J. Pharm. Pharmac., 1975, 27, 516–522 *Received January* 1, 1975

A comparison of solute migration in a test granulation dried by fluidization and other methods

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The intragranular migration of sodium chloride in granules made by the wet massing of heavy kaolin B.P. with salt solution has been studied in batches dried by fluidization and a vacuum tumbling method. The larger granules from the fluidized batch exhibited considerable intragranular variation with the outer crust containing over twice the average salt concentration. Solute loss from this layer by abrasion on prolonged fluidization was slight but the dust eluted from the dryer had a salt content above average. Analysis of sieved fractions of the dust showed that this enrichment was concentrated in the fine material passing a 53 μm mesh. The vacuum dried granules had less migration and were less resistant to crushing than those dried by fluidization. The dust produced had a salt content only slightly greater than the average composition and the overall solute content of the sized fractions were all close to this average. The same system was used to study intergranular migration in a fixed bed when the granules were dried by infrared radiation, by microwave radiation, by convection from air and in a vacuum. The greatest migration occurred in samples dried by infrared radiation and the maximum solute concentration was near the middle of the bed. The air dried granules had less migration and the maximum concentration was in the surface layer. The granules dried in a vacuum and by microwave radiation were fairly uniform in composition throughout the bed. The above results are explained on the basis of the capillary theory of drying together with the modifying influence of the drying method on the probable heat and mass transfer rates.

The movement of soluble materials during the drying of wet massed granules is a phenomenon that can adversely affect tablets made from them. Ridgway & Rubenstein (1971), who studied the intragranular migration of the binding agent polyvinylpyrrolidone, found that it formed a hard crust round the dried granule which they considered might influence the dissolution and disintegration of tablets containing it. The intergranular migration of sodium warfarin in a tray dried granulation was shown by Chaudry & King (1972) to cause such variation in the compressed tablets that only 12% of those sampled by a single tablet assay were within the U.S.P. limits for drug content. Drug migration also occurs during the drying of moulded tablets and glyceryl trinitrate tablets made by this method may subsequently lose active agent by volatilization from the tablet surface (Fusari, 1973).

In the last decade fluidized bed drying of tablet granulations has largely replaced tray drying in shallow layers unless inflammable granulating fluids such as isopropanol are present. In fluid bed drying each granule is isolated from its neighbours by the

heated air and intergranular migration of solute is not possible. Conditions are, however, seemingly favourable for intragranular migration to give a solute rich layer round each granule. Subsequent attrition and elution of the dust could then lead to serious loss of active ingredient. However, Scott, Lieberman & others, (1963) could find no visual sign of intragranular migration in a fluidized granulation containing a soluble dye, but they made no quantitative measurements nor did they consider the possible effect of the other inclusions. For example, Chaudry & King (1972) have shown that the use of acacia as binder greatly impedes the migration of sodium warfarin, and Fusari (1973) was able to stabilize his moulded tablets by including glycols in the formulation.

A test granulation to study solute migration should therefore be as simple as possible, and one made by wet massing heavy kaolin B.P. with an aqueous solution of sodium chloride was found to have sufficient cohesion and strength and to fluidize well. This paper describes the effect of various drying methods on the solute migration in this test granulation.

MATERIALS AND METHODS

Preparation of granules

Heavy kaolin B.P., 200 g dried at 70°, was rapidly massed with 50 ml of sodium chloride solution (10% w/w) in a Kenwood mixer. The mass was scraped down twice during mixing and the aggregates broken up with a pestle. This gave a mass of suitable uniformity for granulation through a 2800 μm mesh sieve.

Drying of the granules

(a) *By Fluidization.* The wet granules were fluidized for 30 min in an Aeromatic AG laboratory dryer at an inlet air temperature of 50°. This dryer had a tapered drying chamber with the exit closed by a dust bag filter which remained in place when the chamber was removed. Before the bag was removed the mouth was covered with a piece of cardboard to obtain the dust trapped within. Total recovery was better than 95% of the calculated dry weight.

(b) *In a split bed by various methods.* The bed consisted of a number of dural sections (Fig. 1), and an asbestos mask. It was filled with wet granules, about 30 g, level to the top of the sections, and these were dried by one of the following methods:
1. In an infrared dryer (Fowler, 1952) and set at a peak wavelength of 3·6 μm, for 1 h.

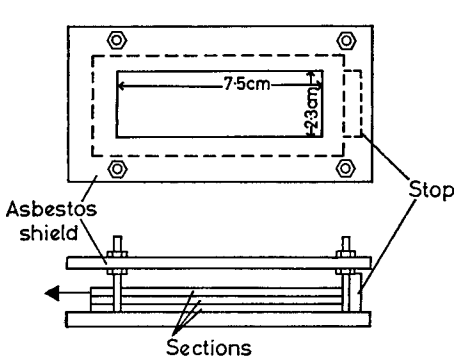


FIG. 1. The "split" bed. The top three sections are omitted.

2.Suspended in a vacuum by wire strands from the top of a Townsend and Mercer vacuum oven set at 70°, for 24 h. 3. In an incubator room at 37°, with good air circulation for 48 h.

In all cases the sides and base of the bed were insulated by glass fibre wadding taped in place.

A tray of the same dimensions made of polypropylene fixed with nylon screws was used for microwave heating because metal causes short-circuiting. The tray was passed on a moving belt under a transmission line, set at an input of 5 kW at 896 MHz. The rig had an active length of 4 m and the belt speed was 0·1 ms^{-1}. The granules were therefore in the dryer for 40 s though for technical reasons the field exposure time was about 20 s. Two passes were sufficient to dry to constant weight.

In all cases the bed was separated into six samples by carefully moving each section horizontally in turn, and brushing the granules onto a sheet of paper.

(c) *By a vacuum tumbling method.* Wet granules (70 g) were placed in a lacquered brass vessel with O ring seal (Fig. 2). The side connection was attached to vacuum via a vapour trap. The vessel was rocked back and forth while immersed in a water bath at 50° so as to simulate the action of a vacuum tumbler dryer (cf. Goodhart, Draper & Ninger, 1970).

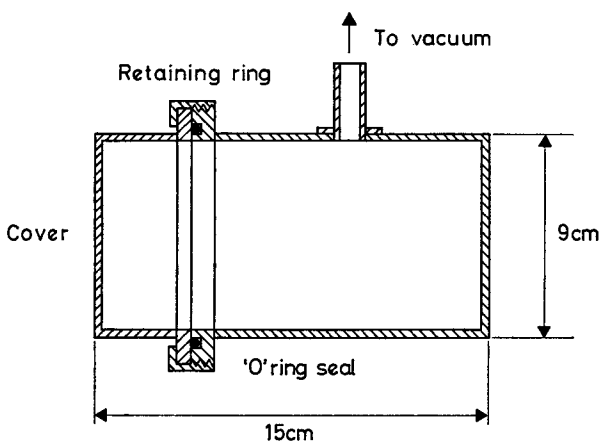


FIG. 2. The vacuum vessel.

Treatment of the dry granules

The granules, dried by fluidization and tumbler drying, were separated into sized fractions by sieving and the mean salt content of each determined by crushing and titrating a weighed amount, suspended in 50 ml of distilled water, with 0·1 M silver nitrate solution from a 10 ml piston burette with digital reading (Metrolm Dosimat E415).

A weighed quantity of the larger fractions was examined for intragranular migration by prolonged sieving on a Finex Sifter with 250 μm mesh sieve which slowly abraded sufficient powder for analysis. The plot of salt content of the abraded powder samples against the cumulative percentage of the initial sample weight abraded gave the "solute profile" of the granule fraction (Fig. 3A, B).

The samples from the split bed were crushed and analysed to determine the mean solute content, but were not separated into sized fractions.

Granule crushing strength

A crushing strength apparatus was constructed of vertical aluminium rod, 1·25 cm diam. and 5 cm long, located as a sliding fit in a hole in a horizontal aluminium block 2½ cm above a lower block which formed the anvil. Individual granules were loaded

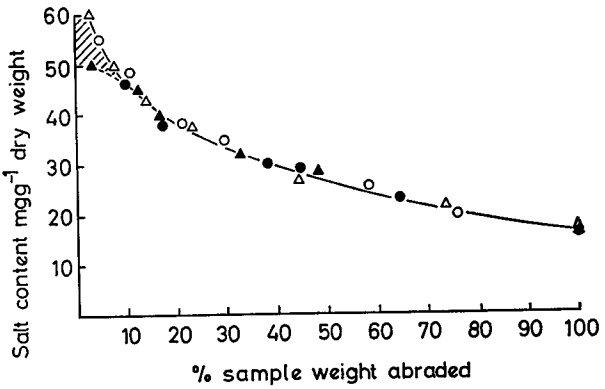
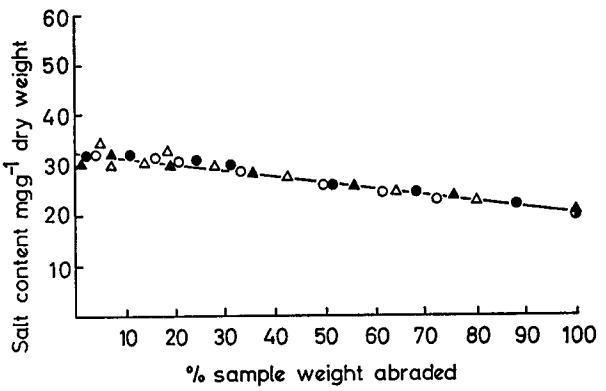


FIG. 3.A. Solute profiles of granule fractions dried by fluidization at 50°. △ Retained on a 2057 μm mesh sieve after 30 min drying. ○Retained on a 1680 μm mesh sieve after 30 min drying. ▲● Same fractions after 8 h drying.



B. Solute profiles of granule fractions dried by vacuum tumbling for 30 min. Same size fractions as those of (A) but two separate batches dried at 50 ° ○ ● and △ ▲.

using a Correx tension gauge bearing on the top of the rod. The crushing strength was taken as that reading, plus the rod weight, giving perceptible movement and obvious fragmentation.

RESULTS AND DISCUSSION

Intragranular migration during fluid bed and vacuum tumbling drying

It is apparent from the solute profiles of the two largest granule sizes (Fig. 3A, B) that fluidization produces the greater migration. Migration is caused by movement of solution towards the surface of the granule occurring because of capillarity effects in the network of interparticulate spaces (Pearse, Oliver & Newitt, 1949).

Newitt & Conway-Jones (1958) pointed out that wet granules owe their cohesive strength to moisture which could be present in one of three states. It may entirely fill the void spaces (capillary state). Alternatively it may be present as a continuous film with the voids partially filled with air (funicular state) or at low moisture content, as lens-like rings at the point of particle contact (pendular state). Film continuity is essential for capillary movement and solute migration can only occur while there is sufficient moisture to maintain the capillary or funicular states. When continuity is broken the granule dries from the surface inwards but migration may still take place from below the plane of drying. The solute is deposited to give the profile shown. This mechanism accounts for the migration illustrated in Fig. 3A, B but does not explain why fluidization produces the greater movement. The evaporation rate will be controlled by the rate at which the necessary latent heat can be transferred to the granule surface. Solute migration is likely to be greatest when the evaporation rate is fairly slow at low rates of heat transfer. At higher rates fluid friction will act to retard the moisture movement so that the granule surface becomes dry at a stage when less overall movement has taken place.

A conductive drying process such as vacuum tumbling drying will have higher heat transfer rates than will a convective process such as fluidization. This may account for the shallower profile of Fig. 3B. It is also probable that on drawing a vacuum "flashing" occurs, first at the surface and then into the intraparticulate voids as heat is conducted into the granule. This would hinder moisture movement by disrupting the moisture film near the plane of drying.

Since sodium chloride is fairly soluble, it will become concentrated into the pendular moisture which will finally dry to form salt bridges at the points of interparticulate contact. A similar effect is responsible for the caking of granular fertilizers (Mitchell, 1954), and the dry granule strength will be largely derived from these bridges. As much of the salt is present in the outer crust of the fluidized granules, this will confer a "hoop strength" which makes them more resistant to crushing than the vacuum-dried granules. The results obtained by crushing twenty individual granules from those retained on the 2057 μm sieve were 319 g, s.d. 55 g for the fluidized granules and 122 g, s.d. 25 g for the vacuum-dried granules. This dry strength is probably attained

Table 1. *Solute content of the sized fractions dried by fluidization and vacuum tumbling.* Calculated solute content 26·0 mg g^{-1} dry weight.

Sieve aperture (μm)	Fluidized granules: % retained on stated aperture	Fluidized granules: Salt content mg g^{-1} dry wt	Vacuum dried granules: % retained on stated aperture	Vacuum dried granules: Salt content mg g^{-1} dry wt
2057	10·9	25·0	15·3	25·9
1680	12·0	25·5	10·9	25·9
710	33·8	25·5	40·1	25·8
600	6·5	25·0	7·0	25·7
355	12·5	25·0	13·0	25·9
250	5·9	24·4	5·2	26·0
180	5·6	26·3	2·8	25·6
150	3·0	28·7	1·2	25·6
125	2·6	29·0	1·0	25·6
105	1·1	28·4	0·7	26·8
53	4·0	33·5	2·0	27·3
45	1·1	44·1	0·2	27·9
Thro'45	negl.		0·6	25·1

in the final stages of drying since Rubinstein & Ridgway (1974) have reported that even a small amount of residual moisture can greatly reduce the strength and hardness of a granule as measured by its resistance to abrasion. The results given in Table 1 suggest that abrasion of the solute-rich outer layer during fluidization and elution of the dust can result in an overall loss of around 4% of the initial content and a considerable enrichment of the finer fractions collected in the filter. The dry granules were much more resistant to abrasion and the solute profile of Fig. 3A is but little changed on prolonged fluidization.

Vacuum tumbling drying has the advantage over fluidization that although similar quantities of fine dust are produced, there is little difference in its composition. Hence if it were discarded as fines, it would not deplete tablets made from the remainder of the granules.

Intergranular migration in the split bed

Table 2 gives the salt content of granules at different depths below the surface of the bed when drying is complete by the different methods. For granules dried by infrared radiation the maximum concentration occurs near the middle of the bed.

Table 2. *Variation of solute content with depth below surface of the bed for granules dried by different methods.* Calculated salt content is 26·0 mg g^{-1} dry weight. Duplicate determinations (1) and (2).

Mean depth below bed surface mm	Method of drying and salt content mg g^{-1} dry weight							
	Infrared radiation		Microwave radiation		Suspended in vacuum at 70°		Convection from air at 37°	
	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)
1·65	25·1	25·1	25·8	26·1	25·7	26·1	32·8	31·6
4·95	26·8	26·3	26·3	26·2	25·8	26·3	27·5	28·1
8·25	30·7	29·9	26·0	26·2	25·9	26·2	25·3	25·7
11·55	33·6	34·5	26·1	26·4	25·3	25·8	23·4	22·1
14·85	17·7	14·4	26·3	26·3	25·5	26·1	23·1	21·8
18·15	6·2	8·6	25·7	25·9	27·7	27·1	22·8	21·7

Radiation has little penetrating power and if absorbed appears as heat at or near the surface. The top granules would, therefore, dry quickly and then drying must take place from an internal plane whose position would be fixed by the rate at which heat can be conducted through the dry layer. This plane will be at a depth where the evaporation rate is slow enough for migration to be sustained from beneath it until the pendular state is reached when it recedes deeper into the bed. As a result the bottom layer is depleted to barely a quarter of the initial salt content. Infrared drying of pharmaceuticals which attracted some early interest (Patel, Jenkins & De Kay, 1949; Fowler, 1952) has never attained industrial popularity, and these results indicate one objection to its use. In contrast there has been revived interest in high frequency radiation for drying granulations (Schepky, 1974) following the work of Bikin, Jenkins & De Kay, (1949). Earlier methods used the principle of dielectric heating at relatively low frequencies but recently microwave methods have enabled much greater energies to be used with consequent rapid drying. In the test rig employed in the present work inputs of 25 kW were possible. Lyons (1969), reporting on the microwave drying of textiles, stated that the method controlled the troublesome migration of waterborne resins and dyestuffs, since the radiation pene-

trates the whole of the fibre with heating throughout. This internal heating with evaporation taking place throughout the bed, accounts for the uniform composition recorded in Table 2.

There is appreciable migration in the bed dried in air at 37° but since heat transfer by convection is slow, the evaporation is also slow enough to maintain a flow to the surface such that the solute concentration attains a maximum near the top of the bed. Consequently no layer is so badly depleted as those dried by the infrared method.

The uniformity of the granules dried suspended in a vacuum is surprising. Under the experimental conditions heat transfer could occur only by surface absorption of radiation as in the first case, but as radiation intensity is proportional to the fourth power of the absolute temperature, heat transfer would be much slower at the low oven temperature of 70°. Hence there should be steady moisture movement to the surface to yield a distribution similar to the beds dried in air. The result can be explained as the effect of flashing into the intergranular voids in a manner similar to that previously discussed for the tumbler-dried granules. This action would not prevent back diffusion, which Rubinstein & Ridgway (1974) have shown can occur from concentrated solution formed near the drying plane, and it is significant that the bottom layer is the richest in solute.

Acknowledgements

I am indebted to Mr. R. J. Meredith of Magnetronics Limited, Barkby Road, Leicester for the use of the microwave test rig and to Mrs. R. Faulkner who prepared the illustrations.

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