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Solute migration during granule drying

M. H. RUBINSTEIN* AND K. RIDGWAY

Department of Pharmaceutics, The School of Pharmacy, University of London, Brunswick Square, London, WC1N 1AX, U.K.

Spherical granules of magnesium carbonate, incorporating polyvinylpyrrolidone (PVP) as granulating agent, have been dried at various temperatures under controlled conditions in a drying tunnel. At each drying temperature the rate of loss of moisture was continuously recorded. The PVP distribution, modulus of elasticity, Brinell hardness and friability of the granules were measured as a function both of moisture content and of depth from the granule surface. The radial distribution of PVP at different stages of the drying process and at three drying temperatures, and its effect on the physical properties of the granules, were thus found. This gave a picture of binder distribution within the granule and its effect on local strength as drying occurred and also of the overall change caused by alteration in drying temperature.

The process of wet granulation is intended to produce a free-flowing material, of uniform composition, suitable for subsequent compression into tablets. In the drying stage, soluble constituents can migrate to the outer layers of the granules. The phenomenon has been studied by Michell (1954) in the caking of fertilizer granules containing ammonium chloride as the soluble constituent, and by Newitt & Conway-Jones (1958) who investigated the mechanical properties of sand agglomerates formed using varying proportions of added sodium chloride.

There appear not to have been any investigations carried out with pharmaceutical materials. The present authors (Ridgway & Rubinstein, 1971a) showed that the soluble binder, polyvinylpyrrolidone (PVP), when used as a granulating agent, can migrate to the outer layers of the granule, and that soluble dyes will migrate similarly and cause mottling. This work was carried out at one temperature only; the present paper reports the effect of change in temperature on the migration of PVP by making measurements at two further temperatures. The effect of temperature on solute migration has not previously been studied.

METHODS

The powder used was heavy magnesium carbonate B.P. $3MgCO_3$, $Mg(OH)_24H_2O$ (BDH) as in the earlier study (Ridgway & Rubinstein, 1971a). The mean particle size was 20 μm, with 95% by weight larger than 10 μm and 5% larger than 32 μm. Selected 12 mm diameter 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). Drying air, at temperatures of 19·6°, 44·0° and 59·8°, was blown through the tunnel at a controlled velocity of 3 ms^{-1}. At a drying temperature of 44·0°, 5 granules were taken from the tunnel after 30 min, plunged into liquid nitrogen and then freeze dried for 12 h, to prevent further migration of solute

* Present address: School of Pharmacy, Liverpool Polytechnic, Byrom Street, Liverpool, L3 3AF, U.K.

within the granule. Further groups of 5 granules were removed from the tunnel after $1\frac{1}{2}$, 3, 4 and 24 h. At a drying temperature of 19·6°, granules were removed from the drier at 1, $2\frac{1}{2}$, 5, 7 and 24 h; at 59·8°, the times were $\frac{1}{4}$, 1, 2, $2\frac{3}{4}$ and 24 h. The initial PVP concentration was 4·9 % by weight of the dry solids content of the granulate.

The indentation hardness and elastic recovery of the outer surface of the granules were measured as described by Ridgway, Aulton & Rosser (1970). The outer layers of the granules were removed by attrition in the apparatus of Ridgway & Rubinstein (1971a) and the attrited powder assayed for PVP content by infrared spectrophotometry (Ridgway & Rubinstein, 1971b). The core weight was then recorded and the diameter was measured. Elastic modulus and hardness measurements were then made, and the process was repeated until the core weight was reduced to about 10% of the original weight.

For each granule the shaking in the multiple attrition cell apparatus gave a measure of the friability of the granule by finding the gradient of the plot of log (% weight intact) against attrition time.

RESULTS AND DISCUSSION

The drying curves for 25 granules dried at 19·6°, 44·0° and 59·8° are shown logarithmically in Fig. 1. In the initial stages of drying, PVP migrates to the surface of the granules, is deposited and forms a crust. The slopes of the first falling rate periods (A–B) are approximately the same, indicating that drying temperature has no effect

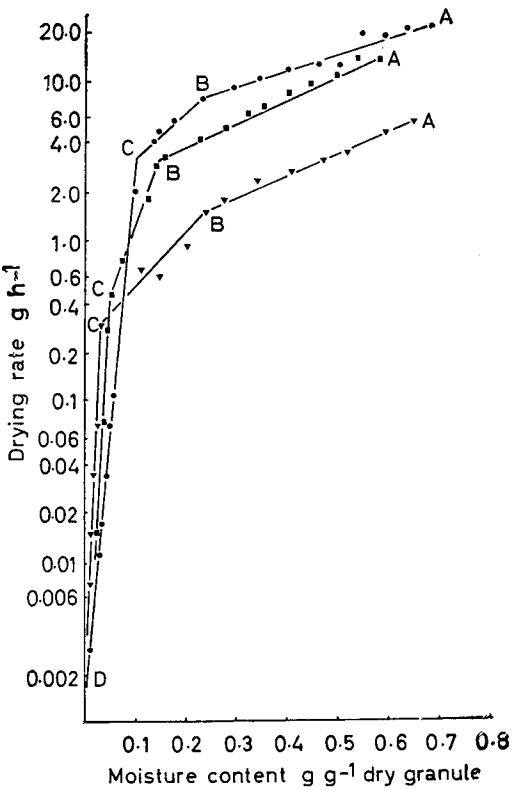

FIG. 1. Drying curves for 25 granules dried at ● 59·8°; ■ 44·0°; ▼ 19·6°.

upon the mechanism of drying at this stage but simply increases the rate. The lengths of the second drying rate periods (B–C), however, do appear to be influenced by the drying temperature, an increase in temperature shortening the period. The final falling rate period (C–D) occurs at low moisture contents where removal of water is by internal vaporization, and where vapour diffusion to the surface is the rate-limiting factor. The drying rate at the high drying temperature (59·8°) is much greater than that at 19·6°. This is basically due to an increase in the temperature gradient between the granule surface and the evaporative interface. This increased temperature gradient will promote a greater diffusion of water vapour from the interior of the granule and so increase the drying rate. Drying temperature thus appears to influence the rate of drying much more at low than at high moisture contents.

The Brinell hardness number is shown as a function of radial position within the granule in Fig. 2. Each point is the mean of the measurements made on each of the five granules taken at each sampling time. The range of the measured values of the

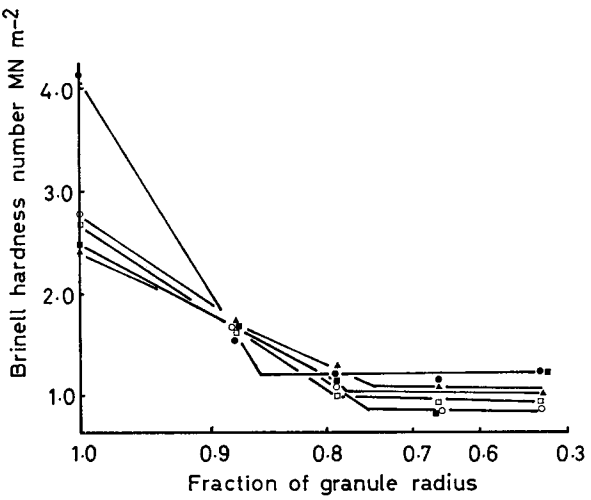

FIG. 2. The variation of granule hardness (MN m^{-2}) with depth from the granule surface at 59·8°. Time of drying (h) ●, 0·25; ■, 1; □, 2; ▲, 2·75. At zero moisture content, ○.

various properties quoted was not more than 10% of the mean. Depth below the granule surface has been plotted as a fraction of the radius. All the graphs show two distinct regions. There is a decrease in hardness from the surface inwards to a certain radius fraction, and thereafter the hardness is roughly constant. Thus granules dried in this manner have an outer shell about five times as hard as the softer inner core. The total strength will therefore be a function of the hoop strength of the granule crust, the inner core contributing little to the overall granule strength. Since the graphs are similar for each drying temperature, it would appear that drying temperature does not govern the hardness distribution within the granules. Fig. 3 depicts the variation of Brinell hardness number with granule moisture content at the surface and in the centre of the granules at the three drying temperatures. The core hardness at 44° is higher than at 59·8° or 19·6°. The periphery at 44° is also harder than at the other two temperatures, indicating that production of the hardest granules is achieved when the granules are dried at 44°.

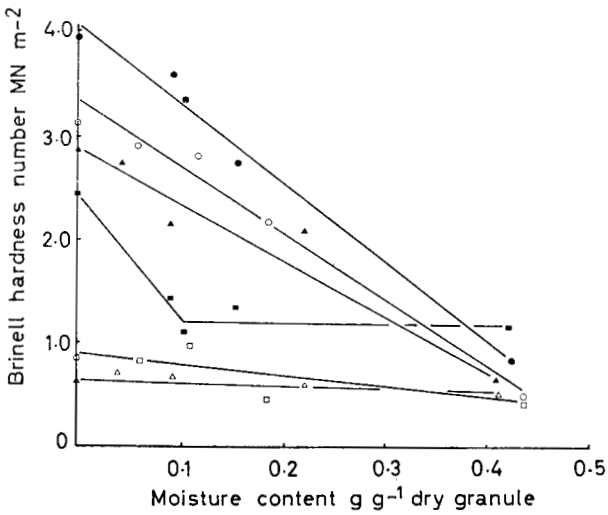

FIG. 3. The variation of hardness with granule moisture content. Granule periphery: ○ 59·8°; ● 44·0°; ▲ 19·6°. Granule core □ 59·8°; ■ 44·0°; △ 19·6°.

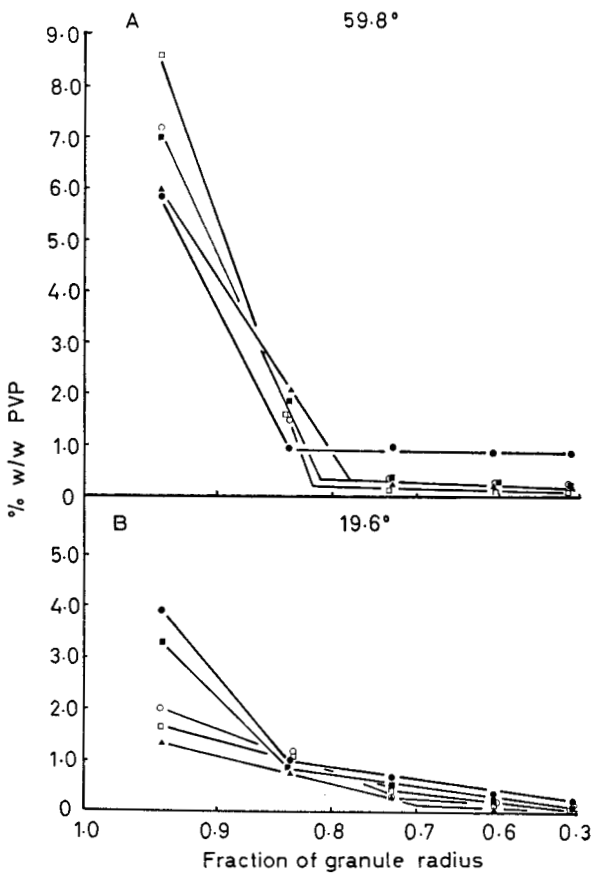

FIG. 4. PVP distribution as a function of radial distance A, at 59·8°, time of drying (h): ●, 0·25; ■, 1;. □, 2; ▲, 2·75. B, at 19·6°, time of drying (h): ●, 1; ■, 2·5; □, 5; ▲, 7. In A and B zero moisture content, ○.

The variation of Young's modulus of elasticity with depth beneath the granule surface at the three drying temperatures followed the same general pattern. The outer granular layers had relatively high elastic moduli. Towards the middle of the granules, Young's modulus decreased until a point was reached where it remained constant. At 19·6° the difference between the outer and central granular elasticity was much less than at the two other temperatures. This would indicate that a more even distribution of elasticity will result when granules are dried at low temperatures. At all temperatures, however, the core elasticity had about the same value, 8 MN m^{-2}. The graphs obtained when the modulus of elasticity was plotted against granule moisture content were also similar to those shown in Fig. 3. The outside elasticity increases with decrease in moisture content and reaches a maximum at zero moisture content.

Fig. 4 depicts the percentage of PVP in the granule as a function of radial position. The PVP content is high in the outer granular layers. Towards the middle of the granules the PVP concentration decreases to a point after which it remains constant.

At 19·6° the difference between the PVP concentrations in the periphery and in the core is much less than it is for granules dried at the higher temperatures, supporting the back-diffusion theory discussed in our earlier paper. In all cases the percentage of PVP at the centre of the granule is low. Such maldistribution of PVP is likely to be paralleled by maldistribution of the active constituent. Any subsequent attrition during storage or use will then give fines which are of different composition to the bulk granulation, and any tablets at the beginning or end of a tableting run may contain a larger proportion of such fines and a higher active content than that intended.

Shown in Fig. 5 are graphs of percentage w/w PVP at the surface and centre of the granules as a function of moisture content at the three drying temperatures. This shows the surface increase and central decrease of PVP concentration. The downward slope of the curves for drying temperatures of 44 and 19·6° is the consequence of back diffusion. PVP migrates back from the surface due to the reverse concentration gradient overcoming the transport outwards of aqueous PVP solution. At 59·8° the drying rate is so high that back-diffusion is prevented. The logarithm

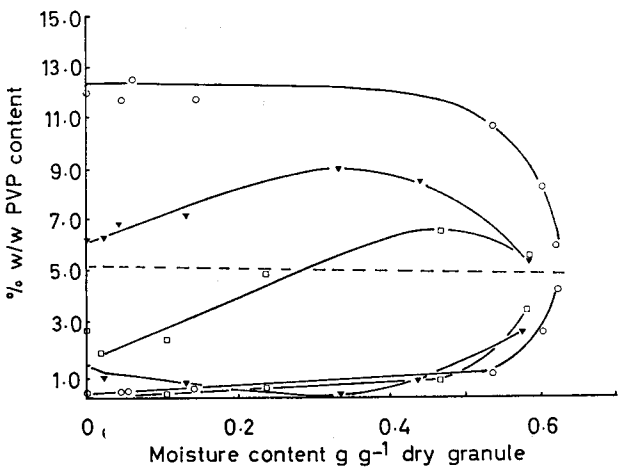

FIG. 5. PVP distribution in the core (lower three curves) and at the surface (upper three curves) of the granules. ○ 59·8°; ▼ 44·0°; □ 19·6°. - - - - - Initial PVP concentration.

of the difference between the central and peripheral PVP concentrations is a linear function of the temperature.

For each granule treated in the multiple attrition cell apparatus a plot of the logarithm of the percentage weight intact against attrition time was made. These graphs produced straight lines, of which the gradient, k, was evaluated. For each attrition measurement the gradient k was plotted against the corresponding moisture content to produce Fig. 6, which is a graph of k against moisture content for different drying temperatures. The value of k is a measure of friability, larger values indicating greater friability.

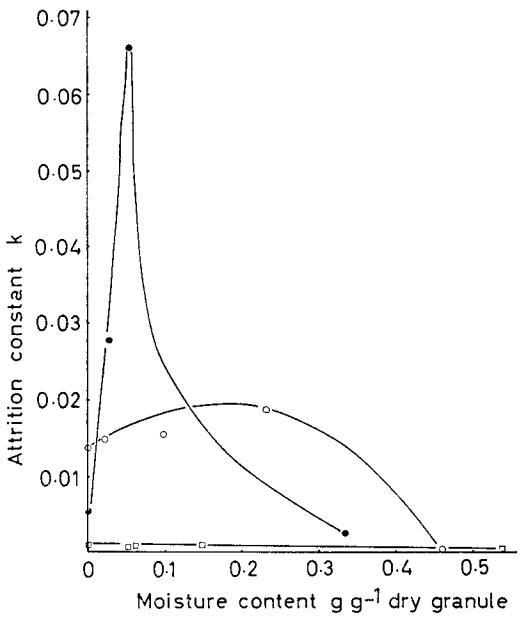

FIG. 6. Variation of the attrition constant k with granule moisture content. □ 59·6°; ● 44·0°; ○ 19·6°.

From Fig. 6, at 59·8° the friability does not vary at all, whilst at 44·0° a peak is reached at the end of the second falling rate period. At 19·6° there appears to be a slow increase in friability up to the end of the first falling rate period. Thereafter the friability declines slowly to zero moisture content. Although these three graphs are very dissimilar, it can be seen that for granules to be appreciably attrition-resistant they must be totally dry. As can be seen, at 44° a moisture content of 5% w/w will increase the friability factor of the granules six times above that of the same granules with zero moisture content. In addition, the drying temperature appreciably affects the final friability of the dried granules.

REFERENCES

MICHELL, W. A. (1954). *J. Sci. Food Agric.*, **5**, 455–462.
NEWITT, D. M. & CONWAY-JONES, J. M. (1958). *Trans. Inst. Chem. Eng.*, **36**, 422–434.
RIDGWAY, K., AULTON, M. E. & ROSSER, P. H. (1970). *J. Pharm. Pharmac.*, **22**, *Suppl.* 70S–78S.
RIDGWAY, K. & CALLOW, J. A. B. (1967). *Ibid.*, **19**, *Suppl.* 155S–167S.
RIDGWAY, K. & RUBINSTEIN, M. H. (1971a). *Ibid.*, **23**, *Suppl.*, 11S–17S.
RIDGWAY, K. & RUBINSTEIN, M. H. (1971b). *Ibid.*, **23**, 587–589.