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Effect of vibration time, frequency and acceleration on drug content uniformity

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The effect of different vibration conditions on the segregation tendency of three ordered powder mixes was studied. Segregation of the powders was measured using a cylinder, composed of interlocking units for sampling purposes, mounted on a vibration rig. Ordered mixes containing either Emdex or recrystallized lactose carrier particles mixed with 0·5% fine-particle potassium chloride were stable, except for slight segregation that occurred under severe vibration conditions at frequencies below 50 Hz and accelerations above 22 m s^{-2}. Powder mixes of Dipac with potassium chloride were unstable at most vibration conditions from 20 to 1000 Hz and 7·4 to 29·4 m s^{-2}. The intensity of segregation in vibrated mixes of Dipac with potassium chloride was most marked at frequencies below 50 Hz and accelerations above 22 m s^{-2}. These vibration conditions were found to occur in several commonly-used types of tableting presses. When vibration was prolonged, for periods of 30 to 60 min, there was increased segregation found in ordered mixes.

Powder segregation occurs as a result of differences in the physical and mechanical properties of constituent particles. Conditions which promote interparticle movement are responsible for the relocation of sets of particles having similar properties to different areas of the powder bed. Powder movement capable of producing segregation can occur during flow, fluidization or vibration. Vibration is a major cause of segregation when powders are processed: particles move up or down, and across the powder bed according to factors such as particle packing arrangements, percolation effects, churning, and even vibrofluidization if the vibration is intense (Staniforth 1982a).

In ordered mixes, vibrational segregation can cause separation of drug-rich and drug-lean ordered units or separation of the fine-particle drug fraction from the coarse-particle excipient fraction (Yip & Hersey 1977). We have shown previously (Rees & Staniforth 1978) that ordered mixes of a fine-particle model drug with two different coarse-particle excipients had different segregation tendencies when vibrated under the same conditions.

In the study reported here we describe a technique for assessing the segregation tendency of drug-excipient ordered mixes when vibrated at different frequencies and accelerations for various periods, within the range of conditions encountered during normal pharmaceutical tableting manufacture (Staniforth 1982b).

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MATERIALS AND METHODS

A model drug, 'P' (potassium chloride, B.D.H. Ltd, Poole, Dorset) with a particle diameter <45 μm was used in a concentration of 0·5% w/w to form ordered mixes with two different proprietary direct compression tableting excipients, 'E' (Emdex, Edward Mendell Inc., U.S.A.) and 'D' (Dipac, Amstar Corp., U.S.A.), and also with a recrystallized form of lactose, 'L' of particle size 250–500 μm similar to that of D and E.

Ordered mixes were produced using a Y-cone blender (Erweka G.m.b.H., Frankfurt, W. Germany). Samples containing 200 mg powder were analysed for P content using conductance measurements (Wayne Kerr Autobridge conductance meter). Powder mixing was continued until 20 spot samples removed from different areas of the bed had a coefficient of variation (c.v.) below 2%—the equivalent c.v. complying with pharmacopoeial standards for P was 2·78%. The ordered powder mix was then discharged from the blender into a specially constructed unit of stacked cylinders shown in Fig. 1. The individual Perspex cylinders were located by interlocking joints (Fig. 1b). After assembling the 20 stacked cylinders, a retaining Perspex outer sleeve was slid into place; the total enclosed volume of the inner stack was approximately 250 cm^3. The complete unit with lid was clamped to a vibration table (Type VP5b, Derritron Ltd., Hastings). The desired vibration conditions were generated and monitored using the system shown schematically in Fig. 2. The oscillator (Type TG66A, Levell) generated sinusoidal waves with frequencies which could be varied precisely over the range 20 to 20 000 Hz. The

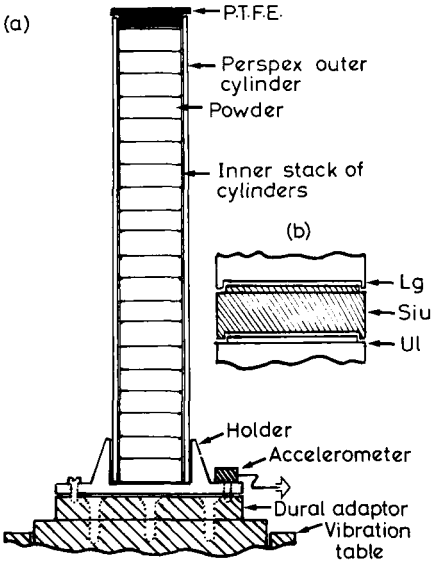

FIG. 1(a). Arrangement of stacking cylinders assembled and fitted on vibration unit with accelerometer attached.

FIG. 1(b). Assembly of stacking cylinders showing interlocking joints. Lg = lower groove. Siu = single interlocking unit. Ul = upper lip.

frequency of vibration at any instant was monitored by a signal counter (Advance Ltd., London). The selected sine wave was fed to a power amplifier (Type 250 WLF, Derritron Ltd.) which was used to adjust accelerations over the range 0–30 m s^{-2}. These were monitored by an accelerometer (Type DJB 101, Bruel & Kjoer, Naerum, Denmark) mounted on the Perspex cylinder housing and connected to a charge amplifier (Model DVA, Ling Dynamic Systems, Royston) and a voltmeter (Advance Ltd).

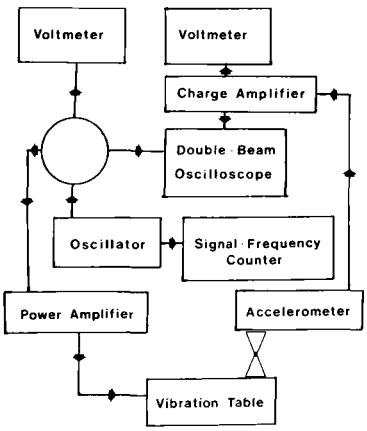

FIG. 2. Schematic representation of apparatus for vibration of powders, showing control systems.

Any difference between the waveform being fed into the vibration table and that detected by the accelerometer was monitored using a double-beam oscilloscope (Type D61a, Telequipment).

Following vibration the whole cylinder was unbolted from the table for sampling purposes. The lid was removed to expose the powder surface and the inner cylinder was pushed clear of the outer cylinder. A sample could then be taken from the top stacking unit, which was subsequently removed. Further samples, each weighing 200 mg were taken as each fresh powder surface was exposed. The stacked cylinders were assembled in the orientation shown in Fig. 1(b); in this way, the protruding inner rim protected the unsampled lower layer of powder when the upper cylinder was raised slightly and slid sideways to expose the next sample surface. The 20 samples were analysed using the conductance method and the c.v. at each vibration condition was calculated. A total of three replicate determinations were carried out using the same procedure.

The use of a model drug, sampled and analysed directly was preferred to the use of tracer particles, which do not necessarily mimic the behaviour of a set of drug particles. Similarly, radioactive techniques were rejected as these are subject to discrepancies due to wall effects, and radiolabelling may interfere with the formation of ordered units.

RESULTS AND DISCUSSION

The effects of different vibration frequencies and accelerations, for various time periods, are shown by the 3-dimensional curves in Figs 3 to 12. It should be noted that the c.v. scale on the ordinate is the same in all these figures except Fig. 12. Although the movement of particles was found by observation to be out of phase with the cylinder movement at certain vibration frequencies and accelerations, particle motion was assumed to be related to that of the cylinder according to the models of Gutman (1976) and Ryzhkov & Baskakov (1974).

At low accelerations the powder was seen to move synchronously with the cylinder and the measured values of acceleration and frequency were therefore the same for both cylinder and powder.

Ordered powder mixes containing E and 0·5% P showed no significant segregation tendency at any condition after 5 min vibration (Fig. 3). A slight increase in c.v. at 29·4 m s^{-2} occurred at higher frequencies after 15 min although this was still below the pharmacopoeial specification level corresponding to c.v. = 2·78%. After 30 min vibration, a slight

segregation tendency was found at some of the lower frequencies in particular 20 Hz at 7·4 m s^{-2} and at 50 Hz above 7·4 m s^{-2} (Fig. 4). This trend continued after 60 min vibration time (Fig. 5).

These results indicate that vibration of Emdex and P ordered mixes induced only slight segregation at certain low frequencies of less than approximately 100 Hz, even after prolonged vibration.

In ordered mixes of L, 250–500 μm particle size fraction, with 0·5% P vibrated for 5 min there was very slight segregation (Fig. 6) which was not apparent in powders vibrated for 15 min. When the vibration time was increased to 30 min there was evidence of some segregation at low frequencies of 20 to 50 Hz with 14·7 m s^{-2} acceleration (Fig. 7). This trend continued in powder vibrated for 60 min, considerable segregation occurring at 20 Hz with accelerations of 14·7 m s^{-2}. There was a tendency for this system to segregate also at other vibration frequencies when acceleration was greater than 14·7 m s^{-2} (Fig. 8). Summarizing these results for L mixed with fine-particle P, an increase in vibration time from 5 to 60 min produced a small increase in segregation at higher acceleration forces.

For the ordered mixes based on Dipac, after only 5 min vibration there was considerable segregation of P particles from D (Fig. 9). This was most marked at low frequencies and high accelerations, the c.v. showing a distinct maximum at 50 Hz and 29·4 m s^{-2}. The segregation tendency of this system decreased at high vibration frequencies and low accelerations forming a low-level plateau region enclosed by vibration conditions of 7·4 and 14·7 m s^{-2} at 100 and 500 Hz and extending to 29·4 m s^{-2} at 1 kHz. After 15 min vibration (Fig. 10) this plateau region, over which there was no segregation of practical significance, decreased to include only those powders vibrated at 7·4 m s^{-2} from 100 Hz to 1kHz and at 1 kHz from 7·4 to 29·4 m s^{-2}. Under all other vibration conditions there was a greater tendency for P to segregate from D. When vibration time was increased to 30 min the segregation of P from D continued to increase (Fig. 11). In addition to the increasingly high peak c.v. values at low frequencies there was also more marked segregation at low accelerations and high frequencies. The only conditions not producing segregation were those at 7·4 m s^{-2} and 14·7 m^{-2} and a frequency of 1 kHz. When the vibration time was increased to 60 min segregation advanced under all conditions (Fig. 12) the maximum effect being approximately double that found in the Dipac system vibrated for 30 min.

For all the powder systems studied at each vibration time the surfaces of the 3-dimensional curves show the same upward sweep from conditions producing little or no segregation—viz. at any frequency with low accelerations or any acceleration at high frequency—to a maximum under conditions combining high accelerations, e.g. >20 m s^{-2} and low frequencies, e.g. <50 Hz. The slopes of the 3-dimensional surfaces leading to conditions of maximum segregation become steeper with increased vibration time. The surfaces of the 3-dimensional curves become more convoluted at prolonged vibration times and secondary maxima were produced at low frequencies (Figs 11, 12), probably as a result of resonance effects. Resonance produces nodes and anti-nodes at different points in the cylinder alternately promoting and restricting powder movement.

Although there was only minimal segregation tendency in systems based on either E or L, the curves showed a similar upward trend at low frequencies and high accelerations to that found with D.

The E and L carriers both formed segregation-resistant, stable mixes. This indicates that for these two excipients the large differences in particle size between carrier and model drug particles—usually indicative of a segregating system in random mixes (Williams 1968/69)—were not critical in these ordered systems. Indeed, the E and L systems were less segregation prone than many random mixes with only slight size differences between component powders. In a sense, this approach to confirming the stability of a powder mix could conceivably be used to actually identify the formation of an ordered mix as well as to quantify its stability or the relative contributions of partially ordered random and pseudo-random systems to specific total mixes as defined by Staniforth (1981).

For the following reasons, the main mechanism responsible for segregation of P from D was considered to be constituent segregation, whereby fine adherent particles become dislodged from carrier particles:

(1) E, D and L all had similar particle size distributions and would therefore be expected to behave comparably when vibrated, indicating that ordered unit segregation which did not occur in E or L probably did not occur in D;

(2) potassium sorbate segregated from D in a consolidating bed where no ordered unit segregation could occur (Rees & Staniforth 1978);

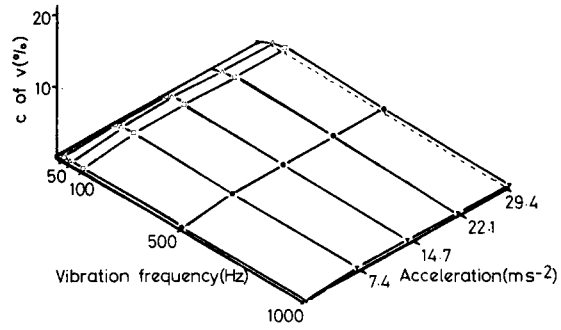

FIG. 3. The coefficient of variation of 0·5% potassium chloride/Emdex mixes after 5 min vibration showing the effect of vibration frequency and acceleration.

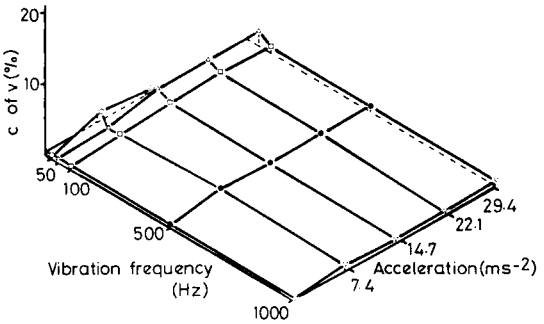

FIG. 4. The coefficient of variation of 0·5% potassium chloride/Emdex mixes after 30 min vibration showing the effect of vibration frequency and acceleration.

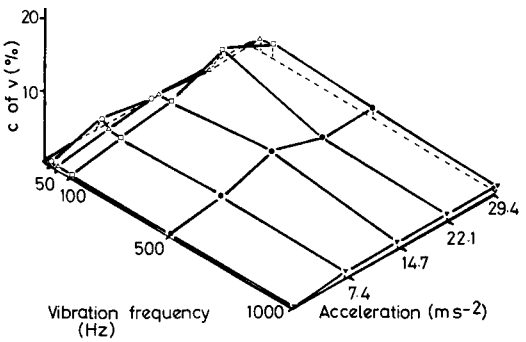

FIG. 5. The coefficient of variation of 0·5% potassium chloride/Emdex mixes after 60 min vibration showing the effect of vibration frequency and acceleration.

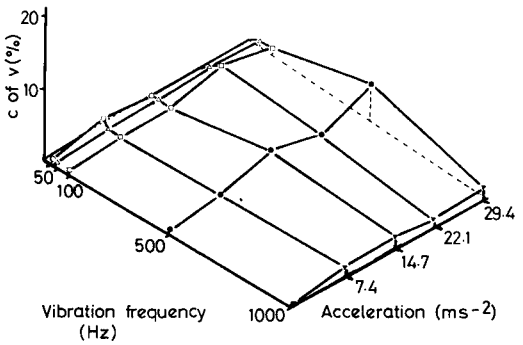

FIG. 6. The coefficient of variation of 0·5% potassium chloride/recrystallised lactose mixes after 5 min vibration showing the effect of vibration frequency and acceleration.

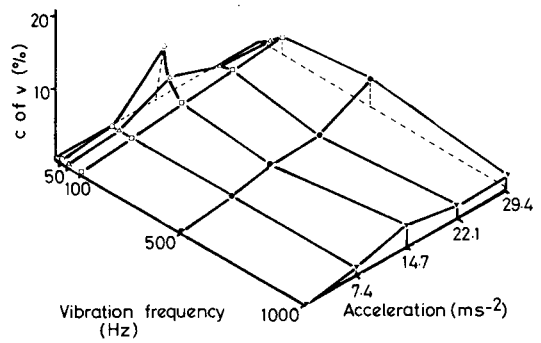

FIG. 7. The coefficient of variation of 0·5% potassium chloride/recrystallised lactose mixes after 30 min vibration showing the effect of vibration frequency and acceleration.

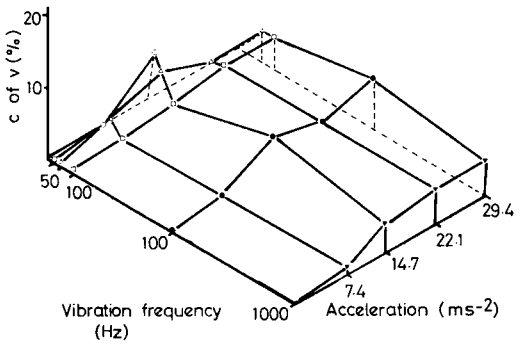

FIG. 8. The coefficient of variation of 0·5% potassium chloride/recrystallised lactose mixes after 60 min vibration showing the effect of vibration frequency and acceleration.

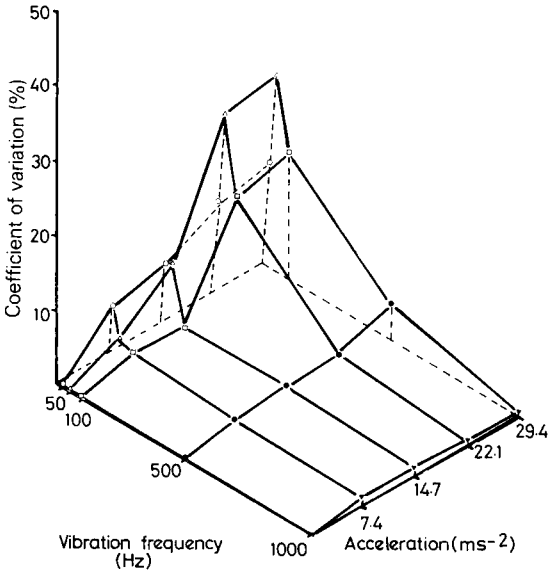

FIG. 9. The coefficient of variation of 0·5% potassium chloride/Dipac mixes after 5 min vibration showing the effect of vibration frequency and acceleration.

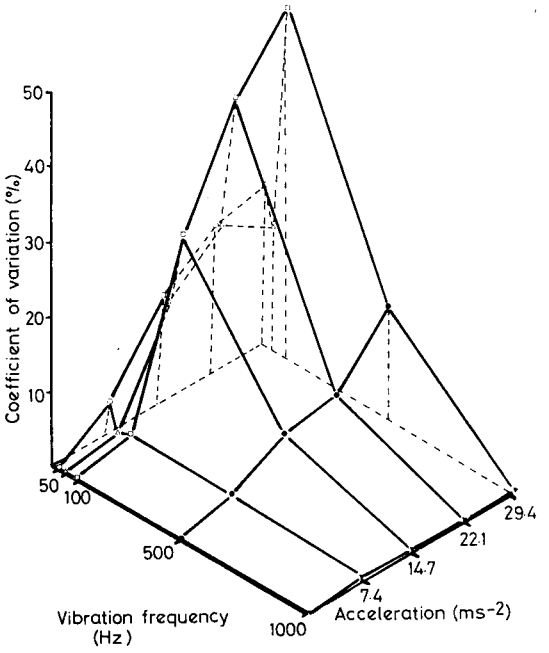

FIG. 10. The coefficient of variation of 0·5% potassium chloride/Dipac mixes after 15 min vibration showing the effect of vibration frequency and acceleration.

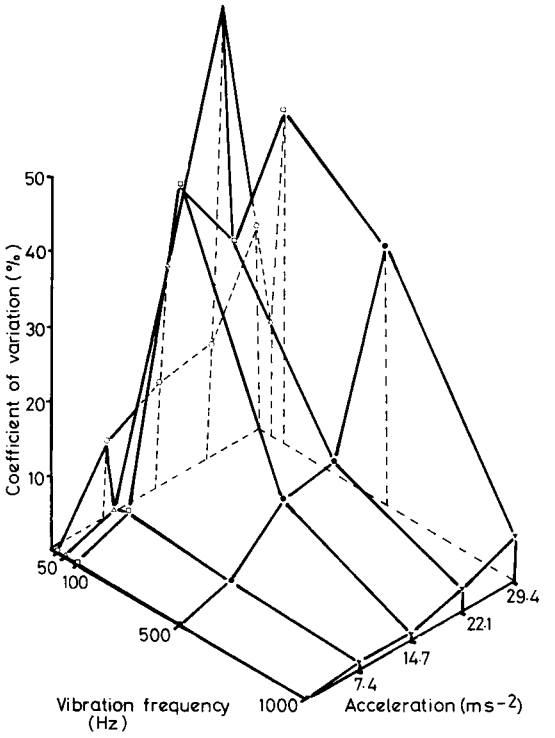

FIG. 11. The coefficient of variation of 0·5% potassium chloride/Dipac mixes after 30 min vibration showing the effect of vibration frequency and acceleration.

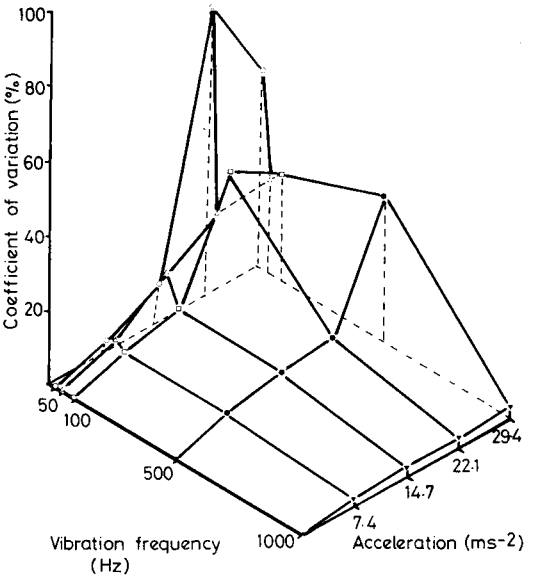

FIG. 12. The coefficient of variation of 0·5% potassium chloride/Dipac mixes after 60 min vibration showing the effect of vibration frequency and acceleration. Note the different vertical axis scale (c.v.) compared with Figs 1–11.

(3) P segregated from D in conditions where bulk rearrangement of the bed did not occur;

(4) the intensity of segregation observed in D and P mixes was too large to be accounted for by ordered unit segregation without massive multilayer adsorption, which was not observed during separate s.e.m. studies;

(5) in some vibration conditions a layer of discrete drug particles was found at the upper powder surface probably as a result of microfluidization (Lai et al 1981).

The differences in stability of the three ordered systems appears to result from the ability of the adsorbed drug particles to remain attached to the carrier particles. Some factors which influence the carrier particles' ability to form strong adherence sites include: surface rugosity; pore size distribution; accessible surface area and charge effects (Staniforth 1980). Both E and L particles had much more porous, rough surfaces with larger surface areas than did particles of D.

The increased segregation tendencies of powders vibrated at low frequencies or high accelerations can be explained by increased particle flight duration. Particle flight occurs when particles possess sufficient momentum to maintain upward motion when the vibrating cylinder is stationary or moving downwards or when the particle velocity is greater than the cylinder velocity. Once in flight, particles with different physical properties, such as size, will follow different trajectories and will therefore relocate to different areas of the cylinder.

Particle flight was seen to occur mainly in systems vibrated with accelerations greater than 7·4 ms^{-2}, the duration of flight being shorter as the vibration frequency increased. Some segregation was found in powder vibrated under sub-flight conditions, probably due to percolation, but the magnitude of this effect was much less. Two conditions of particle flight were identified, one in which the entire powder bed was dilating and consolidating *en masse*, but out of phase with the cylinder motion, and a second condition in which powder particles were moving indiscriminately producing an effect known as churning or vibrofluidization. Both of these conditions provide considerable opportunity for fine P particles to become dislodged from the carrier excipient by abrasion or impact and subsequently to move freely through the powder bed; hence the much larger segregation effects found under these conditions.

Conclusions

Vibration conditions are shown to influence the segregation of certain ordered mixes.

Segregation tendency is reduced when adherent fine drug particles do not become dislodged from carrier excipient particles by vibration.

The segregation mechanism of P particles from D is consistent with constituent segregation followed by factors such as percolation or microfluidization.

Segregation maxima occur at vibration frequencies below approximately 50 Hz, coupled with high accelerations above approximately 20 m s^{-2}. These induce prolonged particle flight, thereby increasing the number and intensity of interparticle and wall collisions which detach drug particles from the carrier surface by impact dislodgement or abrasion. In addition, prolonged flight affords increased scope for movement of those drug particles dislodged, thus increasing segregation intensity.

In order to minimize the segregation tendency of an ordered mix, excipient carrier particles should be capable of entrapping finer drug particles with adhesion forces strong enough to prevent disruption of ordered units by processing conditions such as vibration.

These criteria are fulfilled by excipient particles possessing certain physical properties: high surface rugosity; pore size distribution comparable with the size distribution of adherent particles; compatible surface charges (Staniforth & Rees 1982c).

However, particle size differences between drug and excipient, considered to be of paramount importance when processing random mixes, appear to be relatively unimportant.

To reduce the potential for large-scale segregation of powder mixes, vibration produced by processing equipment should be reduced to levels where particle flight does not occur.

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