batch was also increased. For example, at a massing water concentration of 12% the concentration of borax was fairly uniform throughout the granules, (Fig. 1). It varied from a minimum 1·94% to a maximum of 2·06%. When the massing water concentration was increased to 16%, the variation ranged from a maximum of 2·18% to a minimum of 1·54%. Again, a decrease in borax concentration was noted with the finer granules, and statistically significant peak concentrations were found with the intermediate sized granules.

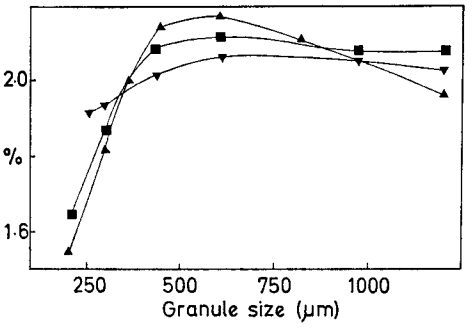

FIG. 1. The effect of massing water concentration on the distribution of borax (%) throughout a batch of granules (massing time 10 min). Massing water concentrations: ▼ 12%, ■ 14%, ▲ 16%.

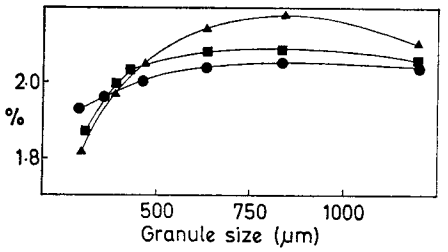

FIG. 2. The effect of massing water concentration on the distribution of borax (%) throughout a batch of granules (massing time 0·5 min). Massing water concentration: ● 12%, ■ 14%, ▲ 16%.

The results in Figs 1 and 2 show that massing time had little effect on the distribution of borax throughout the granules. This was especially so for granules prepared with a low massing water concentration.

Fig. 3 shows the effect of massing time and massing water concentration on the particle size distribution of the granules, at a massing time of 0·5 min. An almost identical set of results were obtained for granules massed for 10 min.

The similarities in the particle size distributions of granules, prepared at the same massing water concentration but different massing times indicates that the binder solution was as evenly distributed throughout the mass in 0·5 min as it was in 10 min. This is in contrast to work using a Z blade mixer (Selkirk, 1974).

The amount of −12+16 mesh granules was directly related to the amount of binder added to the mass, a result consistent with that of Hunter & Ganderton (1973).

During the drying stage of a wet granulation process, solute migration of the soluble constituents can occur

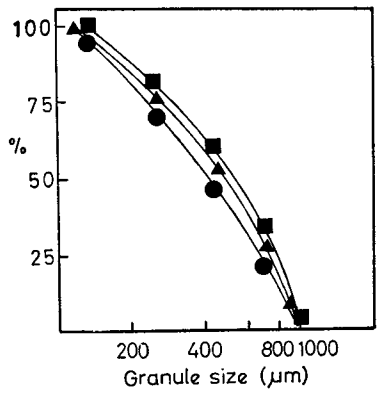

FIG. 3. The effect of massing water concentration on the size distribution of lactose granules containing 2% borax (massing time 0·5 min). Massing water concentration: ● 12%, ▲ 14%, ■ 16%. y-axis—% by weight oversize.

(Rubenstein & Ridgway, 1974). Lactose is considerably more water soluble than borax. Thus it will migrate to the granule surface to a greater extent than the borax. It is then more likely to be dislodged from the granule surface during dry screening. This accounts for the low borax concentrations found with the fine granules. A dried, but not dryscreened granule, may be considered to have a steadily decreasing borax concentration extending from the centre of the granule to the periphery. The granule may also be considered to have an outer "lactose rich" crust due to the preferential solute migration of the lactose. Such crusts have been previously reported in systems where solute migration occurs (Rubenstein & Ridgway, 1974). As the granule surface is abraded during dryscreening, the outer lactose crust is removed. This results in a smaller granule, which contains a higher proportion of borax. It accounts for the peak concentrations found with the intermediate sized granules.

Table 1. *The effect of granule abrasion on the concentration of borax in the granule.*

	% Borax	
Granule size	Abraided	Non Abraided
−8 + 16	—	2·07
−16 + 22	2·11	2·10
−85	1·75	1·54

To support this concept of solute migration, some large granules (−8+16 mesh; 16% massing water concentration; 10 min massing time) were gently abraded on a sieve.The −16+22 mesh granules and the fines (−85 mesh) so formed were assayed for their borax content. The results are shown in Table 1. The original concentration of the granules was 2·07%. After abrasion to the −16+22 mesh size, the concentration rose to 2·11% which compared very favourably with the 2·10% found with the original −16+22 mesh granules of the batch. More significantly, the fines produced by abrasion had a concentration of only 1·75%, indicating that preferential intragranular migration of lactose was occurring.

The results obtained with the granules, prepared at a 0·5 min massing were different from those obtained previously using a Z blade mixer, (Selkirk, 1974). These differences tended to disappear with granules prepared with 10 min massing times. The results show that, for the above system, the planetary mixer is more efficient in its distribution of binder solution throughout the mass. The deduction is consistent with the sieve analyses already described for granules prepared using the planetary mixer.

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Estimation of the degree of binding of tetracyclines in human plasma

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The binding of tetracyclines in human plasma has been studied extensively since bound antibiotic can be considered to be temporarily inactive (Kunin, Craig & others, 1973). Table 1 lists the available data for the four tetracyclines of greatest clinical importance. Although these data show plasma binding to be significant the variation in the values quoted for each drug is such as to make a reliable estimate impossible. The values for percentage binding of tetracycline, for example, range from 24 to 64% (Table 1) whereas the percentage of free (and therefore active) doxycycline could be 9 or 27% of the total drug in the plasma (Table 1). Furthermore, some of the concentrations used (Table 1) have been markedly higher than the therapeutic concentration of 0·8 to 5·0 μg ml^{-1} (Fabre, Milek & Kaliopoulos, 1971). Because of this confusion we have re-examined the binding of these four tetracyclines in human plasma at concentrations covering the therapeutic range. Samples (as hydrochlorides) of tetracycline and doxycycline were gifts from Pfizer (Lot Nos. 203–71716 and 305–58708 respectively), oxytetracycline was purchased from Sigma (Lot No. 41C-0800) and minocycline from Cyanamid (Batch 205).

The two methods most suitable for evaluating drug binding in plasma are ultrafiltration and equilibrium dialysis, the latter method was used in this work since we found the tetracyclines bind extensively and variably to ultrafiltration membranes which may account for some of the variation in previously reported values (Table 1). In contrast, only relatively low binding (6%) of tetracyclines to the equilibrium dialysis apparatus occurred and this was corrected for by sampling from both sides of the membrane. The same basic procedure was used for each tetracycline: a solution of the drug in pooled citrated human plasma (5 ml) was dialysed against sterile Sørensen's phosphate buffer (pH 7·4 5 ml) using a Perspex dialysis cell and sterile, washed Visking membrane. The pH of the buffer is critical since the degree of binding is known to vary with pH (Williamson, 1969), this may also account for some of the variation in previously determined values (Table 1), consequently the buffer used was at physiological pH since calcium citrated-plasma was used, Ca^{2+} variations were not considered likely to affect the results. Preliminary studies showed that, with shaking, equilibrium was achieved between 48 and 72 h and that no dilution of the plasma occured and that the pH at equilibrium was 7·4. The dialysis cells were thus shaken for 72 h and at 4° in the dark to prevent decomposition. Eight samples were used for each tetracycline giving a range of concentrations between 0·1 and 10 μg ml^{-1} in the plasma at equilibrium and the procedure was repeated to give duplicate values. In previous studies bioassay methods have generally been used (Table 1),

Table 1. *Percentage binding of tetracyclines in human plasma (literature values).*

Tetracycline concn (μg ml^{-1})	Method	Assay	% Bound	Ref.
Tetracycline				
5–20	Dialysis	bioassay	24	1
1–10	Dialysis	radiochem.	34	2
1·5–4·1	Ultrafiltr.	bioassay	54	3
N.S.	Ultrafiltr.	bioassay	58	4
a	Dialysis	bioassay	36	5
30	Ultrafiltr.	bioassay & uv	55	6
30	Dialysis	bioassay & uv	56	6
1–10	Ultrafiltr.	bioassay	64	7
1	Dialysis	radiochem.	53	8
Oxytetracycline				
5–20	Dialysis	bioassay	20	1
0·69	Dialysis	bioassay	27	9
30	Dialysis	bioassay & uv	35	6
30	Ultrafiltr.	bioassay & uv	34	6
1–10	Ultrafiltr.	bioassay	35	7
Doxycycline				
N.S.	Ultrafiltr.	bioassay	73	10
1–30	Ultrafiltr.	bioassay	91	11
Minocycline				
N.S.	N.S.	N.S.	59	12
N.S.	Ultrafiltr.	bioassay	76	13

N.S. = not specified.
(*a*) Binding determined in human plasma 2 h after i.v. injection of 500 mg tetracycline.
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