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# Segregation of vibrated powder mixes containing different concentrations of fine potassium chloride and tablet excipients

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The effect of different drug/excipient concentrations on the segregation tendency of three ordered powder mixes was studied. In addition, the influence of vibration frequency on the segregation intensity and mechanisms of segregation was also studied. Differences in content uniformity of the powders were measured by comparing samples from regions at different depths between the upper exposed powder surface and the base of the cylindrical container. Ordered mixes containing recrystallized lactose excipient and fine-particle potassium chloride as a model drug were found to be least susceptible to segregation at most vibration conditions for all potassium chloride concentrations. Dipac excipient/potassium chloride particles were most susceptible to segregation under all test conditions. In general, segregation intensity was most marked in conditions where high potassium chloride concentrations, above 2% w/w, were subjected to low-frequency vibration, below 100 Hz. Segregation mechanisms were considered to be mainly dependent on vibration conditions, although carrier excipient type markedly modified mechanisms and influenced segregation intensity.

In previous work, ordered mixes containing free-flowing direct compression excipients and fine-particle potassium chloride were found to be generally less stable when subjected to vibration at low-frequency and high-accelerations (Staniforth & Rees 1982). Segregation of potassium chloride-excipient mixes was considered to result from one or more mechanisms predominating in particular conditions (Staniforth 1980). For example, when vibration was intense the predominant mechanism was found to be 'constituent segregation' where fine potassium chloride particles became dislodged from coarser carrier particles. In other conditions segregation occurred predominantly as a result of ordered unit segregation. The number of fine drug particles which a coarser excipient particle can carry to form an ordered unit is limited by the stereometry and surface properties of both sets of particles. At some finite drug concentration the excipient carrier particles can no longer bind all drug particles in ordered units. This relationship may influence the segregation behaviour of ordered mixes such as occurs as a result of vibration.

In the present study, different concentrations of potassium chloride and excipient particles were used to form ordered mixes which were vibrated at different frequencies.

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## MATERIALS AND METHODS

The materials and methods used to form ordered mixes were the same as those previously reported by Staniforth & Rees (1982). Three different excipients were used with comparable, coarse particle size distributions (Table 1): Dipac (Amstar Corp., U.S.A.); Emdex (Edward Mendell Inc., U.S.A.) and recrystallized lactose excipient (Staniforth 1980). Potassium chloride powder, 100% less than 45 μm diameter and median diameter 5 μm was used as a model drug. The concentration of fine-particle model drug was increased from 0·5 to 1·0, 2·0, 5·0 and 10·0 w/w.

Table 1. Particle size distributions of excipient powders based on equivalent sieve diameters by weight.

| Sieve diameter (μm) | Cumulative percentage oversize (weight basis) Emdex | Dipac | Recrystallized lactose |
|---|---|---|---|
| 710 | 0·46 | 0·00 | 16·04 |
| 500 | 8·06 | 0·03 | 23·71 |
| 355 | 25·56 | | 28·34 |
| 250 | 54·51 | 46·96 | 29·22 |
| 180 | 78·04 | 74·29 | 34·24 |
| 125 | | 95·52 | |
| 90 | 97·23 | 99·43 | 55·65 |
| 63 | 99·16 | 99·72 | 73·11 |
| 45 | | 99·81 | |
| 0 | 100 | 100 | 100 |

Vibration conditions were similar to those described previously (Staniforth & Rees 1982) except that in these experiments the powder mixes were vibrated at constant acceleration, 22·07 m $s^{-2}$ for 15 min. The vibration frequency was varied over the range 30–1000 Hz.

## RESULTS AND DISCUSSION

The number of fine potassium chloride particles which a single excipient particle was theoretically capable of carrying in a close-packed monolayer was calculated from the following equation (Table 2):

$$n = \frac{2\pi (D + d)^2}{\sqrt{3}\, d^2} \qquad (1)$$

where, n is the maximum number of adherent particles of diameter d which can be accommodated on the surface of another, usually coarser, particle of diameter D.

Although a potassium chloride concentration of 10% w/w represents a 20-fold increase over the lowest concentration, all three excipients were calculated to have sufficient surface space to accommodate all fine potassium chloride particles in each system as a stereometric monolayer and were thus capable of forming ordered mixes (Table 2).

Table 2. Theoretical number of fine particles each coarse particle carries (Dn) at different drug concentrations, compared with the saturation number of each carrier particle (Sn) calculated from equation 1.

| | Emdex | | Recrystalized lactose | | Dipac | |
|---|---|---|---|---|---|---|
| %Drug content | Dn | Sn | Dn | Sn | Dn | Sn |
| 0·5 | 106 | 3,995 | 183 | 5,556 | 106 | 3,995 |
| 1·0 | 213 | 3,995 | 366 | 5,556 | 213 | 3,995 |
| 2·0 | 425 | 3,995 | 739 | 5,556 | 425 | 3,995 |
| 5·0 | 1,133 | 3,995 | 1,910 | 5,556 | 1,133 | 3,995 |
| 10·0 | 2,429 | 3,995 | 4,048 | 5,556 | 2,429 | 3,995 |

Ordered mixes containing the direct compression excipient, Emdex and 0·5% w/w potassium chloride were found to be stable at all vibration frequencies. An increase in potassium chloride content from 0·5 to 1·0% (Fig. 1) produced segregation at most vibration frequencies. The segregation tendency of the vibrated Emdex mixes increased with increasing potassium chloride concentration, reaching a maximum at the 10% level. In general, the vibration-induced segregation was most intense at frequencies lower than 100 Hz.

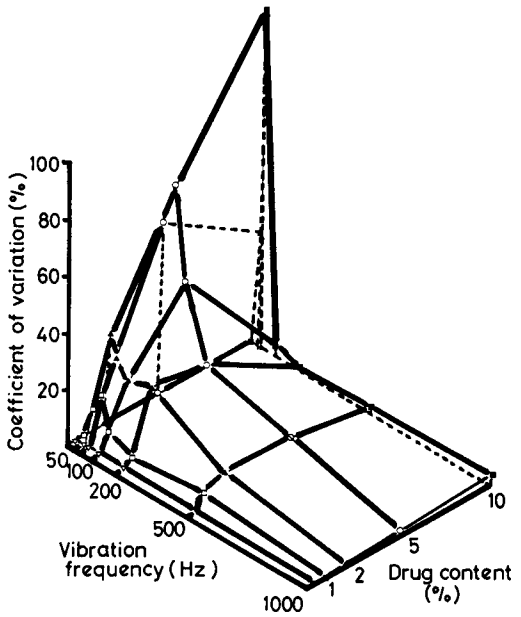


FIG. 1. Relationship between vibration frequency, potassium chloride content and segregation tendency of Emdex powder mixes, at constant acceleration and vibration frequency.

As with Emdex ordered mixes, segregation of fine-particle potassium chloride from coarse recrystallized lactose particles increased with decreasing vibration frequency. At 0·5% potassium chloride concentration, ordered mixes were virtually stable but as potassium chloride concentration increased to 2·0% w/w, there was a marked increase in segregation intensity (Fig. 2). Above 2·0% concentration,

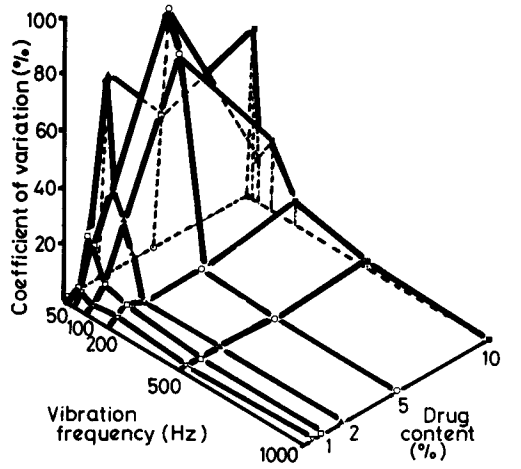


FIG. 2. Relationship between vibration frequency, potassium chloride content and segregation tendency of recrystallized lactose powder mixes, at constant acceleration and vibration frequency.

the segregation pattern became complex in powders vibrated at low frequencies, although no large increase in coefficient of variation occurred after this concentration. At a vibration frequency of 30 Hz coefficients of variation were in the range 80–100%, although for frequencies below 100 Hz the range was larger (Fig. 2). The maximum segregation tendency measured in recrystallized lactose systems was approximately 100% which was considerably lower than the maximum segregation effect measured in either of the other two excipient systems.

The Dipac/potassium chloride ordered mixes showed marked segregation for all potassium chloride concentrations and at all vibration frequencies (Fig. 3). The lower vibration frequencies, less than 100 Hz, caused the most intense potassium chloride segregation and this became extreme in systems containing 10% w/w potassium chloride.

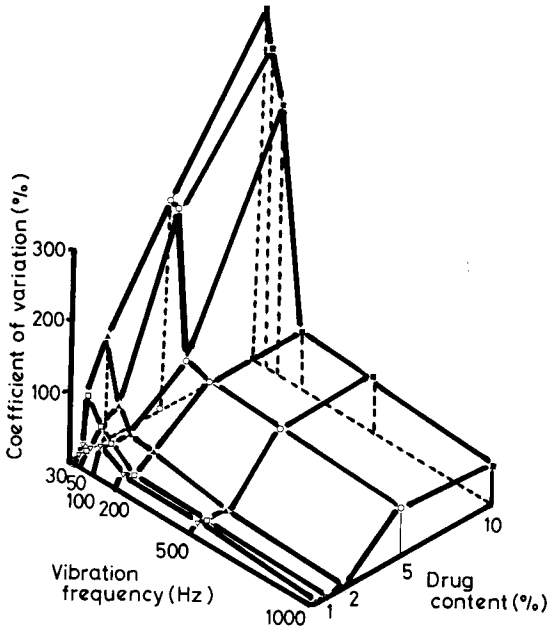


FIG. 3. Relationship between vibration frequency, potassium chloride content and segregation tendency of Dipac powder mixes, at constant acceleration and vibration frequency.

In all the excipient/potassium chloride systems tested there was a distinct change in the intensity of segregation which coincided with vibration frequencies between 100–200 Hz. At or below 100 Hz the segregation effect became more marked, whereas at or above 200 Hz segregation was comparatively less intense. Nevertheless in Dipac/potassium chloride systems containing 5 and 10% potassium chloride there was considerable segregation even at high frequencies. Dipac and potassium chloride particles showed a far greater tendency to segregate at higher concentrations than Emdex/potassium chloride systems, but of the three systems studied, recrystallized lactose mixes appeared to be the most resistant to segregation in most conditions. Table 2 shows that even at the highest concentrations used, all three excipients had suitable solid geometries to allow all potassium chloride particles to be fitted on their surfaces. If all of these geometrically available sites were 'active' and formed adherence points for the fine potassium chloride particles, the coefficients of variation should have remained at comparable and low values for the different potassium chloride concentrations tested. The general increase in segregation with increasing potassium chloride concentration suggested that only a fraction of the available free excipient surface formed inter-particle bonds with sufficient magnitude to produce stable ordered units. The difference in segregation behaviour between the three excipient/potassium chloride systems probably resulted from a combination of effects on particle-surface interactions and on some bulk powder properties such as packing geometries.

As the potassium chloride concentration increased, the quantity of potassium chloride particles calculated to become segregated to different areas of the powder bed also increased in an almost direct relationship. However, the number of particles involved was calculated to be different for each system; the largest quantity being found in Dipac/potassium chloride samples. The fraction of segregating particles in relation to total number of particles in a sample appears to fall or remain stable as potassium chloride concentration increases and this may indicate that adherence sites were occupied by random chance and that the probability of fine potassium chloride particles locating at active or highly active adherence sites is much less than 1 so that only as the quantity of potassium chloride particles increases are these sites likely to be occupied. For most potassium chloride concentrations the probability of particles locating at active sites appears to be greater for recrystallized lactose systems than for Emdex and for Emdex than for Dipac. Recrystallized lactose has a larger available surface area and macroporosity than Emdex which is in turn more porous than Dipac. It is probable that the presentation and physical properties of carrier particle surfaces are more important than pure

stereometry in relation to production of large numbers of potentially stable adherence sites. In addition, as potassium chloride concentration increases, inter-particle pores may become smaller and offer more resistance to large-scale segregation by effectively forming a mechanical filter. Undoubtedly the segregation effects are due to complex mechanistic interactions which are also influenced by vibration conditions.

of either free fine potassium chloride particles or of drug-variant ordered units being promoted and accelerated with the net effect of increasing segregation in the system.

A simple presentation of coefficient of variation (c.v.) is a useful measure of segregation intensity but provides little information regarding segregation mechanisms in specific powders or at different areas in the same powder bed. For example, Dipac/10%

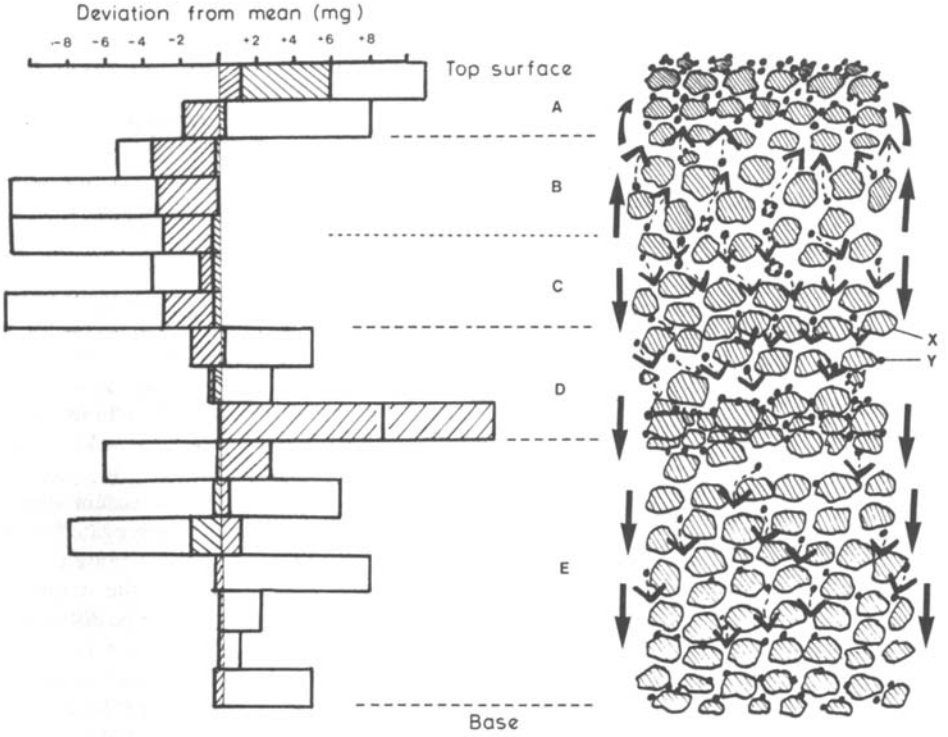


FIG. 4. Relationship between deviation of individual sample potassium chloride content from sample mean at different levels in powder bed for 10% potassium chloride ordered mixes containing Emdex (1-r hatched), recrystalized lactose (r-1 hatched), and Dipac (open) excipients vibrated at 50 Hz for 15 min. The accompanying schematic diagram is a representation of potassium chloride particle movements in different regions of the powder bed.

The influence of different vibration frequencies on segregation of ordered mixes with increased potassium chloride concentrations was similar to that found in mixes containing only 0·5% potassium chloride (Staniforth & Rees 1982). The low frequencies had the greatest influence on segregation—probably because the increased particle flight durations, particle movement and increased abrasion produced under these conditions caused fine potassium chloride particles to become dislodged more easily from carrier particles; any subsequent translocation

potassium chloride mixes vibrated at 50 Hz were found to have a c.v. > 300%, whereas at 500 Hz c.v. < 100% (Fig. 3). Both vibration conditions produced massive segregation but the segregation mechanisms are found to be different when analysed according to deviation in sample potassium chloride content from sample mean as shown in Figs. 4 and 5. Fig. 4 shows that samples removed from areas close to the upper exposed powder surface were potassium chloride-rich whereas those immediately below this region were drug-lean. Points in the lower half of the

bed are generally drug-rich. Similar patterns of potassium chloride movement can be found for recrystallized lactose/potassium chloride and Emdex/potassium chloride systems (Fig. 4), although the scales of segregation are lower. On the right hand side of Fig. 4 is a schematic interpretation of this data. Region A of the bed is drug-rich, resulting from upward movement of free fine potassium chloride particles and some drug-rich, fine ordered units from region B. This upward movement occurs by the mechanism of microfluidization (Lai et al 1981) in the more mobile upper region of the powder bed. In region C the bed is less free to move and any dislodged potassium chloride particles and fine ordered units tend to move down through the bed by the mechanism of percolation. A more dense area in region D appears to trap some of the downward percolating particles and this process of drug depletion and enrichment by successive percolation through open portions of bed and entrapment at denser areas is repeated lower down the bed. These mechanisms produce segregation intensity corresponding to c.v. >300% (Fig. 3). Fig. 5 shows that at 500 Hz the powder surface is drug-lean rather than drug-rich as at 50 Hz. Region A is drug-lean as a result of percolation of free potassium chloride particles or fine ordered units down the powder bed to region B. There was also some upward movement of potassium chloride particles from region C leaving the base of the powder bed drug-lean. Potassium chloride particles may have accumulated predominantly in region B as a result of a vibration node produced under these conditions and centred close to region B. This meant that regions A and C were more mobile than region B which was only vibrating in the vertical plane.

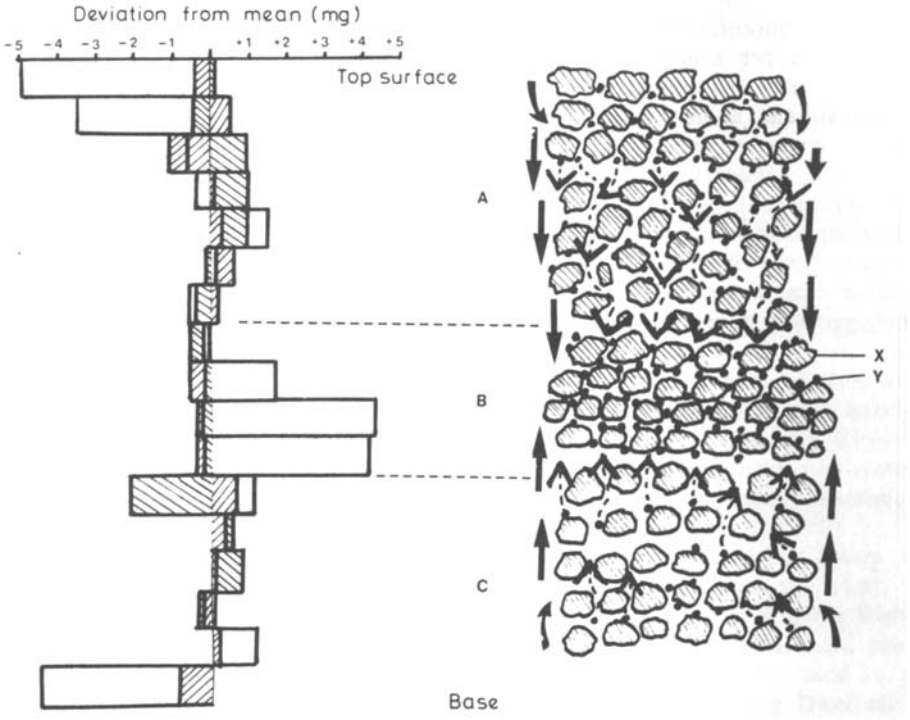


FIG. 5. Relationship between deviation of individual sample potassium chloride content from sample mean at different levels in powder bed for 10% potassium chloride ordered mixes containing Emdex (1-r hatched), recrystalized lactose (r-1 hatched), and Dipac (open) excipients vibrated at 500 Hz for 15 min. The accompanying schematic diagram is a representation of potassium chloride particle movements in different regions of the powder bed.

It can be seen that although different vibration conditions produce segregation, the mechanisms by which such segregation occurs are not necessarily the same even in the same powder system.

*Conclusions*

1. Intensity of segregation was most marked at potassium chloride concentrations greater than 2% w/w and in powders vibrated at frequencies less than 100 Hz.

2. Only a small proportion of the carrier particle surface forms 'active' sites for adherence of fine potassium chloride particles. The number of active sites appears to be linked to the presentation and physical properties of the carrier particle surface.

3. Recrystallized lactose excipient formed ordered mixes which were generally more resistant to segregation at most concentrations for all vibration conditions than either Emdex or Dipac, which formed ordered mixes that segregated at all concentrations when vibrated at any frequency from 30 to 1000 Hz.

4. Mechanisms of segregation were different in powders vibrated at low frequency in comparison with those vibrated at higher frequency.

5. Vibration conditions appeared to have a predominant influence on segregation mechanisms at specific points in a powder bed, whereas excipient particle properties, especially surface properties were considered to be the predominant influence on segregation intensity produced over the whole powder bed.

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