

Studies on mixing cohesive powders

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A tablet of total weight 100 mg, containing 0.1 mg of powdered drug, poses a mixing problem. Theoretical studies show that very fine powders are necessary to achieve satisfactory homogeneity, but give little information about either the rate of mixing or the distribution of minor component if a random mix is not achieved. A practical approach to the problem is reported.

Lactose represents the substance to be assayed, and calcium carbonate or heavy magnesium carbonate the diluent. These were classified by size into very cohesive, cohesive and free flowing fractions of lactose, very cohesive and cohesive fractions of calcium carbonate, and a free flowing heavy magnesium carbonate. A Lodge Morton mixer was used. Mixing was assessed at times between 4 and 50 000 s on 20 spot samples, each of about 100 mg. Random sampling of the mix was by a thief sampler designed for cohesive powders. Subsequent analysis gave the percentage of lactose in each spot sample and the degree of mix expressed as the coefficient of variation (C) on 20 spot samples. The coefficient of variation for a random mix (C_R) was computed by the method of Poole, Taylor & Wall (1964).

Results for mixing cohesive lactose, in concentrations 0.1, to 50%, with cohesive calcium carbonate agree with those of Poole & others (1964), in that, for increasing concentration of minor component, the time taken for C to approach C_R increased, whilst the time taken for C to reach an arbitrary degree of mix, C_A (constant for all mixes), decreased. For 0.1% mixes, both the time taken for C to approach C_R and for C to reach C_A decreased with increasing mobility of the major component, and increased with increasing cohesiveness of the minor component. Mixing 0.1% lactose with very cohesive calcium carbonate resulted in gross inhomogeneities due to compaction of the powder.

Unlike free flowing lactose, agglomerates occur in very cohesive and cohesive lactose which are not readily dispersed into component particles. It is suggested that the rate determining step in mixing these powders is the breakdown of agglomerates into individual particles, and not subsequent randomization of the particles. If this occurs in practice, a random mix will not be achieved until all agglomerates are dispersed. The distribution of minor component for 0.1% mix of very cohesive lactose in cohesive calcium carbonate was shown, on a basis of 120 spot samples, to be positively skewed. Early on in mixing, skewness is most marked, with a few very high lactose contents. Even after 50 000 s the distribution was slightly positively skewed and C_R had not been reached. It is suggested that the skewness was due to agglomeration of the lactose, and such powders should be avoided in pharmaceutical mixes. With free flowing heavy magnesium carbonate as major component, mixing was much faster; this could be due to rapid dispersion of agglomerates by free flowing particles.

REFERENCE

POOLE, K. R., TAYLOR, R. F. & WALL, G. P. (1964). *Trans. Instn Chem. Engrs.*, **42**, T305.**The mixing of micronized sodium bicarbonate with sucrose crystals**

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The mixing of a fine powder with granular material is important in dry granulation techniques but very little work has been done on such mixtures. In the mixing of 3% w/w of sodium bicarbonate (about 5 μm) with sieved sucrose crystal fractions (range 0.710–0.420 mm mesh), adsorption on the host crystals prevented the segregation normally accompanying differences in particle size (Coulson & Maitra, 1950). Prolonged sieving (1 h) reduced the bicarbonate to about 1% w/w. Electron microscopy revealed crystal indentations and irregularities which acted as adsorption sites.

Very little bicarbonate could be eluted by washing with chloroform, indicating that electrostatic adsorption forces are either absent or weak (cf. Jones & Pilpel, 1965).

Bicarbonate exchange between sucrose crystals was studied by mixing a bicarbonate rich