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The effect of particle size and concentration on the adhesive characteristics of a model drug-carrier interactive system

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The effect of concentration and particle size on the adhesive tendency of drug particles in a model interactive system was investigated using a centrifuge technique. The model interactive system consisted of drug powders adhered to coated glass carrier beads. Adhesion profiles of per cent of drug remaining on the carrier versus the square of the speed of rotation were a logarithmic normal function. Increase in the adherent particle size and concentration decreased the adhesive tendency of all drug powders studied. Particle collisions during detachment and the formation of multiparticulate layers even before the monolayer saturation of the carrier surface were responsible for the reduced adhesive stability of the drugs on the carrier as the particle loading increased.

Fundamental studies in solid adhesion generally have employed a small number of adherent particles in the preparation of the interactive system since (a) the detached particles, which were estimated by counting methods, were more easily and accurately determined and (b) the tendency of the adhered particles to interact with each other was minimized. The detachment characteristics of particles in such systems can be studied independently of other particles. However, in pharmaceutical interactive mixtures, high drug concentrations are often required in the design of the formulation. In addition, drug materials available from different sources may possess different particle size distributions. Subsequent comminution procedures before manufacture produce powders with particle size distributions that depend on the laboratory of source since different mills or different milling procedures are used (Dobson & Rothwell 1969–70; Prem & Prior 1979).

Drug concentration and particle size distribution of adhered powders have been reported to affect the mechanical stability of interactive mixtures (Travers 1975; Bryan et al 1979; Nystrom & Malmqvist 1980; Malmqvist & Nystrom 1982; Staniforth & Rees 1983). Sieving and segregation tendency tests have been used as indirect methods to measure the mechanical stability of drugs in such mixtures. In the sieving technique, the application of a constant mechanical shock to the mixture allowed the dislodged particles to pass through a screen and the amount of drug retained on the carrier to be determined. In the segregation tests, the degree of segregation is indicated by comparison of the variance of spot samples from the mixture before and after the mixture had been subjected to external vibration forces. In situations where real drug and carrier systems have been used, an understanding of unwanted effects such as carrier friability, interactive unit segregation due to differences in carrier particle size and sampling limitations is necessary. In addition, the real interactive systems which have been used in previous studies possess variables which are difficult to control, i.e. irregular surface characteristics, carrier shape, and particle detachment due to mechanical interlocking.

Recent studies using a centrifuge method have attempted to study the fundamental characteristics of drug adhesion in a model interactive system (Kulvanich & Stewart 1987). This study aims to extend the research to investigate the influence of drug concentration and particle size on the adhesive characteristics of drugs in such a model interactive system using the centrifuge method.

MATERIALS AND METHODS

Materials

Glass beads (500 μm, Selby Scientific, Australia) coated with hydroxypropyl methylcellulose phthlate (HPMCP, Type HP-55, Shin-Etsu Chemical Co., Japan) using an air suspension technique (Uni-Glatt, laboratory unit, Glatt GmbH, FRG; 5% w/v HPMCP in equal volumes of dichloromethane and methanol, 3 L kg^{-1} beads) were used as the carriers. The coated beads were oven-dried at 50 °C for 24 h to

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eliminate residual solvent, then stored over silica gel (r.h. < 10%).

The following drugs (Sigma Chemical Co., USA) were used to form the interactive mixtures: sulphapyridine (fraction 1; d_v = 15·5 μm, σ = 0·9 μm; fraction 2; d_v = 27·2 μm, σ = 1·1 μm), sulphamerazine (fraction 1; d_v = 14·5 μm, σ = 1·2 μm; fraction 2; d_v = 17·7 μm, σ = 1·4 μm), succinylsulphathiazole (d_v = 23·4 μm, σ = 1·6 μm). All drug compounds were also stored under dry conditions over silica gel (r.h. < 10%).

Particle size classification and measurement

The size fractions of drug powder were prepared using the oscillating air column method of sieving (Sonic Sifter, model L3P, ATM Corporation, USA) fitted with micromesh sieves and a horizontal pulse accessory (model L3-NB). The particle size distributions of sulphapyridine, sulphamerazine, and succinylsulphathiazole powders were determined by a laser diffraction technique (Malvern 2600/3600, Malver Instrument, England) using water as the suspending medium.

Preparation of interactive mixture

Carriers and drug powders were equilibrated in an Environmental Chamber (Thermoline Scientific Equipment Pty. Ltd, Australia) at a controlled r.h. 26·0 + 1·0% and temperature of 25·0 ± 0·5 °C for 24 h. The formation of the interactive system was also accomplished in the chamber at the same relative humidity and temperature by blending 3 g of mixture in a glass jar at a rotation speed of 20 rev min^{-1} for 10 min. The glass jar was positioned at an angle of 42 degrees to the vertical to provide optimum blending conditions. The formation of the interactive mixture was verified using a research microscope (Olympus, BH2). Samples of 100 mg were immediately taken for adhesion measurements. The homogeneity of interactive mixes was determined using 15 × 50 mg samples; the coefficient of variation of the sample contents ranged between 1·5 and 3·9% for the mixes studied.

Scanning electron microscopy

Examination of the carrier surface texture and the interactive mixes was by scanning electron photomicroscopy (Phillip, model 505 SEM, England).

Adhesion measurement

A specially designed aluminium centrifuge cell consisting of a sample and collection compartment separated by a replaceable screen (250 μm) was held in position within the centrifuge rotor so that the screen was normal to the axis of rotation (Kulvanich & Stewart 1987). The distance between axis of rotation and screen was 6·7 cm. Adhesion measurements were performed by means of a IEC B-20A high speed refrigerated centrifuge with a fixed rotor, type 870 (Damon/IEC Division, USA) which allowed rotation speed up to 19 000 rev min^{-1}. The temperature in the centrifuge chamber was 20–25 °C. The drug particles removed were collected at the centrifugation speeds of 2000, 5000, 10 000, 15 000 and 19 000 rev min^{-1}. The rotor was accelerated to the desired speed which was maintained for 30 s before deceleration.

Analysis of drug

The amount of drug detached after each consecutive centrifugation step and the drug retained on the carrier were assayed spectrophotometrically. Complete solution of the drug was achieved in HCl (0·1 M), or NaOH (0·01 M) and the absorbance was measured at the wavelength of maximum absorbance using the Pye Unicam PU8600 spectrophotometer (Pye Unicam Ltd., England). Beer's law calibration curves for all the drug materials over the concentration range 0·002 to 0·020 mg mL^{-1} showed no significant deviation from linearity and the drug concentrations were obtained by inverse prediction. The coating material did not interfere with the absorbance measurements during the analysis of the drugs on the carrier.

RESULTS AND DISCUSSION

The adhesion characteristics of several drug powders on the coated glass bead carrier has been investigated using the centrifuge method (Kulvanich & Stewart 1987). The profiles revealed a logarithmic probability distribution when the per cent of drug retained on the carrier was plotted against the square of the speed of detachment. Fig. 1, which shows the logarithmic probability function for the adhesive profiles of different drug concentrations in a sulphapyridine-carrier interactive mixture, is typical of all the sulphapyridine interactive profiles. In addition, sulphamerazine and succinylsulphathiazole at varying concentrations and particle sizes also exhibited log normal adhesion distributions. The conformity of all these powder interactions to a log normal distribution allowed the adhesion to be characterized by two parameters, i.e. the S50 — the speed required to dislodge 50% of the adhered particles, and σ — the geometric standard deviation of the adhesion distribution.

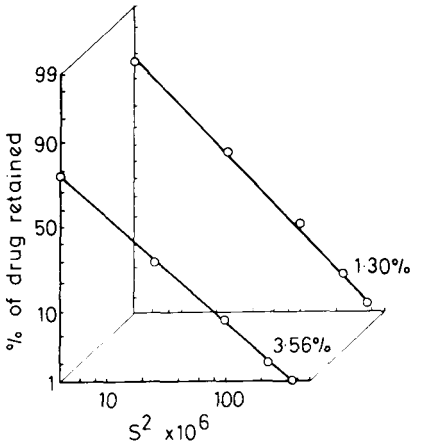

FIG. 1. Logarithmic probability adhesion profiles of percentage of drug retained on carrier against the square of the centrifugation speed for sulphapyridine interactive mixtures.

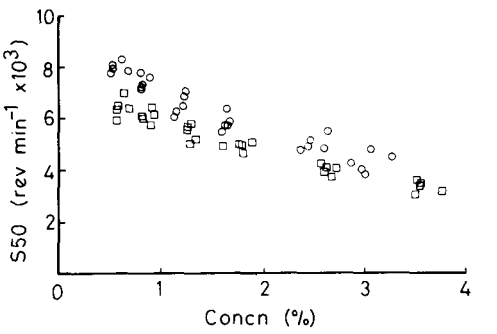

FIG. 2. The effect of particle size and concentration on the adhesive tendency of sulphapyridine interactive mixtures (○ fraction I; □ fraction II).

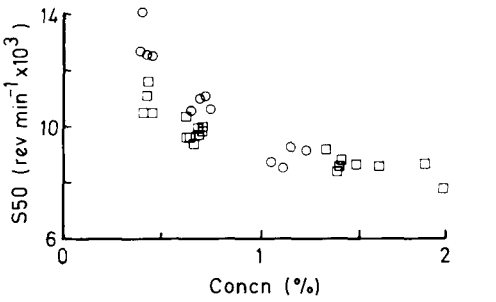

FIG. 3. The effect of particle size and concentration on the adhesive tendency of sulphamerazine interactive mixtures (○ fraction I; □ fraction II).

The S50 determined the degree of adhesion. It was not possible using this method to define an exact adhesion force between the drug and carrier because of the variations in the zenith angle during detachment (St. John & Montgomery 1971) and difficulties in defining the particle sizes of the detached drugs (Kulvanich & Stewart 1987). The variance of the adhesive force (defined by σ) reflected the variation in interfacial geometry, surface roughness, adhesion site, non-homogeneity of the contiguous surfaces, local variation in surface hardness, differences in surface electrical charge and differences in particle size of the adhered drug (Derjaguin & Zimon 1961; Krupp 1967; Loffler 1968; Zimon & Ronginskii 1974).

The effect of particle size on the degree of adhesion is shown in Figs 2, 3. Decreasing particle size increased the degree of adhesion for both sulphapyridine and sulphamerazine.

Previous investigations using different adhesive systems and techniques have revealed varied relationships between particle size and the degree of adhesion. For example, Corn (1961a, b), by a microbalance technique, found a direct relationship between particle sizes and adhesive forces for the interaction between quartz particles and a glass surface; the adhesion forces increased with increasing particle size. This observation was in agreement with the adhesion measurement between small metal spheres dusted onto a plain metal substrate using the centrifuge technique, which also indicated direct relationships between adhesion force and size (St. John & Montgomery 1971). In contrast, the investigation by Derjaguin & Zimon (1961) on the adhesion of spherical glass particles onto a steel surface showed an increase in adhesion force when particle size was reduced. The complete independence of adhesion force and size has been observed by Boehme et al (1962) on the interaction between starch particles and a starch substrate; that study indicated that all sizes of starch particles produced the same adhesion profiles.

In this current study, the adhesion assessment was not expressed directly in terms of adhesion force. However, it was demonstrated that the smaller sized adherents were more resistant to centrifugal accelerations than the larger sizes after the interactive mixes had been prepared under the same condition of blending. A consideration of the equilibrium of interactive and detachment forces at the interactive unit interface shows that the detachment force exerted on small particles of drug would be less than that exerted on the larger particles due to the smaller mass i.e. $F = m(a + g)$. This is consistent with the previous finding that the larger particles are the first to be removed with increasing centrifugal force (Kulvanich & Stewart 1987).

All drug materials under these observations showed a reduction of their adhesion capabilities to the carriers when the amount of drug powder in the mixtures increased (Figs 2–4). Two main factors were considered to be the cause of the decrease in S50: the collision effect (St. John & Montgomery 1971; Laycock & Staniforth 1984) and layer formation.

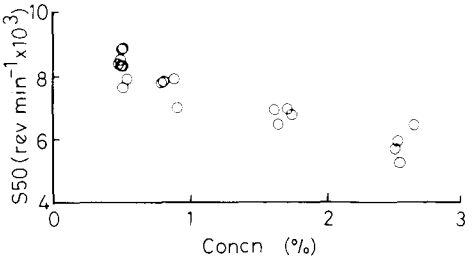

FIG. 4. The effect of particle concentration on the adhesive tendency of succinylsulphathiazole interactive mixtures.

The collision effect could occur by the impingement of detached particles with neighbouring particles which were in the path of the particle leaving the carriers. Such an effect would cause premature dislodgement of other more strongly bound particles. According to the assumptions by St. John & Montgomery (1971), particles might be removed from the substrate by different methods depending on the directions of the forces on the particles. Particles will be directly detached if the forces are applied normal to the surface of the substrate, or they will slide off under application of tangential forces, or will be rolled off by simultaneous shear and tension forces. Because of the geometry of the particle-bead adhesive system employed in this experiment, particles at different locations on the carrier surface will have experienced the centrifugal forces at different angles relative to the substrate surface. This condition promotes the rolling and sliding actions of detached particles leaving the carriers. Consequently, any drug particles being removed by sliding or rolling off the carrier will tend to collide with other particles, resulting in multiple dislodgements of particles. When the amount of drug powder in a mixture increases, decrease in interparticle distance occurs with a greater chance of particle collisions and a further reduction in the S50.

Fig. 5 shows the scanning electron micrographs of interactive mixes containing sulphapyridine powder (fraction II) at various concentrations. The tendency of the adherent drug particles to form particle layers increased with drug concentration. The particle layer formation observed for the higher drug concentrations occurred despite free space still available on the carrier surface.

The theoretical estimation of the maximum sulphapyridine powder concentration (fraction II) that could be adsorbed on the carrier surface was determined assuming that the drug particles formed a close-packed monolayer. The maximum number of drug particles (n) required to saturate a fully packed monolayer can be calculated from the following equation (Jones & Pilpel 1965):

$$n = 2\pi(D + d)^2/\sqrt{3}\,d^2$$

where D and d are diameters of carrier and drug particle, respectively.

The maximum number of particles which could be accommodated on a carrier surface as a monolayer was 1362 corresponding to a powder concentration in the mix of 12·1%. The particle layers therefore were formed well below the saturated concentration. However, for any interactive system the critical concentration of drug at which the powder starts forming particle layers will depend on many factors including the interactive capability between the drug particles and carrier, the cohesiveness of the drug powder, the enhancement of the dispersion of particles on the substrate surface during blending, and the impact induced within the mixture bulk.

The layer formation caused a decreasing tendency of drug particles to adhere, by hindering direct contact with the carrier surface. The binding capability of the outer particle layer relies on the interaction with its own species and might be assisted by long range attractive forces with the carrier. The outer particle layer could therefore form strong autoadhesive bonding but, when the inner particles are dislodged, the whole aggregate would be removed from the carrier. Both collision and layer formation effects could cause reduction in the S50 by initiating the multiple dislodgement of drug particles. However, the collision effect is unlikely to be effective until the number of adherents on the carrier becomes so dense that interparticle distances are equal to the path travelled by removed particles during rolling or sliding before dislodgement. In addition, layer formation effects occurred more frequently with increase in drug concentration.

The effect of powder concentrations on the adhesion tendency has been investigated previously by the sieving technique (Travers 1975) and the segregation tendency test (Bryan et al 1979; Staniforth & Rees 1983; Staniforth et al 1981). These results indicated a decrease in adhesive properties of

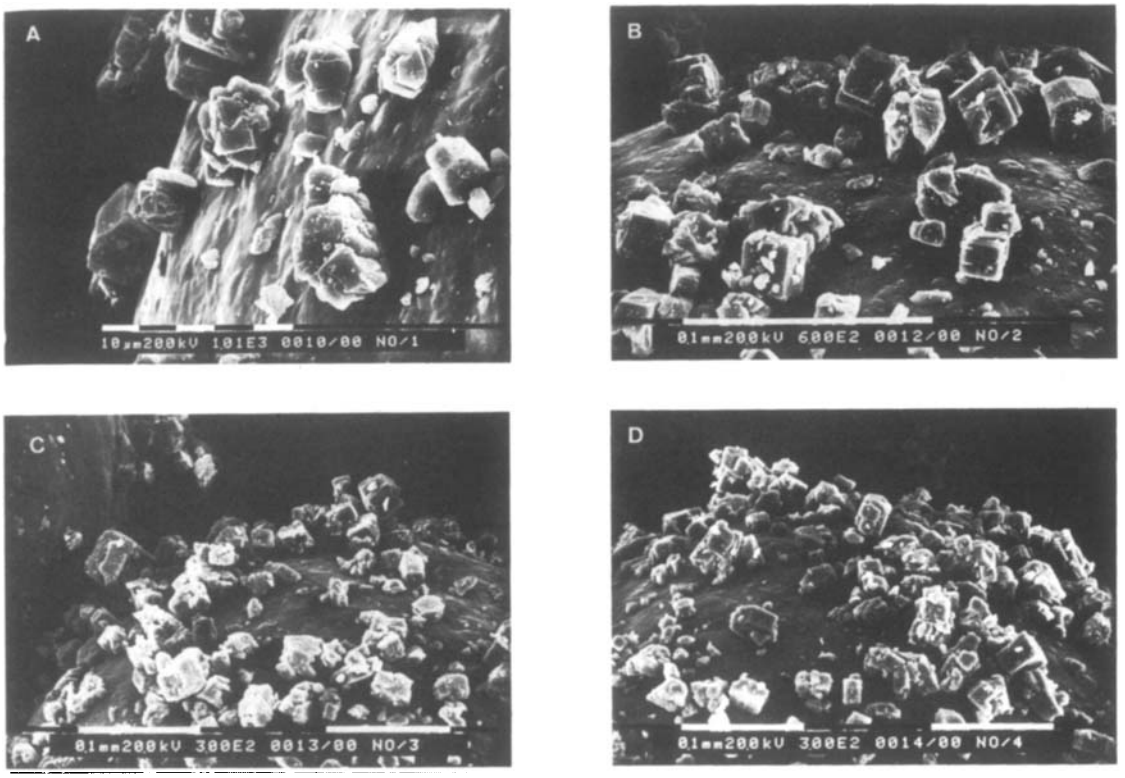

FIG. 5. Scanning electron micrographs of the sulphapyridine interactive mixture (a, 0·9%; b, 1·9%; c, 2·7%; d, 3·1%).

drug powder with increasing powder concentrations. The reduction in adhesion tendency in these studies has been explained by the limitation of active sites on the carrier capable of forming strong bonds with drug particles (Hersey 1975; Staniforth et al 1981). The excess drug particles, therefore, formed weaker associations with the carrier or remained free in the bulk of the mixture.

The other possible drug segregation mechanism that could have occurred in these studies was the multiple detachment of drug particles due to the collision effect and particle layer formation. The surface roughness of pharmaceutical excipient carriers could facilitate the formation of particle layers. Fine powder is likely to fill up the carrier surface irregularities in agglomerates rather than cover the surface in a particulate manner. Although uneven surfaces adsorb more drug powder more strongly than the less irregular carrier surfaces (Staniforth & Rees 1983; Schmidt et al 1984), multiparticle detachment in the form of particle layers or agglomerates might also occur if the binding force between inner particles in contact with the carrier surface is less than the external accelerative forces.

Conclusions

(1) The centrifuge technique has been used to assess the adhesion tendency of drug powders in relation to their concentrations and particle size ranges in a model drug-carrier interactive system. The technique allows the observation of the adhesion properties of drug particles in a narrow range of increasing concentrations. In the experiment described, true interactive units were used; the presence of randomly mixed particles with these interactive units did not occur and thus did not invalidate the determination of the S50. The disadvantage of the model system studied was its inability to investigate high drug concentrations because of the limitations of the adsorptive capability of the carrier.

(2) Increase in particle size and particle concentration decreases the adhesive tendencies of the drug. The detachment of drug particles from carriers could be affected by the detachment characteristics of neighbouring particles. Collision effects and multiparticle detachment in the form of agglomerates occurred with increasing concentration of drug.

(3) Scanning electron microscopy of the interactive units showed the formation of particle layers

even when there was carrier surface available. This observation may support the assumption made by Hersey (1975) that some areas of carrier surface are devoid of binding sites and some sites are stronger than others. We found that the strong active sites were saturated first, the subsequent particles selectively binding with their own species to form particle layers. The calculation of the monolayer concentration of drug particles produced an overestimate of the concentration of particles covering the surface of the carrier. Drug particles were likely to cover the carrier surface in particulate manner only at low concentration of powder.

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