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Determination of interparticulate forces in ordered powder mixes

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The theory of interparticle bond formation is considered with particular reference to ordered powder mixing. A technique is described for measuring the interparticle adhesion forces between drug and excipient particles bound in ordered units. The method uses a specially constructed ultracentrifuge rotor tube insert such that fine adherent particles can be separated from coarser carrier particles in ordered mixes. The ordered units are held behind a screen in the rotor tube insert and when the forces generated by ultracentrifugation become greater than the interparticle adhesion forces the ordered units break down into their component particles. Adhesion profiles were obtained for four different ordered mixes containing drug and excipient powders by plotting force of adhesion against the cumulative percentage of fine drug particles adhering to the carrier particle surface. The adhesion profile is influenced by the quantity of drug powder adhering to the excipient carrier particle surface. Above a critical drug content, each ordered mix shows a 'composite' adhesion profile consisting of two distinct curves linked by a lag period. The initial curve, preceding the lag period, appears to correspond to loss of large amounts of weakly bound drug particles; after the lag period only relatively strongly adhered particles are removed and this phase occurs more gradually. The critical drug concentration is related to the surface properties of the excipient and drug particles which determine the strength of adhesion forces within an ordered unit.

Hersey (1975) first described the formation of ordered mixes in which interparticle adhesion is responsible for the bonding of fine adherent particles of one constituent powder to coarse 'carrier' particles of a second system. Studies carried out on various pharmaceutical ordered mixes (Rees & Staniforth 1978) showed that under certain conditions the interparticle attraction is incapable of preventing adhered particles from being removed from the surface of carrier particles. This suggests that the overall stability of an ordered mix during processing and handling will be determined by the strength of interparticle attractions in ordered units. For this reason, we have devised a method capable of quantifying the adhesion forces between fine and coarse particles in ordered mixes.

Of all the forces acting at particle interfaces, only those with electrical and gravitational origins are relevant in powder adhesion (Staniforth 1980a).

A method was developed by Krupp (1967) to determine the forces of adhesion of fine spherical particles to plane metal substrates. Krupp mounted a metal substrate, e.g. a gold or silver plate, covered in adherent fine metal spheres, vertically in a modified ultracentrifuge rotor tube. After rotation in an ultracentrifuge the number of metal spheres removed from the metal substrate was counted through a window in the cell, using a microscope.

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METHOD

Salicylic acid was selected for evaluation as a model drug with a mean particle radius of 2·5μm (micronized by West Australian Institute of Technology, Department of Pharmacy). An ordered mix of 1% salicylic acid was made with each of four excipient powders: sucrose (CSR, Victoria, Australia): a direct compacting sugar, Dipac (Amstar Corporation, New York, U.S.A.): a spray-crystallized maltose-dextrose, Emdex (Edward Mendell Inc., New York, U.S.A.) and recrystallized lactose (Staniforth 1980b). Approximately 100 g of each powder mix was shaken manually in a dry glass bottle to produce an ordered mix, indicated by uniform coverage of the excipient powder surface with fine drug particles. The sucrose consisted of crystals with a particle size range of 420–625 μm, which was slightly coarser than most of the other excipients tested.

Fig. 1 shows the measurement cell used. The sample of ordered mix was placed in the holder hemisphere of the split sphere and the screen was inserted over the powder (Fig. 1a). The collector

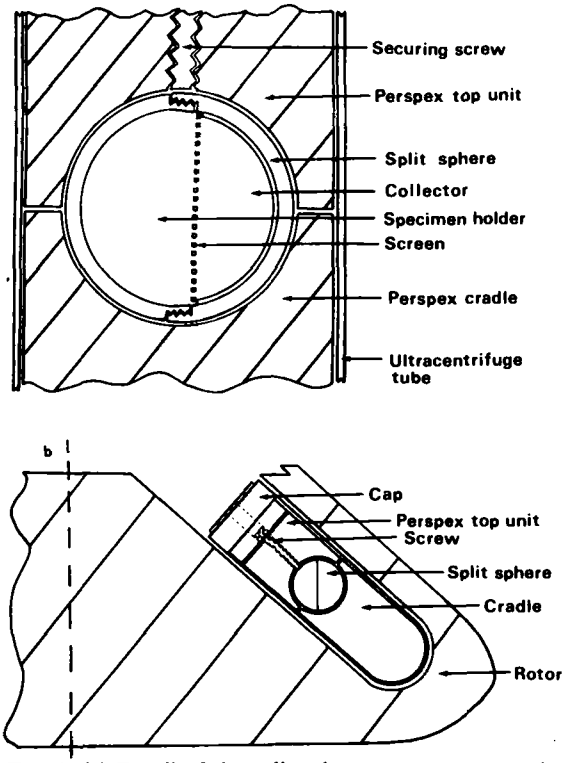

FIG. 1. (a) Detail of the split sphere arrangement used to hold powder samples in the ultracentrifuge rotor.
(b) Diagram showing location of the specially-modified ultracentrifuge tube in the ultracentrifuge rotor assembly.

hemisphere was then screwed onto the holder hemisphere. The split-sphere was orientated so that the screen was normal to the axis of rotation of the ultracentrifuge rotor (Beckman model 40·2) shown in Fig. 1(b). During ultracentrifugation (Model L2-65B, Beckman Instruments California, U.S.A.) the sample was forced against the 50 μm wire mesh screen which was fine enough to retain the smallest ordered units but coarse enough for fine drug particles removed from carrier particles to pass into the collector hemisphere. The rotor was maintained at the desired run speed for 1 min. This was found by experiment to be adequate to allow all dislodged fine particles to travel through the sieve mesh.

Following ultracentrifugation, the assembly was dismantled without disturbing the split sphere. The specimen holder with screen was then unscrewed and the collector hemisphere was washed out into a volumetric flask using an aqueous solution containing 50% absolute ethanol to dissolve any salicylic acid particles dislodged from the carrier particles. To analyse the minute quantities of salicylic acid, a high resolution ultraviolet spectrophotometer (Cary 118, U.S.A.) was used at a wavelength of 300 nm. For each experiment a sample of approximately 12 mg of ordered mix was placed in the specimen holder; this was the largest quantity suitable for use without causing blocking of the sieve mesh or prolonging the time taken for dislodged particles to travel through the screen.

Each powder sample was studied at ultracentrifuge rotor speeds of 2500; 5000; 10 000; 15 000; 20 000; 25 000 and 30 000 rev min^{-1}. The rotor speeds correspond to calculated separation forces acting on the samples as listed in Table 1.

Table 1. Relation between rotor speeds and the forces acting on ordered units in the specimen cell.

Rotor speed (rev min^{-1})	Relative centrifugal force (R.C.F.)(g)	Effective separation force (N)
2500	365·4	0·36
5000	1461·6	1·43
10 000	5846·4	57·29
15 000	13154·4	128·91
20 000	23385·6	229·18
25 000	36540·0	358·09
30 000	52416·4	513·68

In terms of earth's gravity, the relative centrifugal force (R.C.F.) or number of times gravity acting on the ordered units was calculated from the equation

$$\text{R.C.F.} = \omega^2 \cdot r/980 \quad .. \quad .. \quad .. \quad (1)$$

where ω was the angular velocity given by:

$$\omega = (\pi/30) \times \text{rotor speed (rev min}^{-1}) \quad .. \quad (2)$$

and r was the distance of the ordered unit from the rotational axis.

With increasing rotation speeds the increasing forces acting on ordered units separated different numbers of drug particles according to the excipient under test. The adhesion forces which must have existed between the drug and carrier particles to resist separation from ordered units under the influence of ultracentrifugation were calculated from the following expression of St. John (1969):

$$F_{adhesion} = M_o \omega^2 r \quad .. \quad .. \quad .. \quad (3)$$

where $F_{adhesion}$ is the force of adhesion between adherent drug particles and excipient carrier particles; M_o, the mass of adherent particle; ω, the angular velocity and r the distance of the ordered units from the axis of rotation.

RESULTS AND DISCUSSION

The adhesion profile for an ordered mix of sucrose with 1% salicylic acid (Fig. 2) shows the quantity of

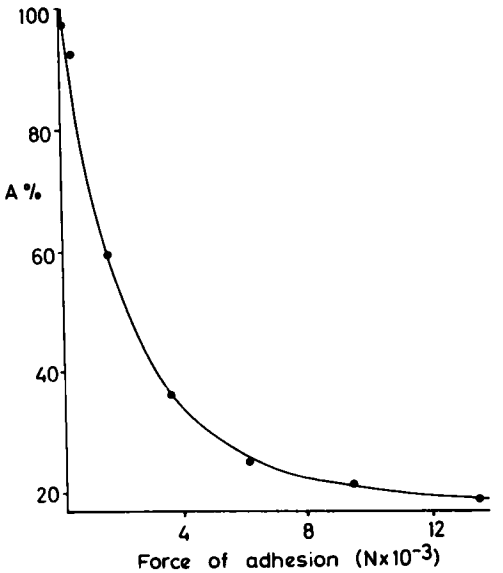

FIG. 2. Force of adhesion of 1% salicylic acid particles, 5 μm diameter, to coarse sucrose particles, 420–625 μm size fraction, measured using the ultracentrifuge apparatus. A = cumulative percentage of drug particles adhering to carrier particle surface.

drug particles which adhered to the sucrose carrier particles with a specific force of adhesion. The median adhesion force at which 50% of drug particles are bound to the excipient surface and the amount of drug still adhering to ordered units with forces exceeding $1{\cdot}36 \times 10^{-3}$N are shown in Table 2.

Table 2. Adhesion properties of different ordered mixes.

Ordered Mix	Median adhesion force ($N \times 10^{-3}$)	Percent fine particles adhering with forces greater than $1{\cdot}36 \times 10^{-3}$ N
1% Salicylic acid/Sucrose	2	18
1% Salicylic acid/Lactose	2·3	18
1% Salicylic acid/Dipac	6·5	24
1% Salicylic acid/Emdex	>13·6	61
2% Salicylic acid/Sucrose	7·7	29
2% Salicylic acid/Lactose	7·8	27
2% Salicylic acid/Dipac	5·3	22
2% Salicylic acid/Emdex	8·5	41
5% Salicylic acid/Lactose	2	06
5% Salicylic acid/Dipac	6·4	24
5% Salicylic acid/Emdex	8·5	44

The adhesion profile for recrystallized lactose (Fig. 3) was similar to that for sucrose, the adhesion properties listed in Table 2 were also comparable.

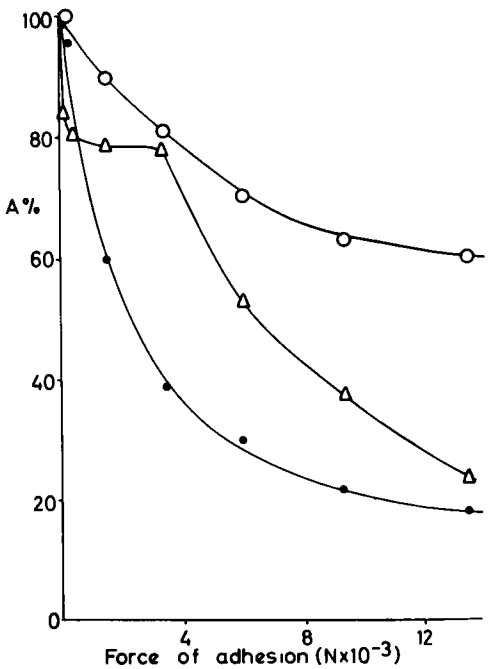

FIG. 3. Force of adhesion of 1% salicylic acid particles, 5 μm diameter, to different excipient particles. A = cumulative percentage of drug particles adhering to carrier particles. △ Dipac. ○ Emdex. ● Lactose.

Fig. 3 shows the adhesion profiles for 1% salicylic acid with Emdex and Dipac. Emdex and salicylic acid particles had an unmeasurably large median adhesion force and even at the maximum measurable adhesion force, 61% of the drug particles were still adhered to Emdex carrier particles (Table 2). The adhesion profile for Dipac differed from that of sucrose, recrystallized lactose and Emdex (Fig. 4). For Dipac the profile consisted of a curve with an initial parabolic section at low adhesion forces and a second curve which suggested an asymptotic approach to zero drug content. The salicylic acid particles on Dipac had a reasonably high median adhesion force (Table 2). The first section of the adhesion profile represents an initial rapid loss of drug particles from ordered units; about 20% of the salicylic acid was separated from the carrier particles by forces of less than 1·5 N corresponding to adhesion forces of less than $3{\cdot}8 \times 10^{-4}$N. At this separation force, Dipac had a much smaller proportion of adherent drug particles than the other ordered mixes containing 1% drug (Table 3).

Of the four different carrier powders, Emdex appeared to form the most stable ordered mixes with 1% drug and most of the ordered units were bound by strong adhesion forces. Since only 39%

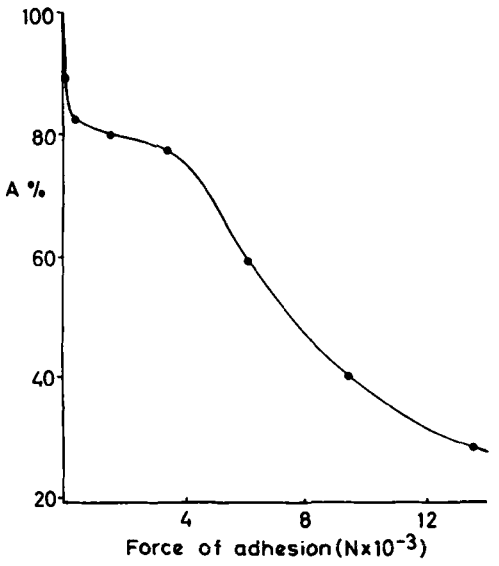

FIG. 4. Force of adhesion of 2% salicylic acid particles, 5 μm diameter, to sucrose particles, 420–625 μm size fraction, measured using the ultracentrifuge apparatus. A = cumulative percentage of drug particles adhering to carrier particle surface.

Table 3. Percentage of fine drug particles adhering to different ordered mixes with forces less than $3{\cdot}8 \times 10^{-4}$ N.

Ordered mix	Percentage drug adhered
1% drug/Sucrose	93
1% drug/Lactose	96
1% drug/Dipac	80
1% drug/Emdex	98
2% drug/Sucrose	82
2% drug/Lactose	95
2% drug/Dipac	76
2% drug/Emdex	92
5% drug/Lactose	81
5% drug/Dipac	74
5% drug/Emdex	78

of the drug on the Emdex carrier particles adhered with forces of less than $1{\cdot}36 \times 10^{-3}$N, large-scale constituent segregation of this ordered system would be most unlikely even at very high separation forces such as those applied by intense vibration. However, the large proportion of weakly-bound drug particles present in 1% salicylic acid/Dipac ordered mixes (Table 2) would be free to move through the powder bed. This large fraction of weakly held drug particles may be responsible for the marked constituent segregation in ordered mixes based on Dipac when subjected to various vibration conditions (Staniforth et al 1980a). The ordered mixes formed between 1% salicylic acid and carrier particles of either sucrose or recrystallized lactose appear to show an intermediate stability at low separation forces, compared with the tightly bound Emdex units and the Dipac units which contained a considerable number of weakly-bound drug particles.

To examine the effect of drug concentration on adhesion forces, ordered mixes containing 2% salicylic acid were made with sucrose, Emdex, recrystallized lactose and Dipac, and mixes containing 5% salicylic acid were made with Emdex, recrystallized lactose and Dipac. Each ordered mix was subjected to separation forces ranging from 0·36 N at 2500 rev min^{-1} to 513·68 N at 30 000 rev min^{-1}.

In several of the ordered mixes containing 2% drug, the adhesion profiles changed compared with those containing only 1% drug. The adhesion profile for sucrose carrier particles with 2% drug (Fig. 4) was similar to that for Dipac with 1% drug (Fig. 3). The first steep section of the curve corresponded to the loss of large quantities of weakly-bound drug particles from the surface of the sucrose carrier particles (Table 3). The second section of the curve was less steep than the corresponding profile in Fig. 2 for the same system containing 1% salicylic acid.

As with the sucrose/salicylic acid system, the ordered mixes of Emdex with 2% salicylic acid also contained a large amount of weakly bound fine particles dislodged from the carrier particles by very low separation forces (Fig. 5). The proportion of

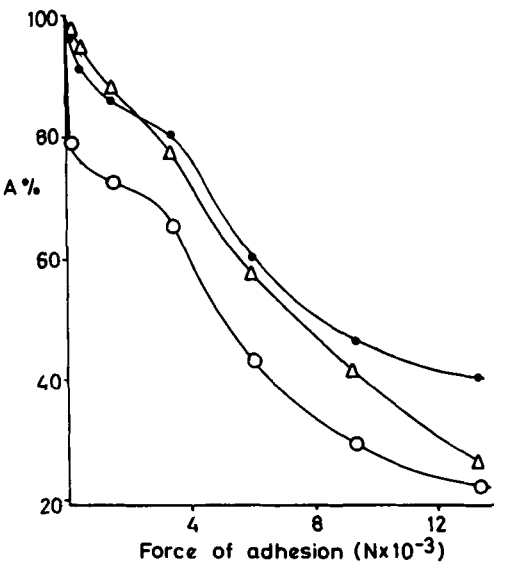

FIG. 5. Force of adhesion of 2% salicylic acid particles, 5 μm diameter, to different excipient particles. A = cumulative percentage of drug particles adhering to carrier particle surface. ● Emdex. ○ Dipac. △ Lactose.

weakly bound drug in the 2% ordered mix was much larger than for the 1% mix (Table 3), and there was a decrease in the median adhesion force (Table 2).

The increase in drug content to 2% in mixes containing Dipac caused a larger percentage of fine drug particles to be lost from the carrier particles at low applied separation forces (Table 3). As with 2% drug/Emdex, the Dipac mixes showed a decrease in the median adhesion force and a decrease in the proportion of drug adhering to carrier particles with forces greater than $1{\cdot}36 \times 10^{-3}$N (Table 2); this effect was less marked with Dipac than with Emdex.

Unlike the other ordered mixes with increased drug content described above, the 2% drug/lactose system showed only very slight evidence of a two-phase adhesion profile (Fig. 5). Both the median adhesion forces and the proportion of drug adhering with forces greater than $1{\cdot}36 \times 10^{-3}$N increased (Table 2), though this trend did not continue in ordered mixes of 5% drug/lactose (Fig. 6).

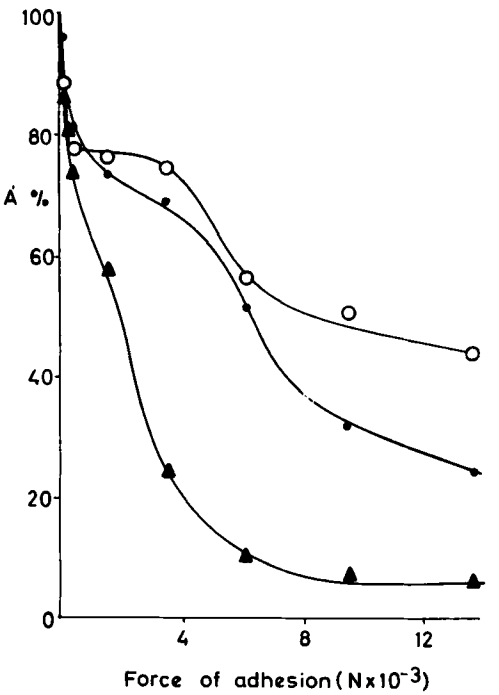

FIG. 6. Force of adhesion of 5% salicylic acid particles, 5 μm diameter, to different excipient particles. A = cumulative percentage of drug particles adhering to carrier particle surface. ○ Emdex + 5% salicylic acid mix. ● Dipac. ▲ Lactose.

In lactose containing 5% drug, approximately 40% of salicylic acid particles were relatively weakly adhered to carrier particles, with forces less than 2×10^{-3}N. This proportion of relatively weakly bound particles was of the same order as that occurring in 1% salicylic acid/lactose mixes. However, in 5% drug/lactose mixes, the carrier particles appeared to lose larger quantities of drug than might have been expected at separation forces greater than 57N. In fact, this massive and rapid decrease in salicylic acid content was not solely caused by separation from lactose carrier particles. It was caused by the fragile nature of the lactose spherulites which led to fragmentation of the coarse carrier particles at applied forces above 57N. The break-up of the lactose particles probably allowed individual dendrites to pass through the sieve mesh still carrying their adhering drug particles.

The other two excipients, Emdex and Dipac, that were used to form ordered mixes with 5% salicylic acid (Fig. 6) showed an even greater tendency than mixes containing less drug to lose large numbers of fine particles at low applied separation forces (Table 3). Associated with this loss of a large amount of loosely bound drug, there was a lag period following the initial decrease. The extent of this lag period varied, but there was relatively little further loss of drug from the carrier particles until the end of the lag period, despite a continuous increase in the applied force.

The length of the lag period appeared to be related to the slope of the second phase of the curve and the lag nearly always ended at an adhesion force of approximately 4×10^{-3}N. Extrapolation of the second curve back along the same slope crossed the y-axis approximately at a point near to A = 100%. This projected curve is represented by slope (a) in Fig. 7 which shows the lag section of the 2% drug/sucrose adhesion profile as a dotted line. Extrapolation of the initial steep curve, before the start of the lag period, to higher adhesion forces showed that a much weaker adhesion profile would be predicted from the behaviour of the 2% salicylic/sucrose system at low separation forces (curve (b), Fig. 7). The various ordered mixes which displayed a composite adhesion profile with a lag section shown by the dotted line in Fig. 7 appear to contain two types of particle arrangement—in one case the adhesion forces are high and in the other adhesion forces are lower. Slope (a) in Fig. 7 represents a curve which might be obtained for a stable ordered mix such as 1% salicylic acid/Emdex (Fig. 1). Conversely slope (b) appears to relate to a mix in which the interactive forces between the two sets of powders are either very weak or completely absent. Such a powder system would have a high proportion of particles

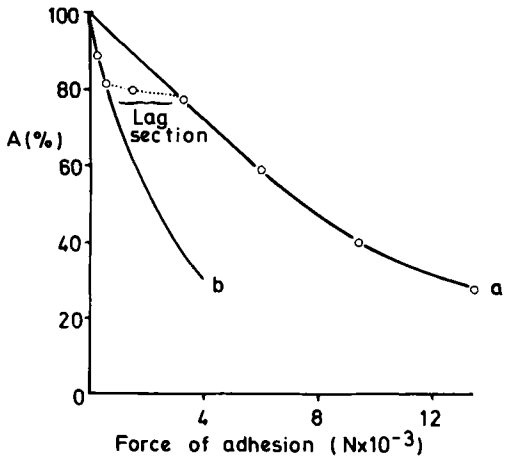

FIG. 7. Diagram showing composite nature of adhesion curve. Curve a, the second part of the adhesion profile extrapolated back to A = 100%, and b the initial part of the profile extrapolated to show the probable low adhesion forces of particles following this curve. Curves a & b are linked by the 'lag section'. A = cumulative percentage of drug particles adhering to carrier particles.

capable of mixing randomly. The lag period shown in Fig. 7 links curves (a) and (b) and appears to form a transition between the very weakly interacting powders of curve (b) in which random mixing could predominate and the more strongly bound particles of curve (a) characteristic of a stable ordered mix. Considered as a whole, the composite curve in Fig. 7 may represent a system previously described as partially ordered random by Hersey et al (1979), which forms one of several links between ordered and random mixes known collectively as total mixes (Staniforth 1981).

An expression relating the theoretical force of adhesion, F^p, between two sets of particles was developed by Krupp (1967):

$$F^p = \hbar\omega^2/64.\pi^3.z_0^5 \,.\, H(t) \quad .. \quad .. \quad (4)$$

where Krupp's estimate of the cohesive van der Waals constant $\hbar\omega$ was taken as 2eV; Z_0 was the distance of maximum force of adhesion (adhesional distance) assumed by Krupp to be 4×10^{-10}m, and H(t), the hardness of the carrier particles estimated to be less than 10^3N cm^{-2}.

From these values, the estimated theoretical median adhesion forces binding ordered units of the model drug, salicylic acid and excipient carrier particles was approximately 2×10^{-3}N. The experimentally determined median adhesion forces for salicylic acid and sucrose particles were of the same order as the predicted theoretical adhesion force (Fig. 2, Table 2). However, the rougher surfaces of Emdex, recrystallized lactose and Dipac (Staniforth 1980a) had larger median adhesion forces than the theoretically estimated value; this was considered due to the adhesional force being strengthened by a static adhesive couple associated with excipient particles having surface pores (Staniforth 1980a).

Conclusions

The ultracentrifuge method described here is useful for monitoring the adhesion in ordered mixes of drug and excipients. Adhesion profiles were obtained by plotting force of adhesion, between drug and excipient particles, against the cumulative percentage of drug particles adhering to the carrier particle surface. From the adhesion profiles the median adhesion forces and the percentage of fine particles adhering with specific forces can be estimated, which allows the stability and handling properties of an ordered mix to be predicted. Under certain conditions a composite adhesion profile is obtained for an ordered mix. This is apparently related to two types of particle arrangement existing in the same powder system, known as a partially ordered random mix, and occurs when disproportionately large numbers of drug particles are weakly bound to carrier particles.

For an ordered mix of sucrose particles and salicylic acid, the median adhesion forces obtained from theoretical calculation agreed well with the values obtained experimentally. The deviation from theoretical values for median adhesion force in ordered mixes containing the rougher, more porous particles of Dipac, Emdex and recrystallized lactose was attributed to an increased static adhesive couple caused by improved interparticle contact.

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