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Research Papers

FINE POWDER MIXING IN A VIBRATORY BALL MILL

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SUMMARY

The applicability of the vibratory ball mill to fine powder mixing is investigated using two model 1 : 1000 binary systems of microfine salicylic acid sucrose and milled tolbutamide with lactose. Mill performance is evaluated by measuring the extent of mixing relative to a specified standard and by comparing the rate of mixing to the Revolvo-Cube, a conventional tumbling mixer. It is demonstrated that the vibratory ball mill offers distinct advantages in combining the two unit operations of milling and mixing by rapidly producing highly homogeneous fine powder mixtures. Finally, the mechanism of comminution and mixing in the vibratory ball mill at the particulate level is examined.

INTRODUCTION

Solid–solid mixing in the pharmaceutical industry is the first step in a granulation process and possibly the only step prior to a direct compression tabletting operation or in encapsulation, prior to actual filling. The most important function of these mixing operations is to ensure content uniformity. Mixer efficiency becomes crucial in the production of microdose preparations (Crooks, 1976), where bioavailability problems are frequently encountered. For example in one study (Banes, 1971), huge variations in active ingredient content were found for digoxin 125 μg tablets (60–200% of states content) and 100 μg ethinyl estradiol tablets (35–252% of stated content).

There are extensive reviews in the literature of the various types of commercially available mixers (Harnby, 1967; Fan et al., 1970; Griffin, 1971; Cooke et al., 1976). However, few reports exist on the applicability of comminution equipment to fine powder mixing.

Two major problems encountered in powder mixing, depending on the properties of the constituents of the mix, are segregation (Williams and Khan, 1973) and the inability of mixers to break down powder agglomerates (Egermann, 1979a). Abouzied and Fuerstenau (1979), found that the addition of lucite balls to a continuous drum mixer minimized segregation. Similarly, Shoji and co-workers (1973) demonstrated that the rotary

ball mill mixed efficiently, without segregation, when the charge mass was just sufficient to fill the voids between the balls. Kaneniwa and Ikekawa (1977) showed that an interaction of polyvinylpyrrolidine with various excipients occurred on a molecular level when mixed in a rotary ball mill. Yeung and Hersey (1979) found that a rotary ball mill mixed fine cohesive powders more rapidly when compared to the Revolve-Cube, a tumbling mixer.

Lacey (1954) considered that there are 3 principle mechanisms for mixing: (i) convective mixing, in which there is bulk transfer of particles from one part of the mix to another; (ii) diffusive mixing, which involves the distribution of particles over freshly formed surfaces; and (iii) shear mixing, by the setting up of slip planes within the powder mass. It is possible that due to the high agitation rate and high energy input of the balls, both rotary and vibratory ball mills mix by a combination of all 3 mechanisms, resulting in rapid fine powder mixing.

Johnson (1975) experimentally verified the importance of reducing the particle size of the active ingredient to obtain a high degree of homogeneity, and this had been shown theoretically by Hersey (1972). Consequently many mixing operations are preceded by comminution of either the diluent or active ingredient or both. Thus the combination of the two unit operations of milling and mixing would result in increased efficiency and decreased production costs.

It has been demonstrated that the vibratory ball mill is power efficient and rapid means of particle size reduction (Rose and Sullivan, 1961) Also, in a comparative study of the rotary and vibratory ball mills, Krycer and Hersey (1980) established that comminution in the vibratory ball mill proceeded more rapidly and to a further extent.

The aim of this paper is to investigate the applicability of the vibratory ball mill to fine powder mixing. Two model binary systems were chosen for this purpose and mill performance was evaluated by measuring the extent of mixing relative to a specified standard and by comparing the rate of mixing to a conventional tumbling mixer, the Revolvo-Cube.

MATERIALS AND METHODS

All materials used were of pharmacopoeial quality. Sucrose and lactose were used as supplied, whilst the salicylic acid was micronized in a fluid energy mill and the tolbutamide was ground in a vibratory ball mill. Particle size analysis of the sucrose samples was carried out using test sieves (Endecott) and a test sieve shaker (Cheers), shaking each sample for half an hour. For lactose, particle size changes were quantified with a HIAC 'SS' Automatic Particle Counter, Model PC-305 SSTA. Average diameters, dvs, were determined for the salicylic acid and tolbutamide using the Fisher sub-sieve sizer following the British standard method (B.S., 1971), taking all measurements at constant porosity of 0.40. The densities of all materials employed were determined using a Beckman air comparison pyonometer (Model 940).

Two binary systems were studied. In the first series of experiments, one part of salicylic acid was mixed with 999 parts of sucrose; whilst in the second series, one part of tolbutamide was mixed with 999 parts of lactose. Mixing was carried out in the Megapol vibratory ball mill (Pilamec), which consisted of a polyethylene cannister, diameter 12.0

cm, length 27.5 cm, vibrating at 2800 rpm with an amplitude of a few millimetres. The grinding medium consisted of alumina balls, 100 with 2.45 cm diameter and 50 with 2.18 cm diameter and charge masses of sucrose and lactose, separately or as part of a mixture, were 420 and 400 g respectively. The mass of charge was just sufficient to fill the gaps between the voids and the total occupied volume was about 70% of the cannister. Alternatively, mixing was carried out in a stainless steel Revolvo-Cube mixer (Garwood and Goodyear), capacity 7.5 kg, revolving at 37 rpm. The mixer contained 3.3 kg and 3.0 kg of the sucrose and lactose mixtures respectively. The mass of charge was chosen to only half fill the mixer, as recommended by the manufacturer.

During mixing, 20 samples were removed at preselected time intervals using a concentric cylindrical sampling thief, calibrated to remove 200 mg samples, from random positions selected using a grid and a table of random numbers. In the case of the vibratory ball mill, the balls had to be previously removed to enable efficient sampling.

The sucrose and lactose samples were dissolved in 50 and 30% ethanol – water co-solvent systems respectively, made up to 20 ml in a standard flask and assayed by measuring absorbance at 300 nm for salicylic acid and 228 nm for tolbutamide. A Varian Techtron autosampling unit connected to a spectrophotometer (Model 634) was employed for this purpose. The blank consisted of the appropriate solvent and an equivalent amount of either sucrose or lactose.

RESULTS AND DISCUSSION

The densities of sucrose, salicylic acid, lactose and tolbutamide were found to be 1.593, 1.435, 1.534 and 1.239 g/cm^3 at 20°C, respectively. The average diameters (dvs) of the microfine salicylic acid and the milled tolbutamide employed were determined to be 3.6 and 12.2 μm, respectively.

Table 1 presents the particle size distributions of sucrose samples after pre-determined milling times. The values of the theoretical standard deviation of the completely randomized mixture, σ_R, were calculated for the 1 : 1000 mixture of salicylic acid and sucrose. The formula for σ_R developed by Poole et al. (1964) was employed (Eqn. 1).

$$\sigma_R^2 = \frac{xy}{w}(x(\Sigma f_w)\, y + y(\Sigma f_w)\, x) \qquad (1)$$

where x and y are the proportions of the two ingredients, 0.001 and 0.999 respectively, w is the sample weight (200 mg) and Σf_w is the effective mean weight of the particles denoted by the suffix. It is assumed that negligible particle size reduction of the minor constituent (already reduced in size) occurs in the vibratory ball mill.

It is apparent that the increase in σ_R after 20 min milling is caused by the simultaneous increase in coarse particles. This is due to the irreversible agglomeration of ground particles on prolonged milling. This phenomenon has been reviewed by Hersey and Krycer (1979) and verified experimentally in a later publication (Krycer and Hersey, 1980).

Table 2 presents similar data for the 1 : 1000 tolbutamide and lactose mixture. The number distributions obtained with the HIAC counter were converted to weight distributions by assuming spherical particles. Again the agglomerative phase of comminution

TABLE 1

PARTICLE SIZE DISTRIBUTIONS OF SUCROSE AT VARIOUS MILLING TIMES AND CALCULATION OF σ_R, THE THEORETICAL STANDARD DEVIATION OF A COMPLETELY RANDOMIZED MIXTURE OF 1:1000 SALICYLIC ACID AND SUCROSE

Particle size range (μm)	Mean sucrose particle weight (μg)	Range fraction (f) of sucrose at specified milling times						
		0 min (as supplied)	10 min	20 min	40 min	80 min	160 min	320 min
1250–710	963.81	0.073	0.004	0.0008	0.011	0.061	0.109	0.211
710–600	239.34	0.151	0.025	0.0009	0.005	0.020	0.035	0.091
600–500	142.21	0.322	0.125	0.0053	0.010	0.034	0.058	0.091
500–425	84.15	0.150	0.113	0.013	0.008	0.020	0.029	0.049
425–355	50.65	0.135	0.128	0.036	0.019	0.039	0.046	0.040
355–250	25.15	0.128	0.217	0.148	0.085	0.084	0.108	0.080
250–180	8.93	0.035	0.138	0.182	0.166	0.142	0.130	0.228
180–150	3.84	0.006	0.033	0.050	0.048	0.040	0.037	0.062
150– 90	1.72	0	0.086	0.167	0.205	0.189	0.164	0.025
90– 75	0.48	0	0.029	0.076	0.073	0.098	0.065	0.036
75– 0	0.18	0	0.101	0.321	0.370	0.274	0.219	0.080
$(\Sigma f_w)y$ Equivalent sucrose particle weight (μg)		175.3	50.6	10.6	19.1	76.0	130.8	248.2
σ_R ($\times 10^{-5}$)		2.96	1.59	0.73	0.98	1.95	2.55	3.52

The equivalent particle weight of microfine salicylic acid (dvs = 3.6 μm) is 3.51×10^{-5} μg assuming mono-sized, spherical particles.

TABLE 2

PARTICLE SIZE DISTRIBUTIONS OF LACTOSE AT VARIOUS MILLING TIMES AND CALCULATION OF σ_R, THE THEORETICAL STANDARD DEVIATION OF A COMPLETELY RANDOMIZED MIXTURE OF 1:1000 TOLBUTAMIDE AND LACTOSE

Particle size range (μm)	Mean sucrose particle weight (μg)	Range fraction (f) of lactose at specified milling times						
		0 min (as supplied)	10 min	20 min	40 min	80 min	160 min	320 min
710–500	193.90	0.055	0.022	0.146	0.223	0.338	0.327	0.321
500–350	67.42	0.150	0.074	0.113	0.142	0.184	0.198	0.221
350–250	23.50	0.285	0.252	0.219	0.182	0.157	0.181	0.168
250–150	7.63	0.377	0.452	0.378	0.285	0.194	0.198	0.196
150–100	1.76	0.116	0.173	0.125	0.134	0.097	0.075	0.075
100– 0	0.40	0.017	0.027	0.019	0.034	0.030	0.021	0.019
$(\Sigma f_w)y$ Equivalent lactose particle weight (μg)		30.56	18.94	44.19	59.51	83.30	82.66	82.72
σ_R ($\times 10^{-5}$)		1.35	1.11	1.58	1.81	2.11	2.10	2.10

The equivalent particle weight of milled tolbutamide ($dvs = 12.2\ \mu m$) is 5.73×10^{-3} μg assuming mono-sized, spherical particles.

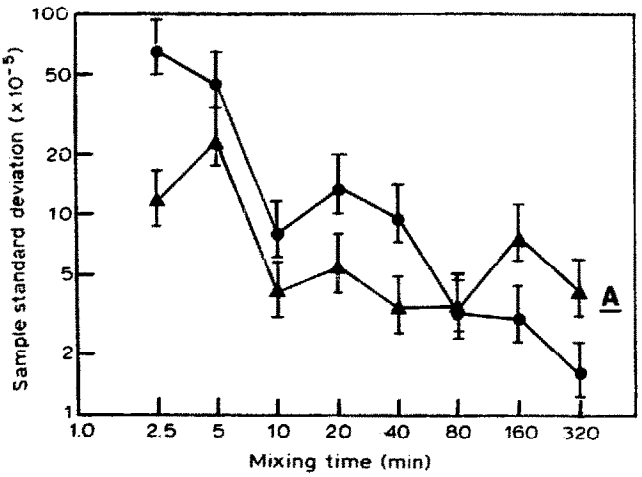

Fig. 1. Mixing of 1 : 1000 salicylic acid (3.6 μm) and vibratory ball milled sucrose in a Revolvo-Cube mixer. (●——●), represents salicylic acid and 20 min vibratory ball milled sucrose. (▲——▲), represents salicylic acid and 320 min vibratory ball milled sucrose. Point A represents σ_A the specification standard deviation, ($\sigma_A = 3.33 \times 10^{-5}$). Error bars are 95% confidence limits.

results in an increase in σ_R after reaching its minimum value at 10 min milling time.

The mixing of salicylic acid with two different vibratory ball milled fractions of sucrose in the Revolve-Cube mixer is presented in Fig. 1. The 20 min vibratory ball milled sucrose fraction was chosen because it has the lowest σ_R and hence should theoretically give the most homogenous mix. However, the 320 min vibratory ball milled sucrose fraction was included in this study, because, with the agitation of the internal impeller in the Revolvo-Cube mixer, the possible breakdown of agglomerates into primary particles could result in a more homogenous mix than that predicted by σ_R. From Fig. 1, it is apparent that the extent of mixing is statistically greater for the mixture incorporating the 20 min milled sucrose fraction. It should be noted that there are considerable sampling errors in the initial stages of mixing of fine cohesive powders due to pockets of minor constituent agglomerates that have not yet been incorporated into the bulk of the mixture (Egermann, 1979b). This could account for some of the irregularities in the graphs presented.

Fig. 2 represents a comparison of 1 : 1000 mixtures of tolubtamide with the 10 min milled lactose fraction and the 320 min milled lactose fraction, in the Revolvo-Cube mixer. It is apparent that although mixing occurs to the same extent for both mixtures, the equilibrium status is attained more rapidly with the mixture incorporating the 10 min milled lactose fraction.

In order to investigate the extent of mixing in the vibratory ball mill, the homogeneity index (ΔH_i) derived by Hersey et al. (1974) was employed (Eqn. 2).

$$\Delta H_i = 2 \log(s/\sigma_A) \tag{2}$$

where s is the standard deviation of the 20 withdrawn samples and σ_A is calculated from pharmacopeial or 'in-house' specifications. This index has the advantage that it gives an indication as to whether an acceptable standard (σ_A) has been attained. In this study, it

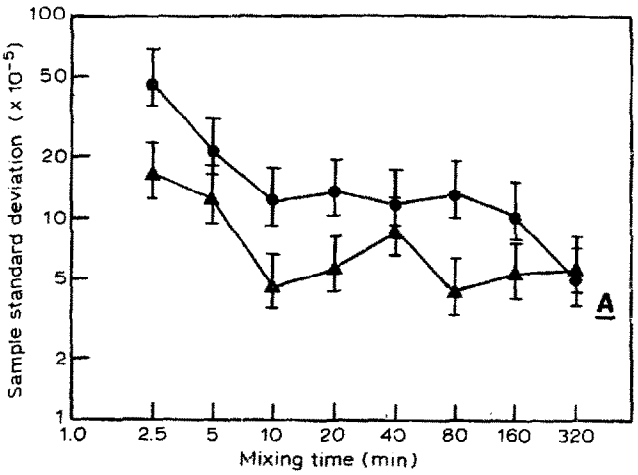

Fig. 2. Mixing of 1 : 1000 tolbutamide (12.2 μm) and vibratory ball milled lactose in a Revolvo-Cube mixer. (▲———▲), represents tolbutamide and 10 min vibratory ball milled lactose. (●———●), represents tolbutamide and 320 min vibratory ball milled lactose. Point A represents σ_A the specification standard deviation, ($\sigma_A = 3.33 \times 10^{-5}$). Error bars are 95% confidence limits.

was arbitrarily chosen that 99.7% of the samples should have a minor constituent content of 10 ± 0.1%. Hence, assuming a normal sampling distribution:

$$\pm 3\,\sigma_A = \pm 0.10 \times 0.001 = \text{tolerance} \times \text{mean} \qquad (4)$$

therefore $\sigma_A = 3.33 \times 10^{-5}$

In this exercise, sample standard deviation cannot be compared to σ_R since the mechanism of random mixing for fine cohesive, agglomerated powders is unacceptable. Additionally, it has been estimated that the contribution of experimental error, in the assay, to sample standard deviation is in the order of 1 to 2×10^{-5} (Orr, 1979; Hersey and Yeung, 1979). Consequently, it is not possible to show mixture homogeneity better than σ_R, even if it exists.

Figs. 3 and 4 present a comparison of the vibratory ball mill with the Revolvo-Cube mixer for the two model binary systems employed. For the salicylic acid–sucrose system (Fig. 3), the Revolvo-Cube mixture incorporating the 20 min milled sucrose fraction was chosen for comparison because the extent of mixing proceeded to a homogeneity better than specification (σ_A). Statistically, the mixture with the 320 min milled sucrose fraction did not necessarily reach the specification standard. From Fig. 3 it is apparent that mixing proceeds more rapidly in the vibratory ball mill; the specification standard is attained in 31 min compared to 78 min in the Revolvo-Cube mixer.

For the tolbutamide–lactose system (Fig. 4) it is apparent that even after 320 min mixing in the Revolvo-Cube, the specification standard is not attained. This observation confirms the superiority of the vibratory ball mill for mixing this sytem.

Ordered powder mixing theory can be used to explain the high degree of mixture homogeneity obtained for the two systems investigated. In the Revolvo-Cube mixer the

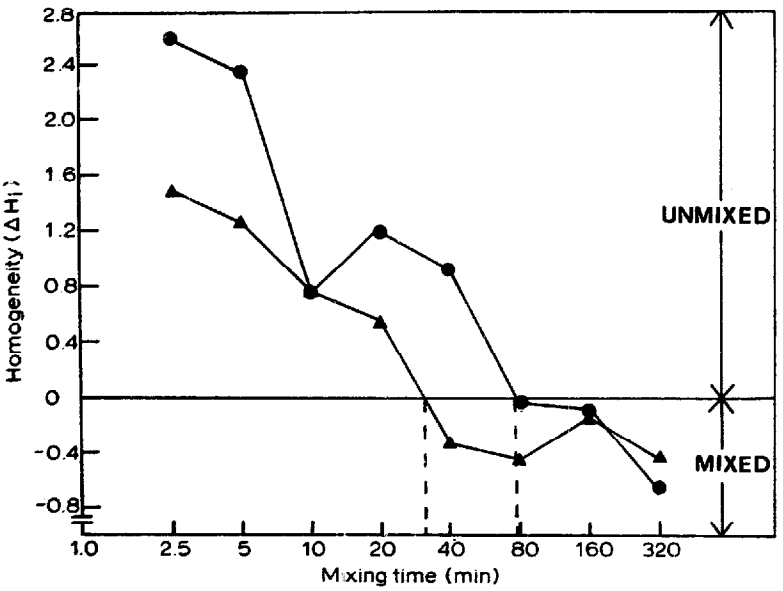

Fig. 3. Effect of mixing time on homogeneity (see text) for 1 : 1000 salicylic acid (3.6 μm) and sucrose mixtures. (●——●), represents salicylic acid and 20 min vibratory ball milled sucrose mixed in a Revolvo-Cube mixer. (▲——▲), represents salicylic acid and sucrose, as supplied, mixed in a vibratory ball mill.

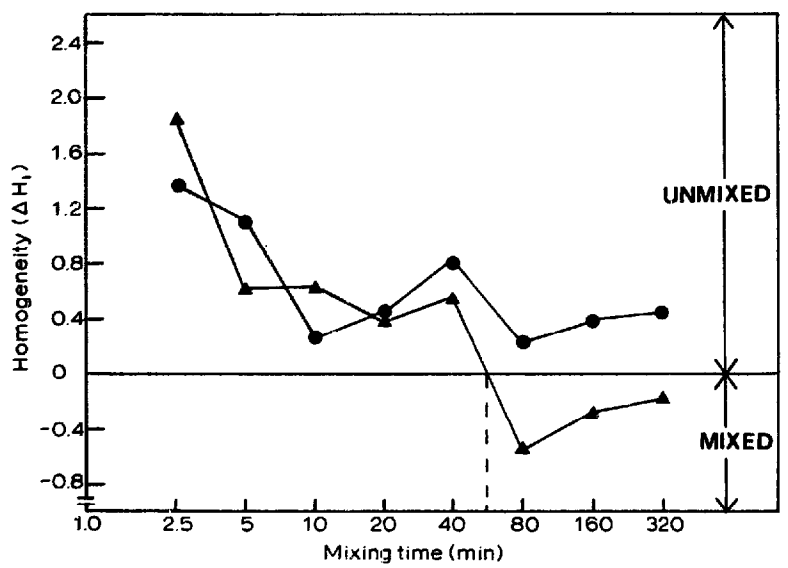

Fig. 4. Effect of mixing time on homogeneity (see text) for 1 : 1000 tolbutamide (12.2 μm) and lactose mixtures. (●——●), represents tolbutamide and 10 min vibratory ball milled lactose mixed in a Revolvo-Cube mixer. (▲——▲), represents tolbutamide and sucrose, as supplied, mixed in a vibratory ball mill.

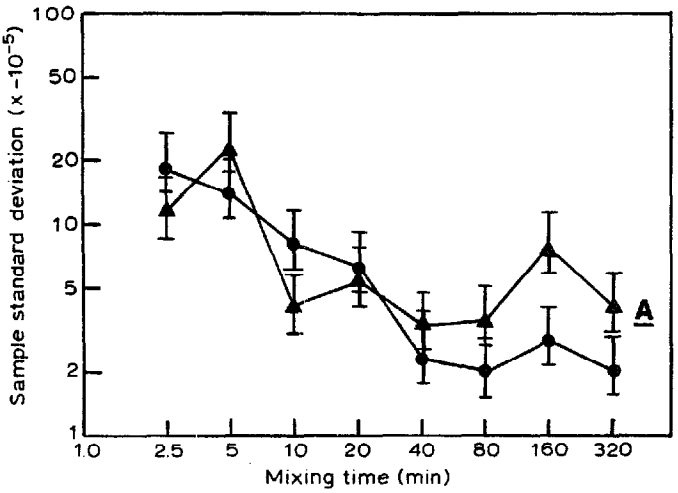

Fig. 5. Mixing of 1 : 1000 salicylic acid (3.6 μm) and sucrose. (▲———▲), represents salicylic acid and 320 min vibratory ball milled sucrose mixed in a Revolvo-Cube mixer. (●———●), represents salicylic acid and sucrose, as supplied, mixed in a vibratory ball mill. Point A represents σ_A the specification standard deviation, ($\sigma_A = 3.33 \times 10^{-5}$). Error bars are 95% confidence limits.

microfine salicylic acid can become electrostatically charged and adhere to sucrose carrier particles resulting in the formation of an ordered (Yeung and Hersey, 1979) or partially ordered randomized (Hersey, Thiel and Yeung, 1979) powder mixture. The heavier tolbutamide particles result in weaker cohesion forces and it is unlikely than an ordered mix, that is, one involving strong forces of cohesion of drug to carrier particles, can form with this system, in a tumbling mixer.

By comparing the mixing of the minor constituent with the 320 min milled fraction of

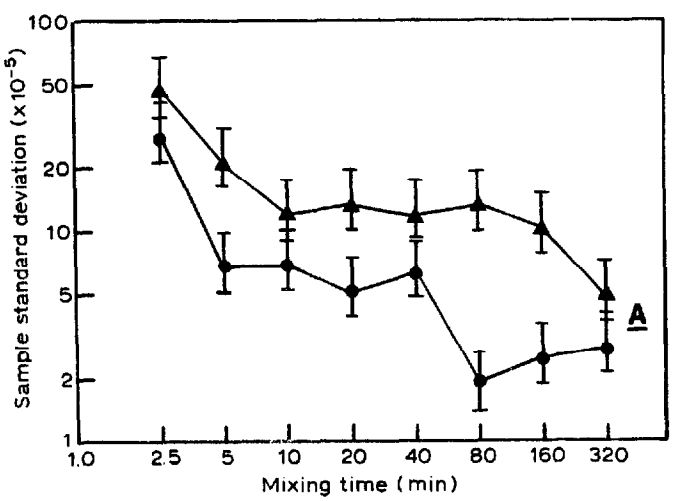

Fig. 6. Mixing of 1 : 1000 tolbutamide (12.2 μm) and lactose. (▲———▲), represents tolbutamide and 320 min vibratory ball milled lactose mixed in a Revolvo-Cube mixer. (●———●), represents tolbutamide and lactose, as supplied, mixed in a vibratory ball mill. Point A represents σ_A the specification standard deviation, ($\sigma_A = 3.33 \times 10^{-5}$). Error bars are 95% confidence limits.

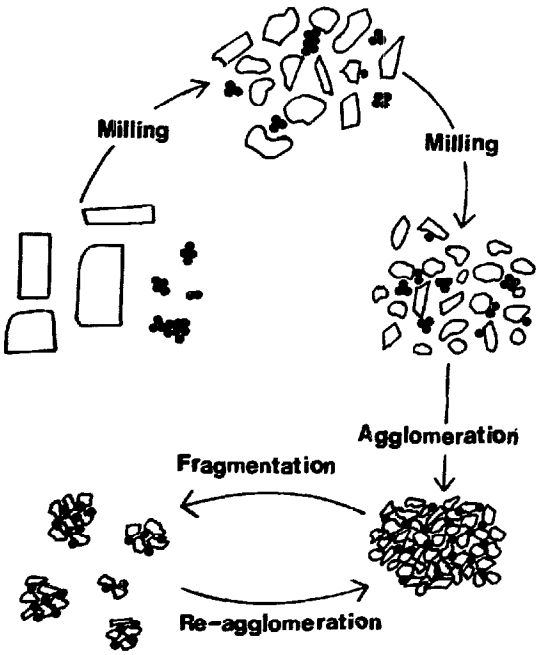

Fig. 7. Diagrammatic representation of the proposed mechanism for mixing and grinding in a vibratory ball mill. On prolonged milling, agglomeration of the minor constituent with the diluent occurs leading to strong cohesion and formation of an ordered mix. Further comminution results in fragmentation and re-agglomeration, without loss of mixture homogeneity.

the diluent in the Revolvo-Cube mixer, with the equivalent system in the vibratory ball mill (Figs. 5 and 6), it is evident that the extent of mixing is statistically greater in the vibratory ball mill. Random powder mixing theory cannot explain this observation; this has led the authors to postulate a mechanism for mixing and grinding in the vibratory ball mill (Fig. 7). On prolonged comminution it is thought that agglomeration of the minor constituent with the diluent occurs, leading to strong cohesion forces and the formation of an ordered mix. Further comminution results in fragmentation and re-agglomeration, without loss of mixture homogeneity.

In conclusion, it has been shown that for the two systems investigated, the vibratory ball mill rapidly produced highly homogenous fine powder mixtures. The application of this technique in the industrial manufacture of homogenous powder mixtures for use in tablets and capsules could offer distinct advantages in rapidly producing homogenous, non-segregating, dosage forms.

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