

Solute migration during granule drying

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Spherical granules of magnesium carbonate, 12 mm diameter, have been dried under controlled conditions in a drying tunnel at 44°, the rate of moisture loss being continuously recorded. The granulating agent was polyvinylpyrrolidone (PVP). Granules were removed at various times for analysis. By controlled attrition, successive layers of powder were removed from the granules. The powder was analysed for PVP by infrared spectroscopy, and the friability, modulus of elasticity and Brinell hardness of the granules were measured as a function of depth from the granule surface. The radial distribution of the PVP and its physical effect on the granule properties were thus found.

The effective preparation of pharmaceutical tablets depends upon the material to be compressed being in a free-flowing form. The usual method of achieving this is to wet-granulate the powder and to dry the granules. Although the process of wet granulation is intended to produce granules of a uniform composition, it is well known that under certain drying conditions the outer layers may have a different composition from the central portion. In particular, any binder included in the mass may form a crust around the granule periphery and the resultant granule, during subsequent tableting, may deform differently from a granule with a uniform distribution. A tablet produced from granules in which the binder is concentrated in the outside layers of the granules is liable to have localized areas of high cohesion, thus resisting subsequent disintegration and dissolution. Any accidental attrition of non-uniform granules will also give fines which have a different composition from the main bulk; the non-uniformity can, in some circumstances, extend to the active constituent.

The drying rate of a surface-dried particulate material has been shown to exhibit a number of distinct drying periods (Fisher, 1932). The material dries at a constant rate until a definite moisture concentration, the critical point, is reached, when a decrease in the drying rate occurs. The first falling rate period then ensues, the drying rate decreasing in a linear manner. In the second falling rate period the decrease in rate is non-linear and is usually an asymptotic, exponential approach to zero moisture content with respect to time.

Ridgway & Callow (1967) have shown that, in the falling rate periods, a linear relation exists between the logarithm of the drying rate and the liquid content. Drying rates have also been shown to be modified by the presence of solutes. Krevelen & Hoftijzer (1949) dried single granules of nitrochalk, and found that, during the constant rate period, the dissolved ammonium nitrate formed an impermeable crystalline film around the granule, so reducing the rate of drying.

Newitt & Papadopoulos (1959) examined the drying of fertilizer granules, and also of sand containing aqueous sodium chloride solution. They found that solutes were transported to the outside of the granule forming a crust, but they made no

quantitative analysis of the resultant solute distribution. Higuchi & Kuromoto (1954) showed that polyvinylpyrrolidone (PVP), which is used as a binder for tablet granules was able to form complexes with many pharmaceuticals, and more recently (Higuchi, Simonelli & Mehta, 1969) found that the rate of release of sulphathiazole from compressed tablets containing PVP was increased if the drug had been previously co-precipitated with PVP. It thus seems possible that the non-uniformity of distribution of at least some drugs in granules may parallel the non-uniform distribution of PVP.

METHODS

The powder used was heavy magnesium carbonate B.P. [$3\text{MgCO}_3 \cdot \text{Mg}(\text{OH})_2 \cdot 4\text{H}_2\text{O}$] (BDH Ltd.). The mean particle size was $20\ \mu\text{m}$, with 95% by weight being larger than $10\ \mu\text{m}$ and 5% larger than $32\ \mu\text{m}$. Granules were made by mixing 290 g of powder with 170 ml of a solution containing 15 g of PVP (BDH Ltd.). The wet mass was passed through an 8 mesh sieve, remixed and repassed through the sieve. It was then rotated in an 11 inch diameter coating pan at 30 rev/min, 30° to the horizontal, to produce spherical granules. 25 of these, of the required size of 12 mm were selected for an experimental run.

The selected granules were placed in two concentric circles on a nylon platform, which was hung from the pan of an automatic recording balance in a drying tunnel (Ridgway & Callow, 1967), through which air at 44° was blown at a controlled velocity. After 30 min, 5 granules were taken from the tunnel, plunged into liquid nitrogen, and then dried in a laboratory freeze drier for 12 h. This procedure prevented any further migration of solute within the granule. Further groups of 5 granules were removed from the tunnel after $1\frac{1}{2}$, 3, 4, and 24 h.

The indentation hardness and elastic recovery of the outer surface of the granules were measured with the ICI pneumatic micro-indentation apparatus and technique described by Ridgway, Aulton & Rosser (1970). The granules were then separately treated in the multiple attrition cell apparatus (Fig. 1) to remove their outer layers. Each granule is placed in one of five cylindrical chambers, and rests inside a stainless steel gauze cage. The cage has a central brass ring soldered to it. The ring rests on the inner flange of a duralumin canister, so that the cage can be both closed and held in position within the canister by means of a screwed rubber-lined lid and a spacer tube. The five duralumin canisters are held in a brass plate which replaces the sieve in a 4 inch deep 8 inch diameter brass cylinder suitable for clamping onto a Finex sifter (Russell Construction Co).

The granules are shaken for a measured time interval; they retain their spherical shape but are gradually worn away. The powder thus attrited from the granule is collected, weighed and analysed for PVP by infrared spectroscopy (Ridgway & Rubenstein, 1971). The core weight is recorded, the diameter is measured and the Brinell hardness number and elastic modulus are determined. The process is then repeated until the intact core weight is reduced to about 10% of the initial weight.

RESULTS AND DISCUSSION

The drying curve for 25 granules dried at 44° is shown logarithmically in Fig. 2. Three stages of drying can be seen. Initially the drying rate falls linearly to the critical moisture content. A further linear fall in rate occurs after $1\frac{1}{2}$ h drying, and finally, there is a third fall to the equilibrium moisture content.

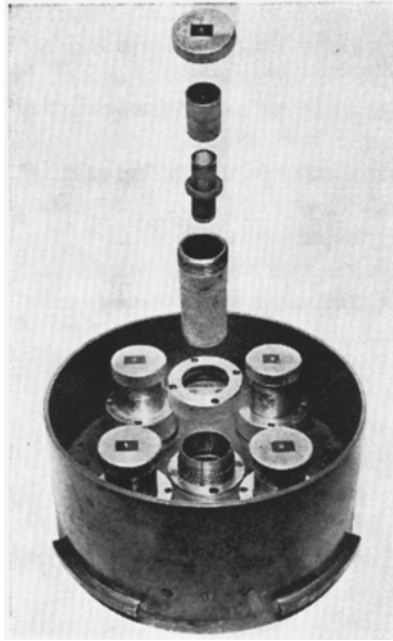


FIG. 1. The multiple attrition cell apparatus. Up to five granules can be held in closed gauze baskets, held inside the duralumin containers which are mounted in a brass plate and sieve surround so that the entire assembly can be vibrated on a sieve shaker. In the exploded view shown, the parts are, from the top downwards, the screwed rubber-lined lid, the spacer tube, the gauze cage, the canister, and the locking ring.

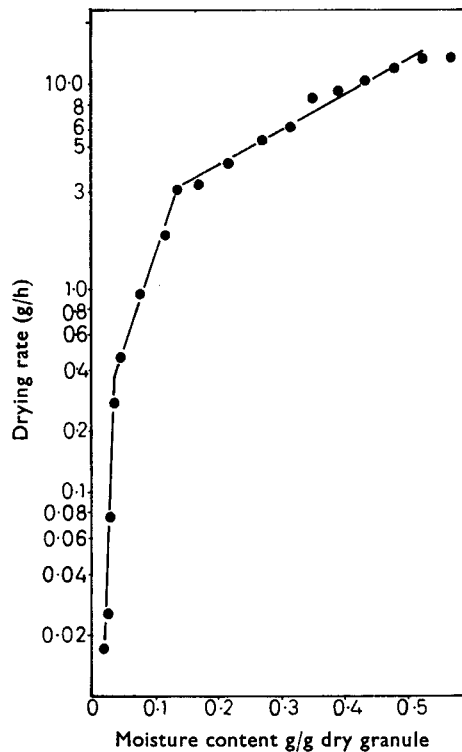


FIG. 2. The drying rate as a function of the moisture content of the granules.

In the initial stages of drying, PVP migrates to the surface of the granule. It is at the air-solid interface that evaporation takes place, with the result that PVP is deposited at the granule surface forming a crust. This deposited PVP blocks the interstices between the magnesium carbonate particles, thereby reducing the surface area available for evaporation and limiting further solution being drawn to the surface by capillarity. Thus a reduction in drying rate occurs and this accounts for the initial fall in drying rate to the critical moisture content (as distinct from the normal constant rate drying period which is found for pure liquids evaporating from beds of powder). The decline in drying rate continues for about $1\frac{1}{2}$ h, when the critical moisture content is reached, and there is a sudden change in slope of the logarithmic drying rate line. At this point the surface of the granule is no longer wet enough to act as a free water surface.

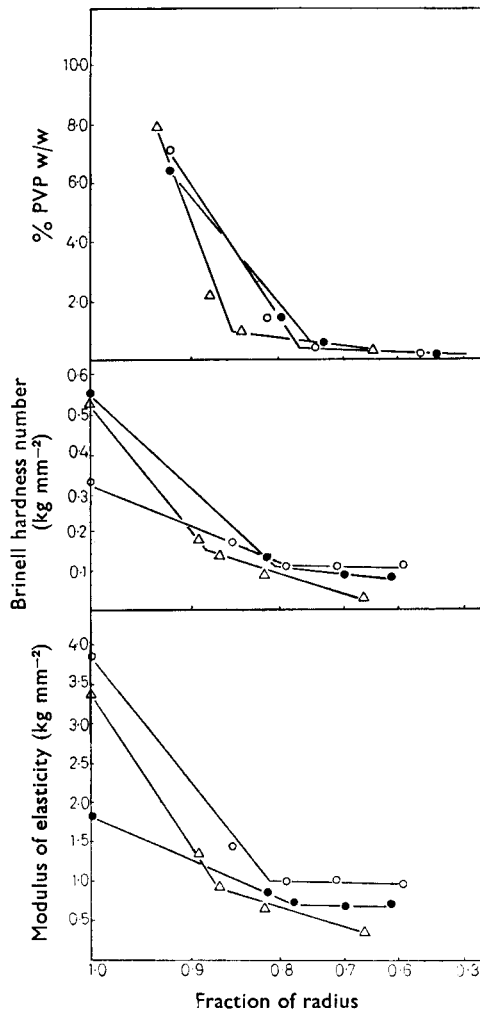


FIG. 3. Variation of % w/w PVP, Brinell hardness number and Young's modulus of elasticity with depth from the granule surface. Δ after $\frac{1}{2}$ h drying. \circ after 3 h drying. \bullet after 4 h drying.

The surface menisci then recede into the surface voids, with a linear fall of drying rate during the period from $1\frac{1}{2}$ to $3\frac{1}{2}$ h. This period will end when all the surface menisci have receded into the voids and the surface will effectively be dry. The final falling rate period occurs after $3\frac{1}{2}$ h drying. Since the surface is now dry the evaporative interface recedes towards the centre of the granule. Removal of water is by internal vaporization; vapour diffusion to the surface is the limiting factor.

The PVP distribution, Brinell hardness number and Young's modulus of elasticity against the radial distance is shown in Fig. 3 for three groups of granules dried for $\frac{1}{2}$, 3 and 4 h. The outer layers of the granules have a relatively high PVP content and their Brinell hardness number and Young's moduli are correspondingly high. Towards the middle of the granule the PVP content, Brinell hardness number and Young's modulus decrease linearly in value. A point is reached where no further decrease is observed and the three parameters remain constant. This point gives a measure of the crust thickness.

Fig. 4 shows how the PVP content, Brinell hardness number and Young's modulus at the surface and in the core of the granules, vary with decreasing moisture content. The top graph of PVP concentration against moisture content represents the total concentration of PVP: this is the sum of that deposited as well as that in solution. During the first $\frac{1}{2}$ h drying, the PVP concentration in the surface layer rises well above, and that in the core declines below, the initial uniform concentration (Fig. 4). Since there is now a greater concentration of PVP in the outer layers relative to the core, PVP must be migrating and concentrating in the outer surface of the granules. Subsequently, there appears to be a steady fall in the concentration of PVP in the surface layers as drying proceeds up to a point representing the end of the second falling rate period. The core concentration of PVP increases slightly over this period. This can be explained by considering that "back-diffusion" occurs. This is the diffusion of PVP from a point of higher concentration in the outer surface of the granule to a point of lower PVP concentration in the core. The movement of PVP is thus governed by evaporative and diffusional transport. In the initial stages of drying the evaporative rate is high and back-diffusion, although occurring, is negligible. As PVP is deposited and the drying rate is reduced, back diffusion of PVP in solution becomes more important; PVP moves under a concentration gradient into the interior of the granule from the surface layers—thus no more PVP will be deposited in the outer surface. Since PVP is soluble to the extent of more than 50% w/w, once a crust has been built up and the evaporative rate reduced, it is unlikely that more PVP will be deposited. In addition, the concentration gradient causing back-diffusion will also be large. Thus in Fig. 4 the graph of % w/w PVP in the core of the granule against moisture content shows a steady increase in concentration, due to back diffusion, until the end of the second falling rate period. The sudden rise in concentration during the third falling rate period is due to the deposition of PVP at the receding evaporative interface. Since that part of the granule between the outer surface and the receding evaporative interface is dry during the final falling rate period, diffusion of PVP cannot occur in this region, and it can be seen from Fig. 4 that the surface concentration of PVP does, in fact, remain constant during this final drying period.

Fig. 5 depicts the variation of crust thickness with moisture content. The thickness of the crust increases from $0.14r$ to $0.22r$, where r is the radius of the granule, as PVP is deposited in the first falling rate period. After the end of the first drying

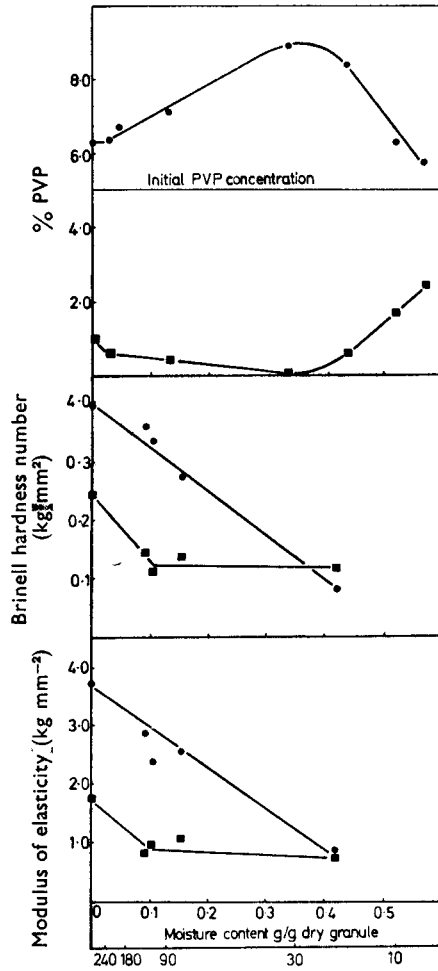


FIG. 4. The variation of PVP content, Brinell hardness and modulus of elasticity with granule moisture content. ● at the surface of the granules. ■ in the core of the granules.

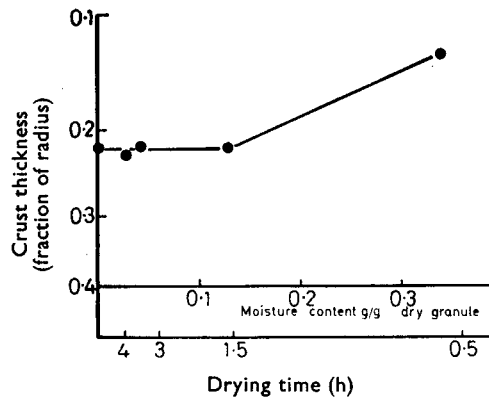


FIG. 5. Variation of crust thickness with drying time.

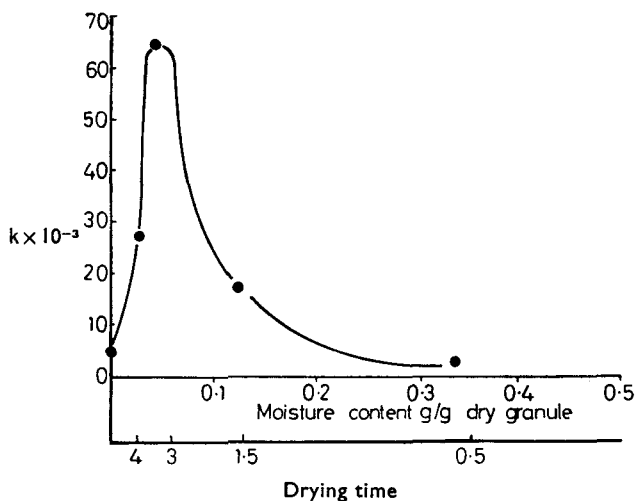


FIG. 6. The effect of moisture content on the granule friability. k is the gradient of the straight line representing the attrition time against the logarithm of the percentage weight intact, for granules shaken in the multiple attrition cell apparatus.

period no more PVP is deposited, since by the process of back diffusion PVP now moves to the central core of the granule. Therefore, the thickness of the crust after the critical moisture content should remain constant and it did.

For each granule a plot of attrition time against the logarithm of the percentage weight intact was determined for each granule shaken in the multiple attrition cell apparatus. These graphs produced straight lines and the average slope of the lines within each group was calculated. This gradient, k , was plotted against the corresponding moisture content to produce Fig. 6. The value of k is a measure of friability: as it increases, a granular solid becomes more friable, and vice versa. Initially the granules are wet and the solid particles are held together by liquid surface tension forces. Thus, the granules will be appreciably resistant to attrition. As drying proceeds, the resistance to attrition is reduced and the graph of k reaches a peak at the end of the second falling rate period, when the surface is just dry and the solid particles are held together by pendular liquid rings. After this point the surface becomes totally dry and as the interior of the granule becomes dry during the final falling rate period, the binding effect of PVP increases the attrition resistance and the k value falls away accordingly.

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