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Letters to the Editor

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Ordered powder mixtures: reality or fiction?

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In 1975, Hersey proposed that the adherence of a finely divided minor ingredient to coarse diluent particles may produce ordered powder mixes of a higher degree of homogeneity than that conforming to the random mix. This concept has become very popular in the past, and even quite recently, ordered mixes were assumed to have been produced (Staniforth 1987).

During the recent years, however, the limitations of ordered mixes have become obvious. From theory, the most serious limitation is the requirement of "ordered adhesion" (Egermann 1980, 1985a). To produce ordered mixes, the mixing operation must accomplish a regular pattern of the adherent fines onto the surface of the carrier component. This assumption is in striking contrast to any evidence available in the fields of particle adhesion and of powder mixing:

(a) In the physics of adhesion, an irregular, random distribution of the adherent particles onto the solids surface is supposed to exist in an equilibrium situation (Krupp 1967; Zimon 1982).

(b) In accordance with this, the many REM-micrographs published of interactive mixes (for refs see Egermann 1984) show an irregular pattern of adherent fines. No micrograph with ordered adhesion could be traced.

(c) Mixing, basically, is a process of disordering. Thus it tends to produce a fully disordered, random distribution of the fines over the total carrier surface in the equilibrium ("random adhesion", Egermann 1980, 1985a).

(d) Adhesion is a process of interaction, not of order (Egermann 1984). To produce ordered mixes, an additional mechanism of order must be available which must enforce the adherent particles to become ordered in the course of the mixing operation. A mechanism of that type has not yet been established.

Without an ordering mechanism being effective, the theoretical best possible mix of interactive constituents is an interactive random mix which shows random adhesion of the fines. The degree of homogeneity of interactive random mixes has been derived from the Poisson-distribution (Egermann 1985b):

$$C_R = 100\ (\bar{m}/G)^{\frac{1}{2}} \qquad (1)$$

C_R is the coefficient of variation of the ingredient content expressed as a percentage of the mean weight G of the ingredient per sample, and $\bar{m}$ is the volume-weighted mean particle weight of the adherent ingredient.

Equation 1 is identical to the equation of Johnson (1972) of the non-interactive random mix as modified by Egermann (1985c). This implies that the highest attainable degree of mixing of interactive powders conforms to that of the non-interactive constituents, and in consequence, that adhesion phenomena cannot produce ordered mixes of higher level of homogeneity under real mixing conditions.

With these theoretical limitations in mind, it is no longer surprising that the existence of ordered mixes still has not been proven by means of experimental evidence. Indeed, some authors, including Hersey (Yip & Hersey 1977) previously claimed to have produced ordered mixes. However, in the light of present knowledge, these claims were a consequence of the erroneous calculation of the quality of the random mix by using the Stange–Poole equation (Stange 1954; Poole et al 1964):

$$C_{Rx} = 100/x\ \{[xy(ym_x + xm_y)]/M\}^{\frac{1}{2}} \qquad (2)$$

C_{Rx} is the coefficient of variation as a percentage of the mean drug content per sample of constant mass M, x and y are the mean proportions of the drug and the diluent per sample, $\bar{m}_x$ and $\bar{m}_y$ are the mean particle masses of the drug and the diluent.

Equation 2, though widely used, applies to constituents of similar particle size only (Stange 1954; Sommer 1976), a fact which has been overlooked in the past. If the diluent component is large in particle size compared with the drug particle size, equation 2 yields too high values of C_{Rx}, as has been verified

recently by theory (Egermann 1985d) and by experiment (Egermann & Pesendorfer 1986).

Yip & Hersey (1977), in their experiments, used 0·1% micronized salicylic acid, mean particle size 2·6 μm, and coarse sucrose of 655 μm particle size as constituents. With this extreme difference in particle size, the Stange–Poole equation yielded highly erroneous values C_{Rx} up to about 3%, dependent on sample size M. From equation 1, however, which actually applies to the systems under consideration, the random content variations C_R may be estimated to be as low as in the order of 0·01%. This is two magnitudes below the coefficients of variation (CV) of 1–2%, which have been found with the mixtures in fact.

With actual ordered mixes, CV must be smaller than C_R of equation 1. Experimental data of this type are not available.

Apart from the theoretical limitations, a practical difficulty of proving the existence of the hypothetical ordered mixes is the high quality of random mixes containing micronized ingredients. C_R may be smaller than the analytical error, thus making impossible the judgement of a lower than the random content variation (Egermann 1985e).

In conclusion, the previous claims of the existence of ordered mixes are erroneous as a consequence of the inadequate use of the Stange–Poole equation to calculate the random degree of mixing. From the above considered theoretical and experimental limitations, it appears questionable whether ordered mixes may ever be verified by experimental evidence. However, with the high quality of the corresponding random systems in mind, not only the evidence but also the practical relevance of ordered mixes with respect to the dose uniformity of drugs may be questioned (Egermann 1985e).

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Comments to 'Order out of chaos'

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Recently, Staniforth (1987) proposed the terms 'adhesive' and 'non-adhesive' rather than 'interactive' and 'non-interactive' (Egermann & Orr 1983) to differentiate mixes of cohesive, interacting powders and of free-flowing, non-interacting constituents. Clearly, 'adhesive' and 'non-adhesive' are superior to the arbitrary use of ordered and randomized of previous years. However in our view, 'interactive' and 'non-interactive' still appear to be more accurate and preferable as standard nomenclature, for the following reasons:

(a) Interactive is the more general term with a broader range of applications. Unlike adhesive, it is not restricted to one type of interaction (adhesion). With cohesive powder constituents, particulate interactions may be—and usually will be—produced both by adhesion and by cohesion, and the powder mix may show cohesive properties. Thus adhesive—in contrast to interactive—does not fully apply.

(b) Interactive and non-interactive are the scientifically accurate terms. Staniforth broadly argues that a truly non-interactive mix could not exist due to the overall presence of gravitational forces. This is a rather surprising view, since the mixing of powders is considered and not the mixing of planets. With powder particles, in contrast to the planets mentioned by Staniforth, the masses involved are so small that the individual gravity fields would not be expected to produce particulate interaction forces of a sufficient magnitude.

The adhesional forces, as a consequence of the free surface energy of solids, will be much stronger than the gravitational fields even for the coarsest, free-flowing particles. Accordingly, taking Staniforth's view, a truly non-adhesive mix also could not exist, and any argument against non-interactive mix would apply to a greater extent against non-adhesive mix. In practice, however, neither gravitational nor adhesional forces are of significance with free-flowing constituents. Free-flowing implies that the particles may move individually under the influence of the gravitational earth force, and that particulate interactions are negligibly small, independent of the source of the interactions.

Further, Staniforth mentions gravity to be a predominantly stabilizing force for non-interactive mixtures. In contrast, any textbook dealing with stability of powder mixes assumes gravity

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