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Relationship between particle packing and the physical stability of powder mixes

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The segregation tendency of powder mixes containing sugar-based direct compression tableting excipients with comparable particle size distributions and flow properties was studied under different vibration conditions. It was found that Tabfine and fine-particle pyridoxine hydrochloride mixes were virtually segregation-free, whereas segregation occurred in each of the other powder mixes containing Fast-flo, Dipac and Nu-tab. The segregation tendency of a specific powder mix following vibration was considered to be influenced by the packing of excipient particles in the powder bed. In general, the more densely packed the particles under given vibration conditions, the lower the segregation tendency. This was considered to be due to the tightly packed powder bed restricting individual particle movement and thereby reducing particle or ordered unit rearrangement.

The principle of dilation (Jenkin 1941) governs the facility of particle movement—in general, the more dilated the powder bed, the more easily relative particle movement can occur. This relationship influences several bulk particle properties, including powder flowability and powder mixing or segregation. Particle size distributions and particle shape can both affect the dilatancy of a powder under given conditions because these particle properties also influence the packing geometry of a powder bed. Williams (1963) recognized that particles with a high degree of freedom of movement tended to be free flowing and were more susceptible to component segregation than powders with lower freedom of particle movement. In general, fine powders less than approximately 100 μm diameter are more cohesive, more tightly packed and less easily dilated, whereas coarser particles are less cohesive, more loosely packed and more easily dilated. A consequence of this relationship appears to be that coarser powders frequently have higher bulk flow rates and segregation tendencies than finer powder systems. However, direct compression tableting requires dry powder mixes which possess very good flow properties and which do not segregate during processing. Formation of ordered mixes using direct compression excipients as the coarse carrier component and fine drug particles as the adherent component can be used as a method of producing free-flowing powder mixes which are resistant to segregation (Staniforth & Rees 1982a). However, not all coarse direct compression excipients produce non-segregating ordered mixes; the reasons for this have been attributed to differences in surface roughness and porosity (Staniforth & Rees 1982a), surface electrostatic charges (Staniforth & Rees 1982b) and the ability of coarse particles to carry adherent particles as a monolayer (Bryan et al 1979).

The aim of the present study has been to investigate the influence of particle packing on the mobility of powders and the relationship with powder segregation in drug-excipient systems.

MATERIALS AND METHODS

Four sugar-based direct compression excipients were selected with similar particle size distributions and flow properties: Tabfine—Type S100I, a direct compression microcrystalline excipient containing 97% sucrose and 3% invert sugar (manufactured by Finnish Sugar Company, Helsinki and supplied by Forum Chemicals, Reigate, UK); Dipac—a direct tableting sugar containing 97% sucrose and 3% maltodextrins (manufactured by Amstar Corp., USA and supplied by Wilfrid Smith Fine Chemicals, Edgware, UK); Fast-flo—a direct compression spray dried lactose (manufactured by Foremost Inc., USA, supplied by K & K Greef, Croydon, UK); Nu-tab—a composite direct compression sugar containing sucrose and magnesium stearate.

Determinations of powder flow were carried out using a recording balance (type 2200, Sartorius A.G., Switzerland) connected through the RS232 port to a microcomputer (BBC model B, Acorn Computers Ltd, Cambridge) and a dot matrix printer (Type FX-80, Epson Ltd, UK).

A qualitative comparison of particle morphology was carried out using scanning electron microscopy (Type 35C, JEOL Ltd, Japan). Representative

specimen particles from each of the four excipients were prepared for microscopic examination by gold sputter coating.

Powder mixes containing each of the four direct compression excipients together with fine-particle pyridoxine hydrochloride at a concentration of 1% w/w (E. Merck & Co., Alton, UK) were formed. Only pyridoxine hydrochloride particles with diameters less than 45 μm were used and an initial geometric mixing stage was carried out to ensure that the drug was deagglomerated and well distributed over the excipient carrier particle surfaces. Subsequently, mixing was carried out in a tumbling cube blender fitted with an array of three intensifier bars (Erweka GmbH, Frankfurt, FRG).

Homogeneous powder mixes were subjected to physical stressing in a vibration model using a method decribed by Staniforth & Rees (1982a). Vibration conditions were selected in the range 9·81–39·24 ms^{-2} (1–4*g*) acceleration and 25–200 Hz frequency. The drug content of different spot samples was quantified using uv spectrophotometry.

RESULTS AND DISCUSSION

In all the powders studied, the conditions were such that particles could interact and it is therefore likely that all of the powder mixtures studied could be described as imperfect ordered or partially ordered random (Hersey et al 1979). The greater the percentage of free or 'randomized' drug particles released by vibration, the higher the segregation tendency.

As previously (Staniforth & Rees 1982a) with different model drug particles, mixtures containing Dipac were found to be prone to marked segregation especially at high accelerations and even at relatively high frequencies (Fig. 1a). Analysis of individual

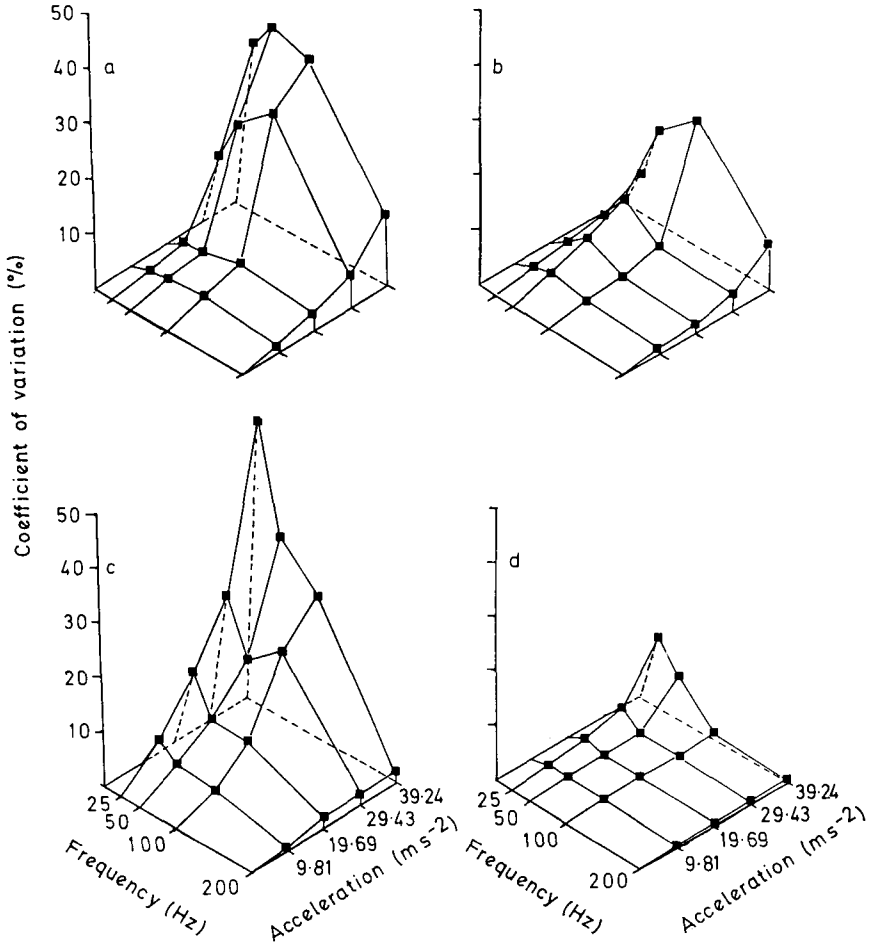

FIG. 1. Coefficient of variation of 1% w/w pyridoxine hydrochloride/excipient mixes after 15 min vibration showing the effect of vibration frequency and acceleration. Key: (a) Dipac, (b) Fast-flo, (c) Nu-tab, (d) Tabfine.

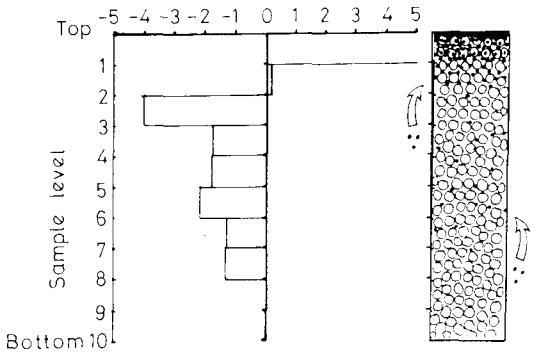

FIG. 2. Relationship between % deviation of individual sample pyridoxine hydrochloride content from sample mean at different levels in powder bed containing Dipac mix vibrated at 25 Hz and 39·24 ms $^{-2}$ for 15 min. The accompanying schematic diagram is a representation of pyridoxine hydrochloride particle and ordered unit movements.

sample deviations from mean drug content allows more information to be derived concerning probable mechanisms of segregation under specific conditions. For example, sample drug deviations suggest that Dipac mixtures vibrated at 25 Hz and approximately 39 m s^{-2} (Fig. 2) segregated by a mechanism known as microfluidization (Lai et al 1981) whereby fine drug particles become dislodged from carrier surfaces and are carried up through the powder bed by entrainment in bubble wakes produced by vibrofluidization. However, an increase in frequency to 50 Hz was also found to produce marked segregation but in this case the mechanism was at least partially due to downward percolation of free fine drug particles. In spite of changes in mechanism and direction of particle movement it appears that the worst segregation of Dipac powder mixes was caused by breakdown of ordered units producing so-called 'constituent segregation' (Yip & Hersey 1977). Again, this is typical of the way in which other Dipac powder mixes behave when subjected to vibration.

Powder mixtures containing Fast-flo were also found to be prone to segregation. Once again, the worst segregation tendency was found in conditions of high acceleration and segregation was also found at relatively high frequencies (Fig. 1b).

The scale of segregation as determined by coefficient of variation measurements was slightly lower in all conditions than for Dipac although the overall form of the stability profile shown in Fig. 1(b) was

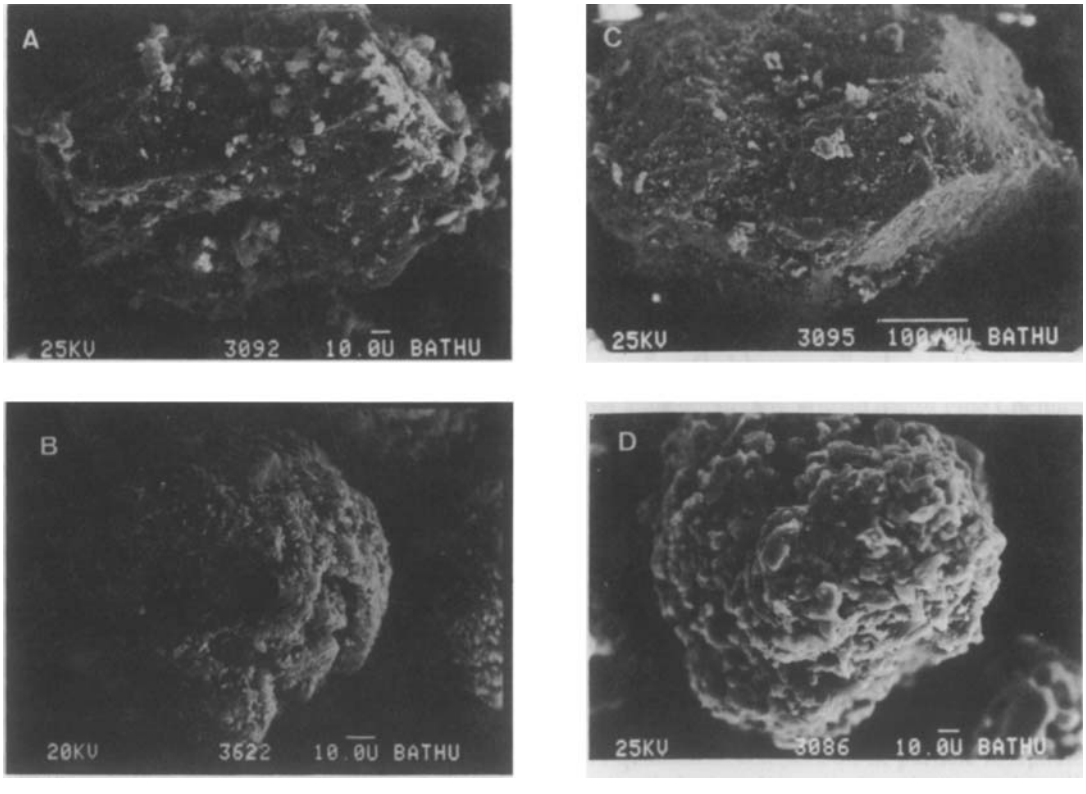

FIG. 3. Scanning electron photomicrographs showing particles of (a) Dipac, (b) Fast-flow, (c) Nu-tab and (d) Tabfine.

comparable with that for Dipac. The overall magnitude of segregation was not as great as that seen in other powder systems and, coupled with evidence from spot sample deviations that even under some relatively mild vibration conditions, where vibrofluidization was not present, upward drug displacement occurred, it is possible that segregation of Fast-flo powder mixes occurred predominantly by ordered unit segregation (Yip & Hersey 1977). Ordered unit segregation occurs when the number of adherent drug particles on each excipient carrier is not equal. For example, a 10 μm carrier particle might have only one adherent drug particle, whereas a 200 μm carrier particle might carry 10 adherent particles. This relationship means that in the spatial volume occupied by a single 200 μm carrier particle having 10 adherent particles, a set of 10 μm carrier particles would be associated with 8000 adherent particles. Consequently, even a small change in the distribution of ordered units can cause large shifts in drug content. Ordered unit segregation is considered to be the major segregation mechanism in Fast-flo ordered mixtures because of the surface properties of Fast-flo particles (Fig. 3) and also because of the extremely high flow rates achievable under many different conditions, which suggest that bulk particle rearrangement would be relatively more easy with Fast-flo than with some other excipients.

In contrast to the segregation behaviour found in Fast-flo, mixtures containing Nu-tab were considered to become de-stabilized by constituent segregation of free drug particles released during vibration. Mixtures containing Nu-tab and pyridoxine hydrochloride were found to be more prone to segregation and to undergo more marked segregation than any of the other excipients tested in this study (see Fig. 1c).

The surface of Nu-tab excipient particles are relatively smooth and are similar to the surfaces of Dipac particles which were also prone to segregation (Fig. 3). The increased segregation tendency of Nu-tab is thought to be due to the presence of small quantities of magnesium stearate on the carrier surface. It is now well known that magnesium stearate destabilizes ordered mixtures, producing segregation in previously homogeneous systems (Lai & Hersey 1979; Staniforth et al 1982). The layer of fine magnesium stearate particles probably acts like a hydrophobic barrier, preventing good adhesion between the hydrophilic drug and carrier particle surfaces. In addition, the unusual electrostatic properties of magnesium stearate are also considered to disrupt formation of stable ordered mixtures.

By coating the excipient carrier surface with magnesium stearate before addition of drug particles, the Nu-tab never allows stong interparticle bond formation between drug and carrier. This would be of even more importance than in other excipients because Nu-tab has a relatively smooth surface and will therefore have a correspondingly reduced number of active sites.

Tabfine S100I ordered mixes were found to have the lowest segregation tendency of the four excipient mixes studied (Fig. 1d). It is considered that the low segregation tendency in conditions of very low frequency and high acceleration may be due to either constituent segregation of a small percentage of unbound or weakly-bound drug particles migrating by percolation, or probably more likely, short-range re-arrangement of drug-rich and drug-lean ordered units. However, allowing for the fact that vibration conditions of 4g at 25 Hz are unlikely to be met frequently in real systems, the Tabfine could be considered to be virtually segregation free.

Other data presented below suggests that the surface morphology of individual excipient particles (Fig. 3) coupled with the particle size distribution of the Tabfine, allows the excipients to form a densely packed interlocking system which may prevent or reduce the scale of movement of free fine drug particles.

This relationship between powder bed porosity and segregation tendency has been studied in more detail and it appears that neither overall porosity, nor change in porosity at different vibration conditions have any significant relationship with segregation tendency (Fig. 4). This is probably because of the way in which porosity is calculated; it is possible

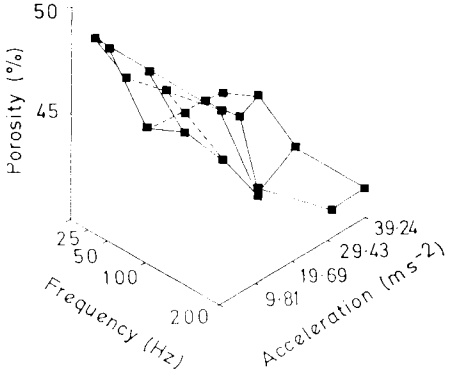

FIG. 4. Porosity of drug/Nu-tab powder mixes after 15 min vibration showing the effect of vibration frequency and acceleration.

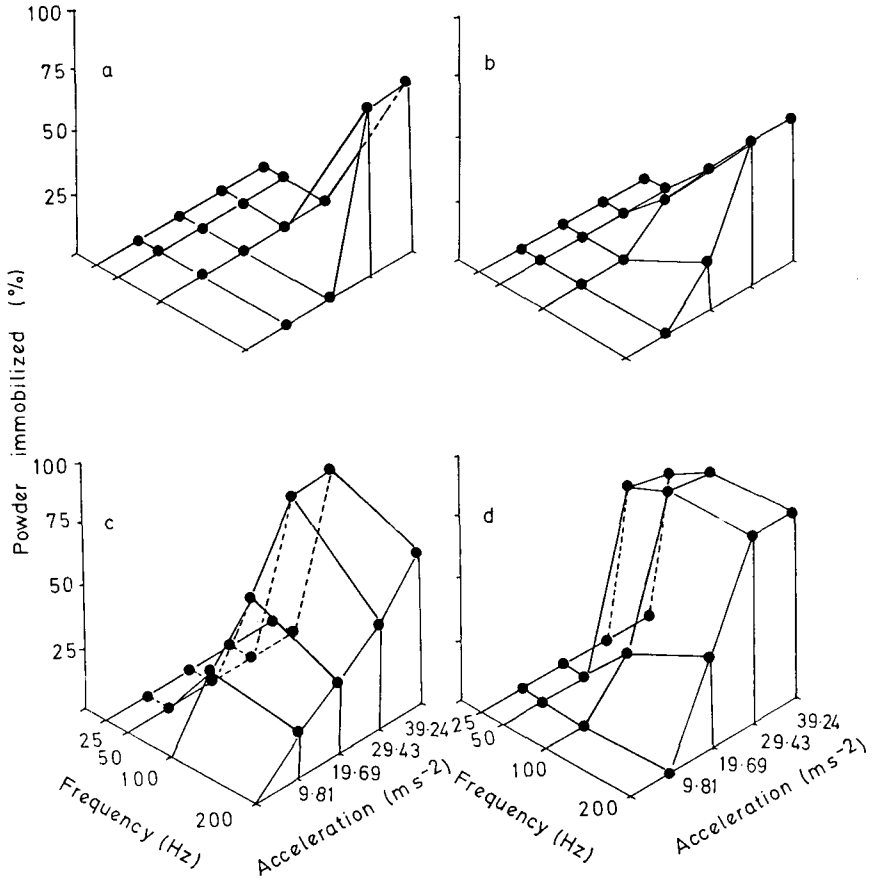

FIG. 5. Mobility of drug/excipient powder mixes after 15 min vibration showing the effect of vibration frequency and acceleration. Key: (a) Dipac, (b) Fast-flo, (c) Nu-tab, (d) Tabfine.

to have two powders with completely different packing geometries and pore size distributions which nevertheless have the same overall porosity. It is therefore more desirable to measure pore size distribution or some function related to packing geometry. This can be achieved by determining the proportion of the powder bed in which the cohesive strength of the particles is great enough to support a stable arch or bridge. By determining the proportion of the bed which is immobilized through arch formation caused by tightly packed particles, some idea of the ease with which ordered units could rearrange can be obtained.

The percentage of particles immobilized in the powder bed changes markedly with vibration conditions, and with the excipient being studied, despite the fact that each of the excipients had similar flow properties before vibration. In general, it was found that under vibration conditions where segregation was most marked the powder bed was at its most mobile, and that excipients such as Fast-flo and Dipac, which were most prone to segregation had the most mobile powder beds (Fig. 5a, b). In contrast, Tabfine had the least mobile powder bed (Fig. 5d) which means that the homogeneity given to the mixture during mixing will be 'frozen' into the powder bed during subsequent processing so long as mass flow from tablet machine or other hoppers can be achieved.

An exception to this general relationship was found in Nu-tab mixtures (Fig. 5c) where at higher frequencies, substantial proportions of the powder bed were immobile. Nu-tab mixtures exhibited most marked segregation in low frequency vibration conditions and segregation in this system was considered to be predominantly through constituent

segregation of free fine particles, rather than through bulk rearrangement of ordered units.

CONCLUSIONS

As reported elsewhere, the segregation of drug-excipient mixes was most marked in conditions of low frequency and high acceleration.

These four sugar-based excipients with comparable particle size distributions and flow properties had different segregation tendencies following vibration under similar conditions. Only Tabfine produced near-stable powder mixes.

The difference in segregation tendencies between the four excipient systems was considered to be at least partially due to different powder packing and mobility when subjected to vibration. In general, the more tightly packed the powder bed, the more segregation-resistant the drug-excipient mix.

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