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SOME FACTORS AFFECTING SOLUTE MIGRATION IN GRANULAR BEDS

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SUMMARY

The intergranular migration of soluble materials during drying in thick beds has been studied. This migration has been shown to be a function of the packing of the bed, the moisture content at commencement of drying and the method of drying. Factors which enhance the transport of moisture through the bed by capillarity also increase the extent of solute migration.

INTRODUCTION

Uneven drug distribution throughout a batch of granules is one source of dose variation in tablets. One way in which this drug distribution may be affected is by migration of soluble constituents to the drying surface during the drying operation, (Selkirk, 1976). Various factors such as particle size (Warren and Price, 1977), method of drying (Travers, 1975) and binder viscosity (Chaudry and King, 1972) have been shown to affect solute migration in pharmaceutical granulations. We have examined solute migration in thick-bed drying and have studied the effects of drying conditions, binder volume and particle packing on this migration.

MATERIALS AND METHODS

The lactose and borax used were both of BP quality.

Preparation of granules

Since dose uniformity problems are generally more serious with low dose drugs, the lactose and borax were mixed in the ratio 50 : 1 in a planetary mixer. Samples were taken at various time intervals and the mixing index of Ashton and Valentin (1966), was used to determine the optimum mixing time. This was found to be 5 min and was then kept constant throughout the study.

The lactose/borax mix was wet massed with water as a binder. Massing water concen-

trations of 14% or 18% volume per dry weight of powder were used in the study. These were lower volumes than may be expected and were due to a mutual increase in solubility of borax and lactose in each other presence (Fig. 1). The mix was massed with the appropriate volume of water for 5 min and the resultant mass force screened through a number 10 mesh to form the granules. These were allowed to fall from the granulator into the appropriate containers for drying.

Drying of granules

The granules fell into and were dried in containers 4.265 cm in diameter and 7 cm deep in a hot air oven. One further batch was dried in a container 8.5 cm in diameter and 14 cm deep.

Drying rates were determined by suspending the containers in the oven from a load cell situated in the roof of the oven. Decrease in weight with drying could then be followed without interference with the oven. A typical drying curve is shown in Fig. 2.

In a number of cases the granules were partially dried in thin layers on large trays in the hot air oven. Once a certain moisture content had been reached they were rescreened through the granulator into the cylindrical containers as described above and drying was continued as before. This enabled granules of a fixed initial moisture content to be dried in the cylindrical containers.

The effect of the method of drying used was also studied by drying batches of granules by vacuum- and freeze-drying methods. Vacuum-drying was carried out at 48°C and at a pressure of 6.8 kNm^{-2}. Freeze-drying was accomplished using a freeze-drier, (Model EF6, Edwards, England).

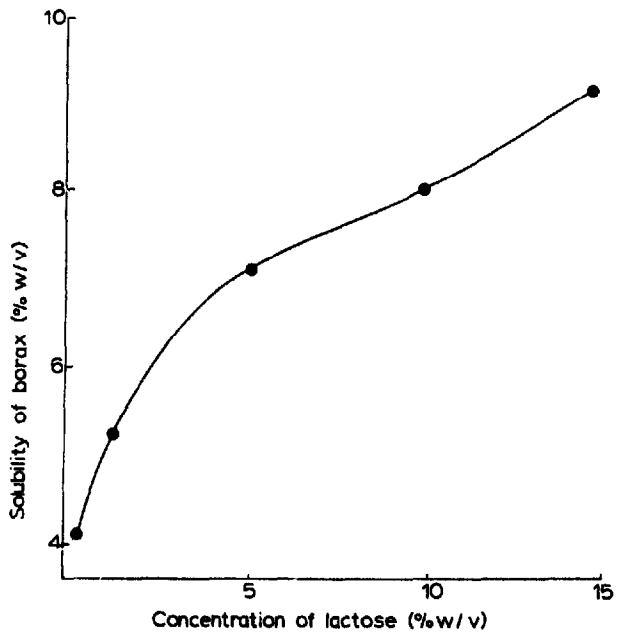


Fig. 1. The effect of lactose concentration on the solubility of borax.

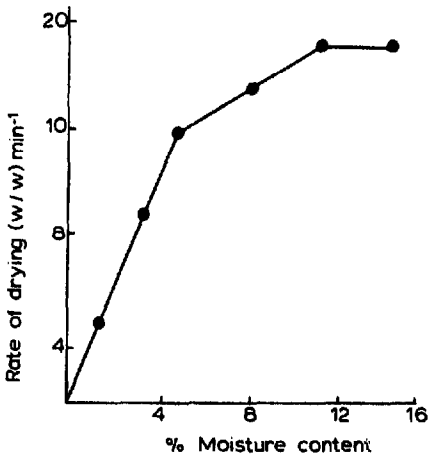


Fig. 2. Drying rate of borax granulation.

One further batch of granules was prepared by tapping down the granules in their container as it was filled from the granulator. The granules were then dried in the hot air oven as before. The tapping was done to determine the effect of particle packing on solute migration.

Analysis of granules

After drying the granules in the containers to a constant weight, the contents were separated into a number of layers. Seven layers each 1 cm deep were separated for the small containers (4.265 X 7 cm) and 3 layers for the large containers (8.5 X 14 cm).

Each layer was analyzed for its borax content by titration with hydrochloric acid using an automatic titrimeter (model TTT IC, Radiometer, Copenhagen).

In addition, the 3 layers of granules separated from the large container were each sized by sieve analysis. The borax content of each size of granule in each layer was then determined as above.

Bulk density determination

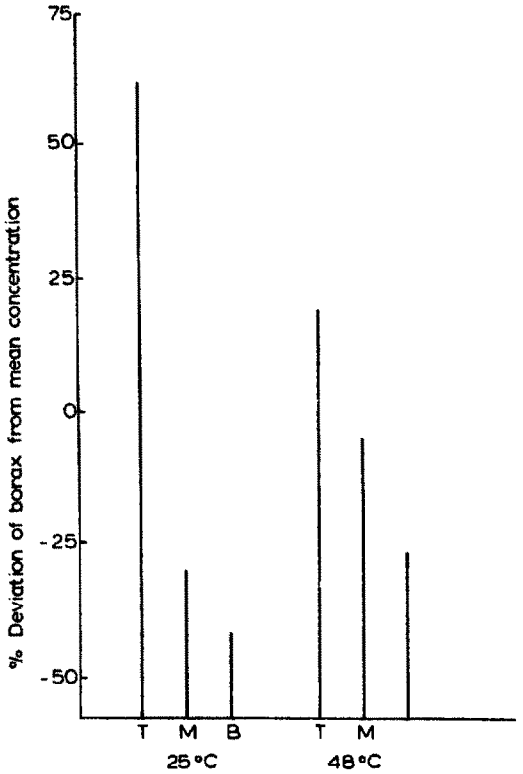
Bulk density determinations were made on the dried granules, with and without tapping during filling from the granulator. As expected the tapped granules showed a higher bulk density, 0.7 g cm^{-3}, when compared to the untapped, 0.5 g cm^{-3}, indicating closer packing with the former.

RESULTS AND DISCUSSION

The system studied is complex in as much as both the borax and lactose are soluble in water. Therefore both may migrate on drying. However, the ratio of borax/lactose in the solution phase is considerably higher than in the solid state. Solute migration will then be shown as an increase in borax concentration. Fig. 3 shows the effect of temperature on the migration of the borax. The results are plotted as the percentage deviation from the mean borax content, i.e. 2%. In both cases solute migration is seen. It is, however, considerably more marked for granules dried at the lower of the two temperatures. This is somewhat unexpected as the slower drying rate with the lower temperature may have been expected to allow more time for back diffusion of the borax. Such back diffusion has been shown to occur during the migration of PVP solution used as a binder (Rubinstein and Ridgway, 1974). In this case, however, the binder solution is completely saturated with borax. This saturation will therefore prevent back diffusion under these conditions, the slower rate of drying would allow longer for an equilibrium situation to be established and therefore result in a greater degree of migration.

The effect of drying method is shown in Fig. 4. As might be expected freeze-drying produced no evidence of solute migration. Vacuum-drying gave results similar to that found by Travers (1975) using sodium chloride and Kaolin, and supports his theory of flash-drying with such systems. Drying in a hot air oven showed a steady decrease in borax concentrations with a maximum at the topmost granule layer, a result again in agreement with Travers (1975). Considerable solute migration occurs with this system.

This migration will only continue while there is sufficient moisture to maintain the system in a capillary or funicular state. Such a state is a function of the size of the capil-



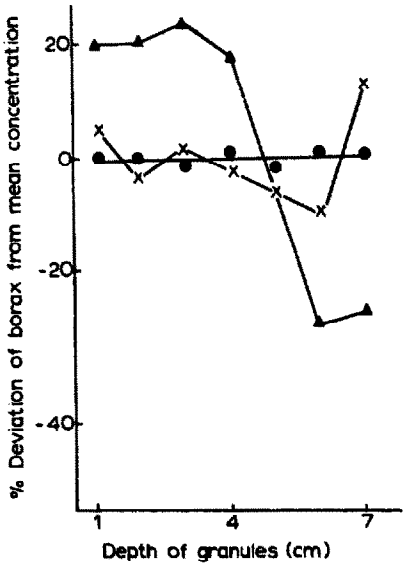


Fig. 3. The effect of drying temperature on the distribution of 0.6% borax throughout a thick bed. T, top layers of granules in bed; M, middle layers of granules in bed; B, bottom layers of granules in bed.

Fig. 4. The effect of the method of drying on the distribution of 2% borax through a thick bed. Tray drying in hot air oven, ▲; freeze-drying, ●; and vacuum-drying, X.

laries in the bed. The smaller the capillaries, the greater the head of liquid they can support and therefore the greater the amount of liquid which can be transported to the drying surface before the surface layers enter the pendular state and the drying plane recedes into the bed. As a consequence of this, the closer the granules are packed in a bed, the greater the solute migration of the soluble constituents. This is shown in Fig. 5. The granules which were tapped during filling from the granulator have a greater bulk density and show a more marked solute migration.

If the premises stated above are correct then solute migration to the surface of the drying bed will be most marked during the constant rate period of drying. The migration will then recede into the bed as the first falling rate period proceeds. Finally when all moisture in the bed is in the pendular state, no migration will be found.

The effect of moisture content on solute migration is shown in Fig. 6. The granules in this case were all dried at 48°C. As can be seen from Fig. 2, granules with a moisture content of over 11% lay within the constant rate drying period. A steady reduction in borax concentration with distance from the drying surface was observed with these granules. This is consistent with the concept that sufficient moisture is being transported to the

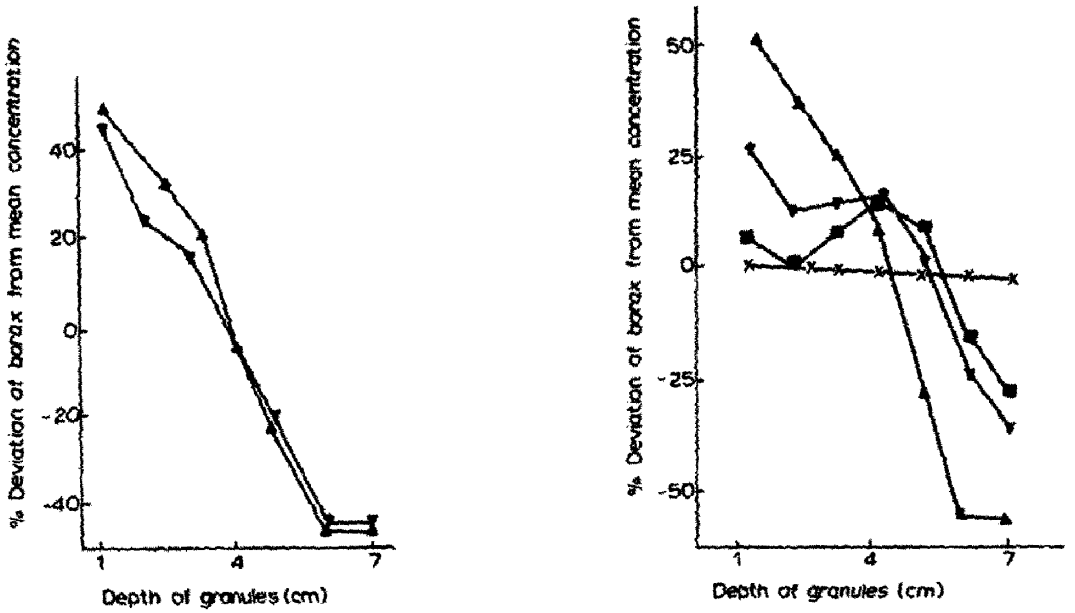


Fig. 5. The effect of packing density on the distribution of 2% borax throughout a thick bed. High density (0.7 g cm^{-3}), ▲; low density (0.5 g cm^{-3}), ▼.

Fig. 6. The effect of initial moisture content on the distribution of 2% borax throughout a batch of granules. ▲, 18% initial moisture content; ▼, 14% initial moisture content; ■, 11% initial moisture content; ◆, 6% initial moisture content.

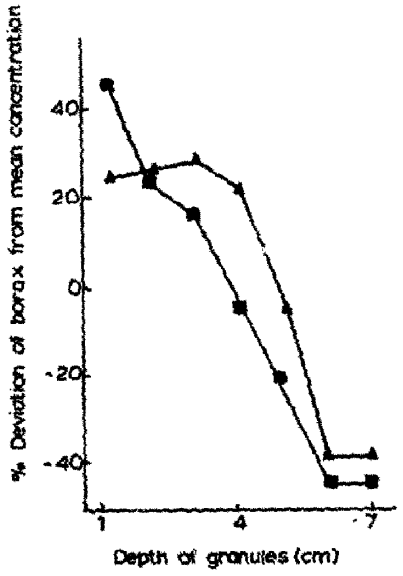


Fig. 7. The effect of massing water concentration on the distribution of 2% borax throughout a batch of granules. ■, 18% massing water concentration. ▲, 14% massing water concentration.

TABLE 1

GRANULE SIZE DISTRIBUTION OF GRANULES DRIED IN A THICK BED

Size of sieve (μm) retaining granules	% cumulative weight of granules			
	Top layer of thick bed	Middle layer	Bottom layer	Whole layer of thick bed
1000	33	30	33	32
710	55	53	56	55
500	72	70	72	71
355	85	84	85	85
250	94	93	93	93
180	97	97	97	97
<180	100	100	100	100

surface to allow saturation of the air immediately above the surface layer.

However, if the granules are dried to a moisture content within the first falling rate period and are then rescreened and repacked into the beds, the capillary forces are now insufficient to saturate the surface air layer and the drying front will recede into the bed at certain points. This will result in a reduction in migration to the surface but with an increase in migration to layers immediately below the surface. This is shown in Fig. 6 by a reduction in the borax concentration of the surface layers with a secondary peak appearing at lower levels in the bed. The lower the initial moisture content, the more marked this effect becomes. Eventually the initial moisture content is so low that all moisture in the bed exists in the pendular state. At this stage there is no evidence of solute migration.

While the initial moisture content of the bed can be controlled by rescreening of the granules after a given period of drying, a more practical control is by varying the binder volume. A lower binder volume would give a lower initial moisture content and therefore less marked solute migration. Such an effect is shown in Fig. 7.

Since solute migration to the drying surface of granular beds does take place, it is of importance to know how it affects granule size distribution in the bed and drug concentration for different sized granules. Binding in granules is considered to take place by crystalline bridges of material forming from solution during drying. Most of this material will migrate to the upper bed layers with these larger granules having a disproportionate amount of drug in them.

The sieve analysis from the 3 layers is shown in Table 1 along with a sieve analysis from an overall unsectioned batch. No significant difference in granule size was found at the different depths or with the bed as a whole.

The effect of granule size on drug concentration for each of the section is shown in Fig. 8.

Migration is shown by the vertical displacement of the curves from each of the sections. However, the shape of each of the curves was similar, each showing a slight drop in drug concentration with the smallest granules. Thus, intergranular solute migration neither influences granule size distribution nor the variation in drug concentration with granule size.

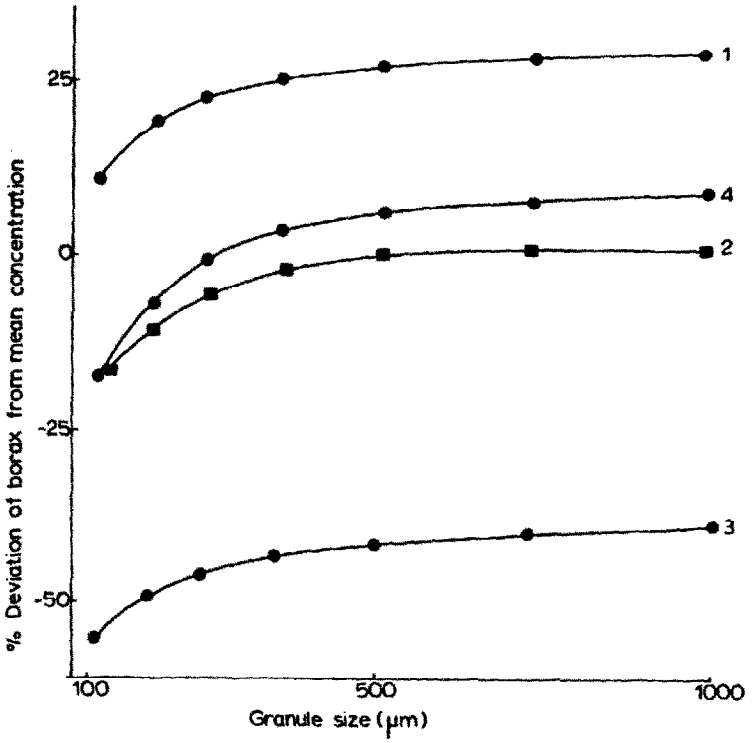


Fig. 8. The effect of thick-bed drying on the distribution of 2% borax in sized granules from the top, middle and bottom of bed compared to overall distribution of bed. 1, top of bed; 2, middle of bed; 3, bottom of bed; 4, overall.

CONCLUSIONS

The results show that solute migration can be a serious problem in drug distribution in a granule bed. The extent of migration is related to the capillary forces occurring during drying. Any factors affecting these capillary forces markedly alters the migration of soluble constituents during drying.

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