J. Pharm. Pharmacol. 1982, 34: 141–145
Received August 6, 1981

0022–3573/82/030141–05 $02.50/0

Interparticle forces in binary and ternary ordered powder mixes

J. N. STANIFORTH†*, J. E. REES†, F. K. LAI** AND THE LATE J. A. HERSEY‡

† *School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, U.K.,* ** *Department of Industrial Pharmacy, Purdue University, W. Lafayette, Indiana, U.S.A.,* ‡ *Institute of Drug Technology, 381 Royal Parade, Parkville, Victoria, Australia 3052*

An ultracentrifuge technique, previously described by Staniforth et al (1981), has been used to study the adhesion profiles of several binary and ternary ordered powder mixes of pharmaceutical interest. The adhesion profile of an ordered mix provides information about the proportion of drug powder adhering with different forces of attraction to the carrier excipient particle surface. The excipient particle size is shown to affect adhesion between the components of a binary ordered mix-recrystallized lactose formed more stable ordered mixes with drug powder when the carrier particle size was increased. Changes in the adhesion profile of each binary system on adding three different fine-powder excipients to form a ternary ordered mix are also examined. The physical properties of carrier particles and the charge interactions of a third powder component with previously formed binary ordered mixes, are found to influence the physical stability of ternary ordered mixes.

MATERIALS AND METHODS

A model drug, salicylic acid (SA), with a mean particle diameter of 5 μm (micronized by the Department of Pharmacy, West Australian Institute of Technology) was used in a concentration of 1% to form ordered mixes with two separate fractions of recrystallized lactose (Staniforth 1980a) having a particle size range of 250–500 and 500–710μm. Ordered mixes were produced by manually shaking approximately 100 g of the powders in a dry glass bottle until the carrier excipient particles were found to have a uniform coating of model drug powder on close surface inspection.

Ordered mixes containing 1% SA were also prepared using sucrose (CSR, Victoria, Australia), as a carrier of size range 420–625 μm. Various excipient powders were then added to these previously-formed ordered mixes so as to produce ternary mixes. The 'minor' components used to form ternary mixes were all fine powders, apparently capable of binding to the sucrose and lactose carrier particles to form ordered units composed of the three constituent powders. The excipients used individually as minor components were: 0·5, 1·0, 2·0 and 4·0% magnesium stearate—a tablet lubricant; 2% talc—a glidant; 2% maize starch—a disintegrant.

Interparticle adhesion forces were measured using the ultracentrifuge method described by Staniforth et al (1981). A specially-constructed insert was used to hold samples of each ordered mix in the rotor tube of an ultracentrifuge which was spun at different velocities (Model L2-65B, Beckman Instruments, California, U.S.A.). The quantity of adherent salicylic acid particles which became dislodged at each stage of the experiment was measured by u.v.-spectrophotometry (Cary 118, U.S.A.) at 300 nm as described previously (Staniforth et al 1981).

* Correspondence.

RESULTS AND DISCUSSION

The effect of carrier particle size on the adhesion force between drug and excipient was studied (Fig. 1) using two size fractions, 250–500 μm and 500–710 μm of recrystallized lactose. Interparticle adhesion forces were much higher in ordered mixes based on the larger carrier particles (Table 1).

Table 1. Interparticle adhesion data for ordered mixes containing two size fractions of recrystallized lactose.

Size fraction (sieve diam. μm)	Mean adhesion force N	Percent fine particles adhering with forces less than $3{\cdot}8 \times 10^{-4}$N	Percent fine particles adhering with forces greater than $1{\cdot}36 \times 10^{-2}$N
250–500	$2{\cdot}3 \times 10^{-3}$	8	18
500–710	$10{\cdot}6 \times 10^{-3}$	4	42

The difference between the forces of adhesion in ordered mixes based on coarse and fine lactose carrier particles was not predicted from calculations of the theoretical number of adherence sites since both sizes of carrier particles are stereometrically capable of binding all the fine-particle drug fraction. The results obtained in practice suggest that the number of 'active' adherence sites is only a small fraction of the total number of theoretical adherence

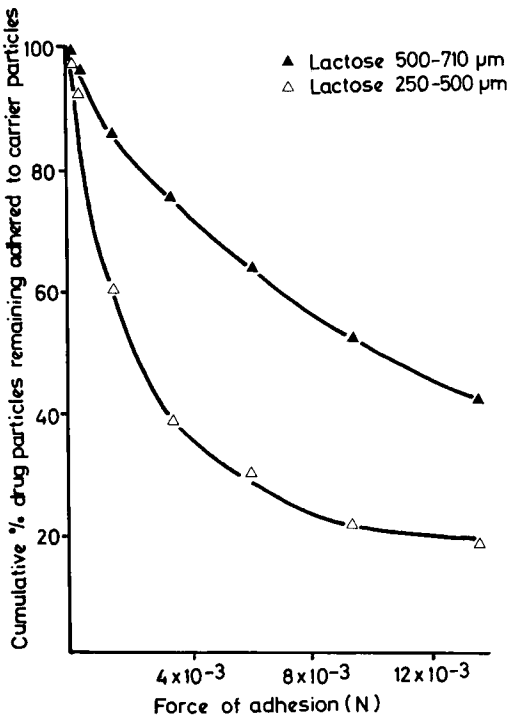
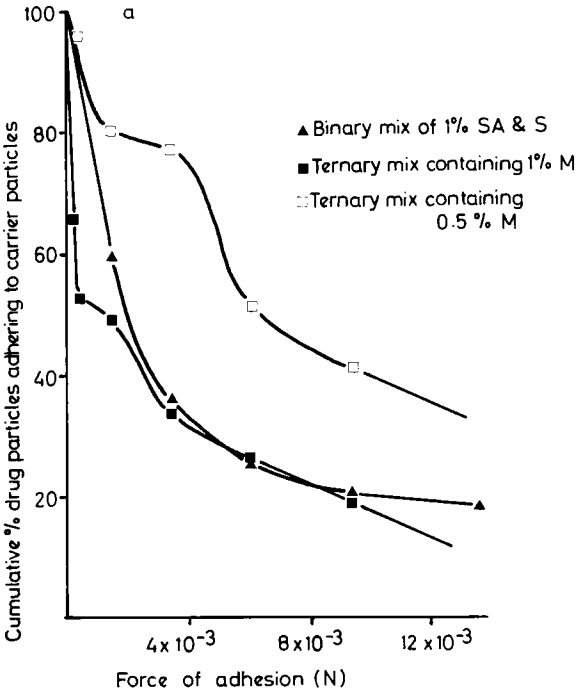


FIG. 1. The effect of carrier particle size on the adhesion profile of 1% SA particles, 5 μm diam. adhering to recrystallized lactose.

sites represented by a close-packed hexagonal monolayer of fine particles adhering to the carrier particle surface.

Compared with the small size-fraction of carrier particles, the coarser carrier particles apparently had a greater number of 'active' sites which were capable of binding the adherent particles more strongly. Certainly, the larger particles of recrystallized lactose had more surface discontinuities, shown by increased surface roughness and a larger number of asperities and large pores; these discontinuities could modify the charge distribution on the particles and would probably increase the interparticle adhesion forces within each ordered unit. Fine drug particles, attracted to the surface discontinuities on the larger lactose particles by the high localized electrical charge, would also be more protected against external applied separation forces; the larger surface asperities and walls of pores act as physical barriers preventing fine particles from being rolled, slid or pulled off the carrier particle surface by interparticle collisions and other effects. Adhesional forces generally have one component acting normal to the substrate surface and also a tangential component due to electrical inhomogeneities around surface discontinuities. An adhesive couple is produced when particles located in clefts make contact with more than one point on the carrier particle surface (St. John 1969). Adhesional forces and couples are highest when the particles are in a static position on the carrier surface, as occurs when they become lodged in grooves or pores. In contrast, under dynamic conditions, for example when particles are rolling on a plane surface, interparticle adhesion forces are lower. The fact that carrier particles with a sufficiently porous surface can entrap fine drug particles would therefore explain the greater adhesional force in ordered units based on coarse recrystallized lactose particles (Fig. 1).

The powders used as third components to form ternary systems with SA and sucrose were selected in view of their possible practical applications as excipients in pharmaceutical tableting systems. Most of the adhesion profiles observed for the ternary mixes containing magnesium stearate were composites of two separate curves; this type of profile has been discussed elsewhere by Staniforth et al (1981). Ternary mixes containing 0·5% magnesium stearate lost 20% of the drug particles at applied separation forces less than 57N, equivalent to adhesion forces less than $15{\cdot}1 \times 10^{-4}$N (Fig. 2). Raising the lubricant concentration increased the proportion of weakly-adhering drug particles in mixes containing 1% magnesium stearate with 1, 2 and 4% SA (Fig. 2 and Table 2). At a concentration of 0·5% lubricant the ternary mix appears to be more stable than the binary mix containing SA and sugar (Fig. 2a). This effect may be due to the low concentration of stearate which was able to bind to the sugar carrier without dislodging large quantities of SA and preventing their subsequent separation. Although an increase in stearate concentration above 0·5% produced an increased proportion of weakly-bound drug particles dislodged from the carrier, above an adhesion force of approximately 2×10^{-3}N the proportion of drug particles dislodged also increased (Fig. 2). According to the segregation mechanism called by Lai & Hersey (1979) 'stripping', magnesium stearate particles displace fine SA particles from their binding sites on the coarse carrier particles. Our results indicate that this effect of magnesium stearate may result from alteration of charge interactions on the surface of sucrose carrier particles (Staniforth & Rees 1982). Magnesium stearate was found to carry a positive electrostatic charge whereas SA and sucrose particles were negatively charged. Thus when added to the binary system, stearate particles are attracted to the active



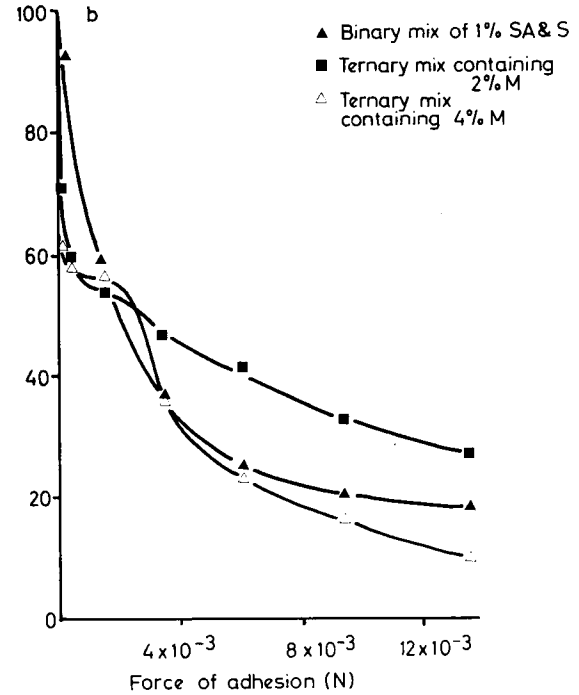


FIG. 2. The effect of magnesium stearate on the adhesion profile of 1% SA particles 5 μm diameter, to sucrose carrier particles.

adherence sites on the carrier surface and thereby tend to displace adhering SA particles; an increase in stearate concentration would then increase the number of displaced SA particles. Additionally, displaced SA particles would be attracted to free particles of the lubricant which limits their tendency to separate through the interparticle voids of the carrier system.

Table 2. Effect of magnesium stearate on interparticle adhesion forces in ternary ordered mixes containing 1% SA fine powder on starch carrier particles.

Magnesium stearate concn	Median adhesion force (N)	Percentage SA adhering with forces:	
		$<3{\cdot}8 \times 10^{-4}$N	$>1{\cdot}36 \times 10^{-2}$N
0·5%	620	3	5
1·0%	130	47	10
2·0%	270	42	28
4·0%	270	43	10

Starch and talc were also evaluated as ternary components added to the SA-sugar system at a concentration of 2%. As with magnesium stearate, the drug adhesion profile of the ternary mix containing maize starch (Fig. 3) was a composite of two distinct curves. The median adhesion force, and the amount of drug adhering to sucrose with high adhesion forces were both increased by adding 2% starch.

The initial displacement of SA with forces less than approximately 2×10^{-5}N was decreased from 15 to 8% in the equivalent starch-free mixes (Fig. 3). The changes in the adhesion profile of SA sugar mixes by addition of maize starch are again probably linked with an alteration of the charge interactions on ordered units caused by addition of a third component powder. When contacted with a glass surface it has been shown that maize starch charges electropositively (Staniforth & Rees 1982). As with magnesium stearate, starch powder may cause stripping of some SA particles from the starch carrier surface and will also be attracted to any dislodged SA particles.

The drug adhesion profile in ordered mixes containing 2% talc as third component differed from those produced by addition of either stearate or maize starch (Fig. 3). The talc produced a simple single-curve profile which showed that the proportion of drug displaced from ordered units was markedly reduced and the interparticle adhesion forces were generally increased (Fig. 3). Only 20% of the total drug content was removed from carrier particles at the maximum applied separation force of

358 N compared with over 80% from the talc-free binary system under the same conditions. The marked stabilizing effect of talc in ordered mixes of SA and sucrose may result from a modification of the electrostatic charge interactions between the three components in addition to the behaviour of talc in filling interparticle void spaces thereby reducing the separation of any dislodged fine particles. Unlike the other two added components, magnesium stearate and maize starch, talc carries an electronegative surface charge (Staniforth & Rees 1982) and would therefore not be attracted by the SA-sugar ordered unit. The additional stability produced by stearate at a concentration of 0·5% and starch and talc is probably a function of charge interactions and the ability of the fine powders to fill interparticle void spaces thus reducing the extent of any separation of SA produced by ultracentrifugation. The effect of charge on the stability of ordered mixes is especially important when considering the choice of equipment used in producing a powder mix. The charge magnitude and charge sign can both be altered by changing the material of which the mixer is constructed (Staniforth 1980), thus starch can be charged either positively or negatively on glass or metal surfaces. This type of change in charge could produce marked changes in surface interactions between component powders and could alter the stability of a powder mix. It is therefore important to assess the stability of ordered mixes in equipment constructed of the same material as that to be used during the actual processing of the powders.

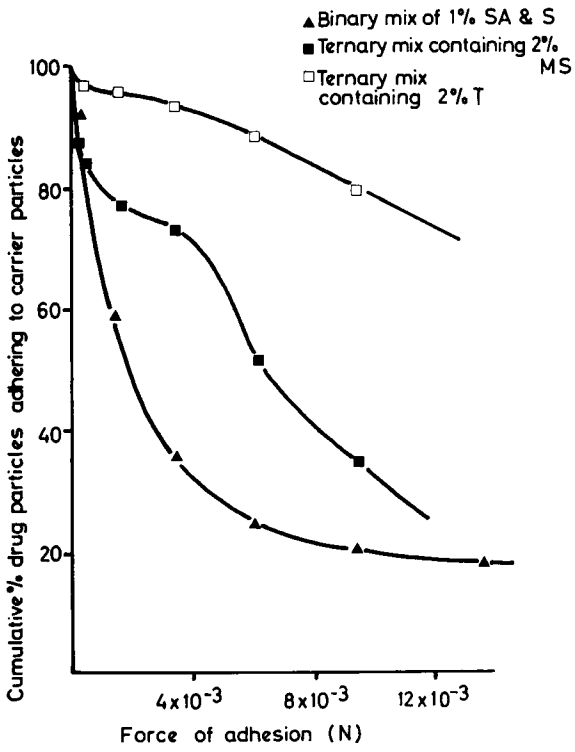


FIG. 3. The effect of adding starch and talc on the adhesion profile of 1% SA particles to sucrose carrier particles.

Conclusions

The ultracentrifuge method provides a technique which is useful for assessing the interparticle adhesion characteristics in binary and ternary ordered mixes of drugs and excipients.

The adhesion profiles showed that large particles of recrystallized lactose (500–710 μm) with a more porous surface structure formed stronger adhesive bonds with fine drug particles than did the smaller particle size fraction of the same carrier. The number of strong adherence sites was apparently related to the surface porosity and roughness of the carrier particles.

Composite adhesion profiles (Staniforth et al 1981) were obtained for ternary powder mixes containing magnesium stearate; these are generally characteristic of unstable ordered mixes. As more magnesium stearate was added the proportion of weakly bound drug particles was found to increase. Starch powder also produced a composite adhesion profile although some stabilization of the SA-sugar ordered mix was noticed. Talc produced a stable ternary ordered mix with SA and sugar apparently linked to its electrostatic properties and its capacity to fill interparticle void spaces.

The different adhesion profiles for binary and ternary systems containing salicylic acid and sucrose with and without a third component indicate the need to be aware of possible effects of added excipients on the segregation tendency of completed formulations.

One or more excipients in a formulation may cause stripping of drug from carrier particles; if so, it may be possible to alter one component to achieve an optimum adhesion profile.

Alternatively, appropriate charging of excipients may be feasible (Staniforth & Rees 1982) to prevent segregation and/or stripping in order to maintain adequate homogeneity of individual drug formulations.

Acknowledgements

J. N. S. wishes to express his thanks to the Winston Churchill Memorial Trust for the award of a Travelling Fellowship which enabled this work to be carried out at the Victorian College of Pharmacy, Melbourne, Australia.

REFERENCES

Lai, F. K., Hersey, J. A. (1979) J. Pharm. Pharmacol. 31: 800

Staniforth, J. N. (1980a) U.K. Patent No. 8018575

Staniforth, J. N. (1980b) Ph.D Thesis, University of Aston, Birmingham, U.K.

Staniforth, J. N., Rees, J. E. (1982) J. Pharm. Pharmacol. 34: 69–76

Staniforth, J. N., Rees, J. E., Lai, F. K., Hersey, J. A. (1981) Ibid. 33: 485–490

St. John, D. F. (1969) Ph.D. Thesis, Michigan State University, U.S.A.

This text is dedicated to the memory of Professor John Hersey, an honoured friend and respected colleague, who died on February 14, 1982.