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The effects of microfine calcium carbonate on the flow properties of granules and their relevance to tabletting

The cohesiveness of powders causes difficulties in many processes. The increasing use of micronized materials in pharmaceuticals has stimulated interest in means by which such powders can be made free flowing.

It is often possible to eliminate stickiness in a powder by the addition of coarse materials (Hawksley, 1947; Jones & Pilpel, 1966; Neumann, 1967; Jones, 1970). We have investigated the application of such a technique to the tabletting of micronized powders. The method is expected to be useful, for example, for drugs that are sensitive to moisture or where the use of granulating liquids causes some physical change, resulting in a reduced dissolution rate.

We have found that measurement of angle of repose or pour density of the micronized powder-coarse particle mixture, as a function of concentration of micronized material, provides a simple test to determine the proportion of micronized drug that can be used to prepare satisfactory mixes for tabletting.

Preliminary work has been carried out using a fine particle size grade of calcium carbonate (Calopake P. C., John Sturge Ltd.) which was shown to have similar flow properties to the drug under investigation. The particle size data as measured by Coulter Counter were:

Coulter diameter, μm	1	2	3	4	5
Wt. percentage oversize	86	70	31	18	11

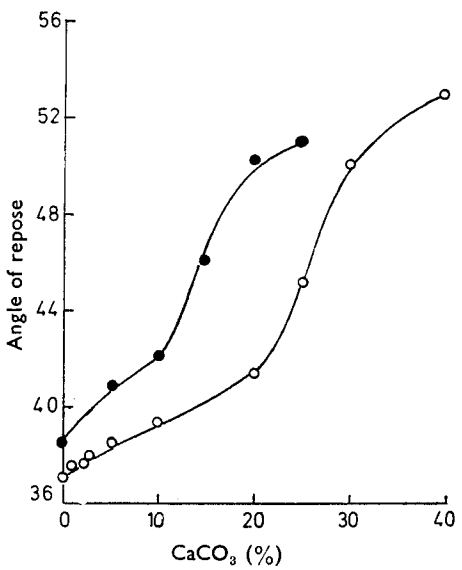

FIG. 1. Effect of calcium carbonate on angle of repose, ○, −20 +40 mesh granules; ●, −40 + 85 mesh granules.

The granules, with which the calcium carbonate was mixed in various proportions, were composed of lactose, 75%; potato starch, 20% and pre-gelatinized starch, 5% (Amijel, Corn Products Ltd.) as binding agent. The granules were prepared by granulation with water and the B.S. mesh fractions −20 +40 and −40 +85 selected for study. The moisture content was 6·0% and the granules were mixed with magnesium stearate (2%) to facilitate tabletting.

Mixtures of calcium carbonate and the granules were made in a Perspex V-mixer which allowed the course of mixing to be seen. Angles of repose were measured using the fixed bed cone method (Train, 1958). The diameter of the base (4·50 cm) was fixed by using a circular dish with sharp edges. 50 g of the samples was gently poured onto the centre from a funnel (orifice diameter, 0·6 cm), which could be raised vertically until a maximum cone height was obtained. Pour density was determined by careful addition of sample (100 g) into a 250 ml volumetric cylinder.

Tabletting of mixtures of calcium carbonate and the −20 +40 mesh granules was by using a D3A press (Manesty Ltd.) equipped with 4 sets of tooling (11 mm diameter) set at 90° to each other. The die table speed was 20 rev/min 500 g of sample was placed in the hopper, which was located in the same position for each run. After setting the depth of fill and compaction pressure for the granules containing no calcium carbonate, no further adjustments were made for the subsequent samples containing the calcium carbonate.

The effect of calcium carbonate on angle of repose is shown in Fig. 1. The curves are qualitatively similar to that reported by Nelson (1955) for various concentrations of fines in a sulphathiazole granulation. The increases in repose angle at about 20% calcium carbonate for the −20 +40 mesh fraction of granules and about 10% for the −40 +85 mesh granules appear to correspond to the concentrations at which the calcium carbonate has substantially reduced the void space. This is supported by a consideration of the pour densities, Fig. 2, which increase up to 10% calcium carbonate for the −40 +85 mesh granules and up to about 18% calcium carbonate for the

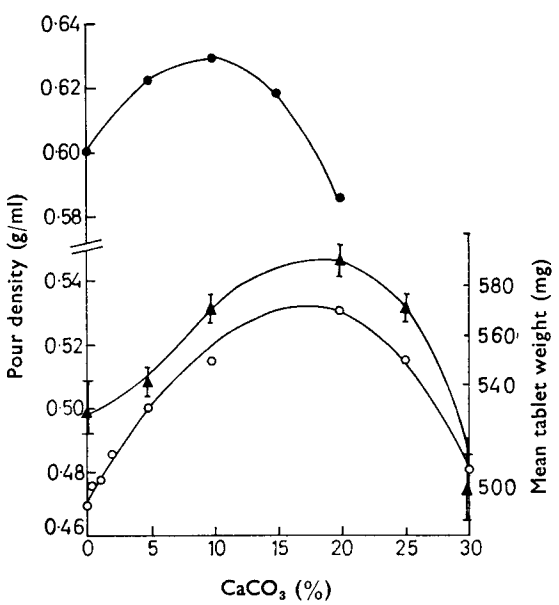

FIG. 2. Effect of calcium carbonate on pour density (○, −20 +40 mesh granules; ●, −40 +85 mesh granules), and on mean tablet weights (▲) (−20 +40 mesh granules as carrier). Vertical lines indicate standard deviations of tablet weights.

larger granules. Above these concentrations the pour densities decrease as expected if the calcium carbonate is present in the form of agglomerates.

That these changes occur at a lower concentration of calcium carbonate for the smaller granules suggests that they are due to a filling of the voids between the granules rather than being purely due to a saturation adsorption onto the granules. However, visual observation indicates that the calcium carbonate is adsorbed to a considerable extent and, furthermore, vibration of the microfine powder-granule mixes below the "critical" concentrations in each case shows no segregation of fine powder.

Fig. 2 also shows the mean weights of the tablets obtained from mixtures of calcium carbonate and the $-20 + 40$ mesh granules. The good correlation of tablet weights and pour densities up to and including 25% calcium carbonate indicates that the flow properties of the samples were satisfactory for tabletting, up to this level of microfine material. A consideration of the pour density and the mean tablet weight of the 30% calcium carbonate sample indicates that the dies were being incompletely filled and the flow properties of this sample were less satisfactory.

In the determination to find the repose angle of the 25% calcium carbonate-large granule mix and the 15% calcium carbonate-small granule sample some separation of the fine material from the granules was apparent, an effect which was not observed at lower concentrations but which was pronounced at higher concentrations in each case. Similarly it was noted during mixing that at concentrations above the "critical values" mixing was incomplete and some fine material was always visible. At lower concentrations the fine material appeared to disappear rapidly into the mix. Consequently it is considered that the maximum concentration of microfine material which should be used for tabletting corresponds to the point at which there is a marked increase in the angle of repose or where the pour density is at a maximum. Such mixes may be expected to show little segregation and to have sufficiently good flow properties to show little variation in tablet weights. Increasing the size of the inert granules will allow a higher dose of micronized material to be achieved.

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