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Relationship between sine random vibrations, resonance and drug content uniformity

JOHN N. STANIFORTH, *School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath, BA2 7AY, UK*

The effect of sine random vibrations on the segregation tendency of 3 ordered powder mixes was studied. Ordered mixes containing either Emdex, Dipac or recrystallized lactose carrier particles mixed with 0·5% fine-particle potassium chloride were prepared. It was found that the coefficients of variation of drug content in samples removed from the ordered mixes following random vibration were, in general, lower than those derived from vibration at equivalent single frequencies. Ordered mixes vibrated at low centre-frequencies were found to be most prone to slight demixing and under these conditions, a vibration bandwidth of 30 Hz produced more de-mixing than a 10 Hz bandwidth. Most ordered mixes were considered to be segregation free following random vibration.

It has been found previously that when ordered mixes containing direct compression excipients and model drug powders are subjected to sinusoidal vibration, segregation occurs which is a potential cause of poor drug content uniformity. The scale and intensity of segregation tends to increase in conditions of low-frequency vibration or high vibrational acceleration as the drug concentration increases over the range 0·5 to 10% w/w (Staniforth & Rees 1982b).

Several approaches can be employed to stabilize ordered mixes and these include selection of excipient systems with a large number of active sites in relation to particle accessible surface area (Staniforth et al 1981a). In certain cases this may be achieved by changing the type of commercial direct compression excipient in a formulation; in other cases it may be necessary or desirable to carry out particle engineering on an existing excipient so as to enhance carrier surface properties (Staniforth et al 1981b), or to alter the particle size distribution of the fine particle fraction to improve mixing (Nyström & Malmqvist 1980). Another approach to ensure production of more stable ordered mixes is to optimize the powder surface-electrical properties (Staniforth & Rees 1982a). However, in cases where powder segregation is known only to occur in conditions where vibration alone is present, it may be appropriate to investigate which particular elements of vibration are causing the content uniformity problems so that these may be reduced, or eliminated, without any change of formulation being necessary.

Method

The work reported here is a study of the influence of sine-random vibrations on the homogeneity of ordered mixes containing one of three coarse-particle direct compression excipients: Emdex (Edward Mendell Inc., U.S.A.); Dipac (Amstar Corp., U.S.A.) and recrystallized lactose (as reported by Staniforth et al 1981) together with a model drug, potassium chloride (BDH Ltd., Poole, Dorset) with particle diameter <45 μm. A sine-random generator (Type 2305, Bruel & Kjaer, Naerum, Denmark) was used to produce random vibrations with different bandwidths centred on specific frequencies. Vibrational acceleration at given frequencies was monitored using an accelerometer attached to the base of the powder container. Fig. 1 shows a sample of random waveform produced by vibrations with a 30 Hz bandspread centred on a frequency of 50 Hz. Table 1a, b, c, lists the centre-frequencies and bandspreads of random vibration signals used to vibrate the different powder mixes for 15 min at 14·7 ms^{-2} acceleration. Centre frequencies with bandspreads of only 10 Hz were used to produce narrow-band random signals. Narrow-band random vibrations were capable of destroying any resonance such as that found in powder systems vibrated by certain sine waves at specific frequencies and which were observed to produce lateral powder movement due to turbulence.

Results and discussion

A comparison of ordered mixes vibrated at a specific single frequency, with those subjected to random vibrations at the same centre-frequency, was used to assess the influence of resonance on the segregation tendencies of powder mixes. Emdex and recrystallized lactose ordered mixes containing 0·5% w/w potassium chloride had content uniformities within pharmacopoeial limits when vibrated randomly (Table 1a, b).

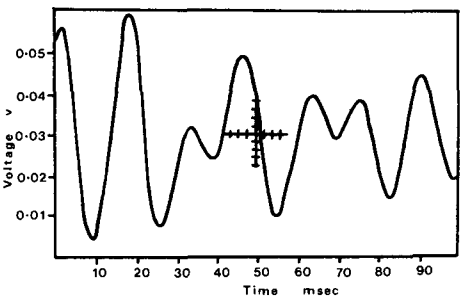

FIG. 1. Sample of random waveform recorded on an oscilloscope for 30 Hz band-spread vibration centred on a 50 Hz carrier signal.

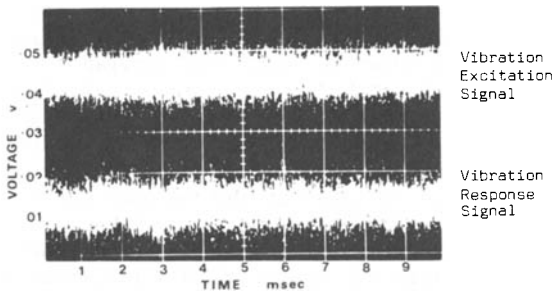

FIG. 2. Sample of broad-band random vibration in the range 20–20 000 Hz (white noise). A comparison of the 2 traces shows the similarity between the excitation signal and the vibration conditions produced.

These systems showed a slight tendency to segregate when subjected to random vibration at low centre-frequencies, in a similar manner to the segregation found in powders subjected to low single-frequency vibrations (Staniforth & Rees 1982). There was also a slightly larger segregation tendency in Emdex and lactose mixes vibrated randomly at a centre-frequency of 50 Hz and a bandspread of 30 Hz, when compared with powders vibrated at the same centre-frequency but with the bandspread reduced to 10 Hz. This probably occurred because the larger bandspread introduced more low-frequency vibrations which have previously been shown to increase the segregation tendency of ordered powder mixes. Mixes of Dipac and 0·5% potassium chloride showed a greater segregation tendency than either Emdex or recrystallized lactose mixes when randomly vibrated (Table 1c). The increased segregation which occurred in mixes of Dipac was similar to the increases found in vibration studies at single frequencies, although the magnitude of the segregation tendency was reduced under random vibration. Dipac mixes vibrated at 50 Hz single frequency had a coefficient of variation of 14·78% compared with 3·48% for mixes vibrated randomly at 50 Hz with 10 Hz bandspread. The random vibrations probably caused less segregation because the powder cylinders were unable to vibrate at their natural frequencies long enough to produce resonance. The increase in powder segregation at the wider bandspread of 30 Hz was probably caused by the introduction of lower frequencies. This effect was destroyed by increasing the bandspread to include many higher frequencies. Broad-band random signals with a frequency range from 20 Hz to 20 000 Hz, referred to as white noise (Fig 2), were used to vibrate all the powder mixes, but even in mixes containing Dipac, there was no segregation tendency.

Table 1. Coefficients of variation (cv%) with upper and lower 95% confidence limits of different powder mixes subjected to sinusoidal random vibrations.

	Centre frequency (Hz)	Band-width (Hz)	Mean cv (%)	Upper limit	Lower limit
(a) Emdex					
Emdex and	50	10	0·44	2·22	0·08
Potassium 0·5%	100	10	0·50	0·95	0·48
chloride	500	10	0·40	0·72	0·39
	50	30	0·91	1·41	0·89
	White noise		0·52	3·46	0·34
(b) Recrystallized lactose					
Recrystallized	50	10	0·24	1·69	0·18
Lactose and	100	10	0·58	3·39	0·46
Potassium 0·5%	500	10	0·04	0·06	0·04
chloride	50	30	0·63	2·45	0·55
	White noise		0·05	0·12	0·05
(c) Dipac					
Dipac and	50	10	3·48	10·86	3·16
Potassium 0·5%	100	10	1·87	4·50	1·76
chloride	500	10	0·20	0·69	0·18
	50	30	4·20	15·89	3·69
	White noise		0·25	0·35	0·24

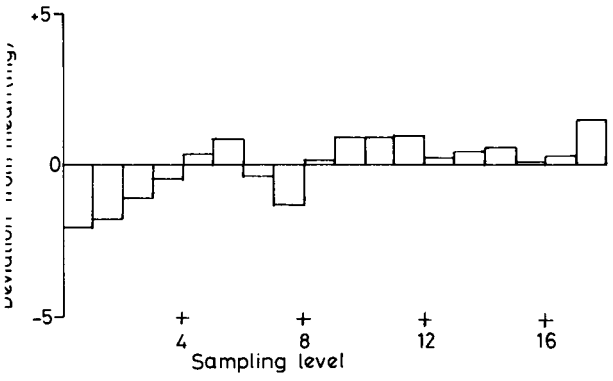

FIG. 3. Relationship between drug concentration at specific levels in Emdex powder bed following random vibration at 50 Hz centre frequency with 10 Hz modulation. Sample level 0 corresponds to samples removed from the upper free surface of the powder bed. The different sampling levels are separated by a vertical distance of approximately 13 mm.

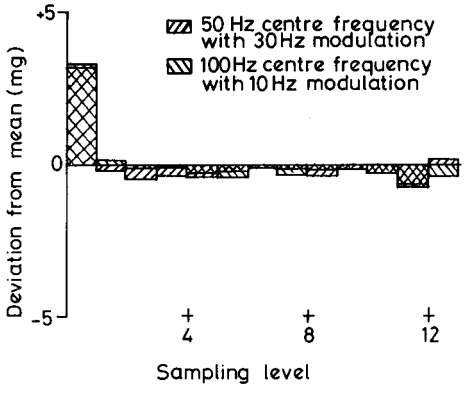

FIG. 4. Relationship between drug concentrations at specific levels in recrystallized lactose powder beds following random vibration under different conditions. Sample level 0 corresponds to samples removed from the upper free surface of the powder bed. The different sampling levels are separated by a vertical distance of approximately 13 mm.

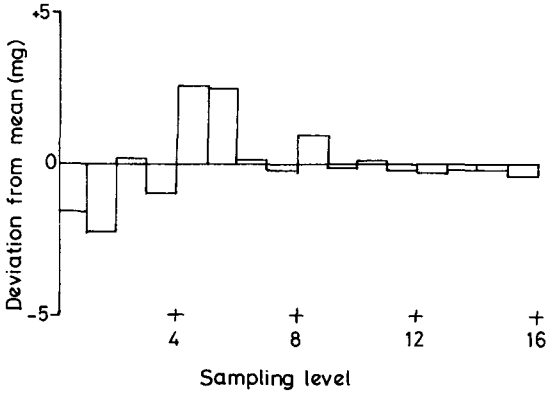

FIG. 5. Relationship between drug concentration at specific levels in Dipac powder bed following random vibration at 50 Hz centre frequency with 30 Hz modulation. Sample level 0 corresponds to samples removed from the upper free surface of the powder bed. The different sampling levels are separated by a vertical distance of approximately 13 mm.

Fig. 2 shows the effects of drug particle movement in the different powder mixes following random vibrations. Random vibration produced no overall segregation in mixes of Emdex and potassium chloride but there was a slight loss of drug from the powder surface in powders vibrated randomly with a centre-frequency of 50 Hz (Fig. 3). The drug particles only percolated a short distance, being restricted to a layer of more mobile particles near the powder surface, and the powder movement involved was very small, most of the samples throughout the bed were within pharmacopoeial limits for drug content uniformity.

In recrystallized lactose subjected to random vibrations, only samples vibrated at a centre-frequency of 50 Hz with 30 Hz modulation and at 100 Hz showed any drug movement (Fig. 4). At these lower frequencies there was a slight increase in drug content at the powder surface and an even smaller drop in concentration at the base. This may have been caused by some diffusional segregation but it is more probable that this small-scale effect was caused by ordered-unit segregation. At the lower centre-frequencies of randomly vibrated Dipac mixes, both short and long-range segregation was present, although both were relatively small effects (Fig. 5). The long-range segregation tendency was apparently caused by percolation of fine drug particles from the powder surface to the bottom of the upper mobile layer. In Dipac, as with the other excipient systems, the higher centre-frequencies of narrow-band random vibrations produced virtually no net movement of drug particles. This was also absent in all the different powder mixes subjected to broad-band random vibrations (white noise) at an acceleration of 14·7 m s^{-2} and all of the powder samples remained within pharmacopoeial limits.

The results from this part of the vibration study suggest that random vibrations reduced powder segregation by preventing resonance effects previously shown to cause segregation in non-randomly vibrated powder. The influence of vibrational resonance on the segregation of ordered powder mixes is thought to be exerted by production of increased interparticle abrasion caused by turbulence and churning in some parts of the powder bed. It may therefore be possible to reduce powder segregation in other systems by eliminating all non-random vibrations in processing equipment, as a more practical alternative to producing completely vibration-free conditions.

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