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Fundamental considerations in the measurement of adhesional forces between particles using the centrifuge method

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Summary

The adhesional characteristics of interactive mixtures of HPMCP-coated glass spheres and several powdered drugs were investigated using a specially designed centrifuge cell. The adhesion profile of percent of drug remaining on the carrier versus the square of the speed of rotation was log normally distributed; the degree of adhesion could be characterized by the speed of rotation to detach 50% of the particles (S_{50}) and the standard deviation of the distribution (σ). All the powders tested using this model interactive system possessed log normal adhesion profiles. The system was validated by testing the effect of the interactive mixture loadings and the time of centrifuging at each rotational speed on the adhesion profile. Loads between 60 and 150 mg, and centrifuging times of 30 and 60 s caused no significant change to the S_{50} value obtained for a sulphapyridine interactive mixture.

Introduction

The centrifuge technique has been used for the adhesion measurement of solid particles to substrates. The adhesive system most frequently used was the plane substrate with particles adhering to its surface. Powder dusted onto the substrate interacted by the mutually attractive forces arising between the contiguous bodies. External forces which can cause particle and surface deformation increasing the degree of interaction do not exist in these systems. The particles detached at each consecutive step of centrifugation were determined optically by means of a microscope (Kordecki and Orr, 1960) or photographed prior to and after centrifuging (Boehme et al., 1962). Such techniques have also been applied to pharmaceutical systems to investigate the cohesional and adhesional properties of drug and excipient powders. A microscope glass slide was used as the substrate for the adhesion measurement of powder at elevated temperatures (Otsuka et al., 1983). The plane surface substrate has been replaced by a compressed tablet surface to measure the interactive force between the same or different kinds of pharmaceutical materials (Okada et al., 1969).

Another adhesive system employed with the centrifuging technique was the fibre filament deposited with particles and used to investigate the adhesional characteristics of fibre filters in air filtration processes (Larsen, 1958; Loffler, 1968). The centrifuge method has also been modified to measure the adhesion of particles on bead surfaces

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by using a two-compartment cell separated by a screen (Donald, 1969). The adhesional characteristics of pharmaceutical interactive powder mixtures have been investigated using such a centrifuge method (Staniforth et al., 1981, 1982). However, the complex nature of the system including the excipient surface properties in particular the surface roughness, the irregular carrier shape, and the packing of carrier material impeding the removal of the detached particles during centrifuging has restricted the interpretation of the adhesion profiles obtained. Break down of the carrier materials, observed at high speeds of centrifuging, could bias the determination of the excipient-drug adhesion chracteristics (Lai, 1981). More recently, a thin brass plate with a small diameter hole to contain an interactive unit was developed to examine the adhesion of drug particles (Laycock and Staniforth, 1983, 1984). Flattenning of carriers against the plate substrate during centrifugation was reported causing difficulty in determining the number of adherent particles by photomicroscopy. In addition, a low percentage of particles was removed from the carrier even at high rotor speeds. Thus, representative adhesion profiles were difficult to obtain.

One major limitation of these experimental methods in verifying the adhesional characteristics of pharmaceutical powders has been the difficulty in controlling the variables in the real systems studied. The purpose of this research study therefore was to: (a) design a simplified interactive system that would allow the fundamental adhesional characteristics of pharmaceutical powders to be investigated using the centrifuge method; and (b) investigate the factors influencing the reliability of the adhesional measurements.

The adhesive model was simplified by using non-breakable, polymer-coated glass carrier beads attached with drug particles. Adhesion was measured by a centrifuge technique with a cell previously described (Donald, 1968; Staniforth and Rees, 1981).

Experimental

Apparatus

A specially designed centrifuge cell was constructed from aluminium (Fig. 1). It consisted of a sample and collection compartment separated by a replaceable screen (250 μm). The centrifuge cell was held in position within the centrifuge rotor so that the screen was normal to the axis of rotation. The distance between axis of rotation and screen was 6.7 cm. The use of low density material in the construction and the centrifuge cell design minimized cell weight without derating the speed.

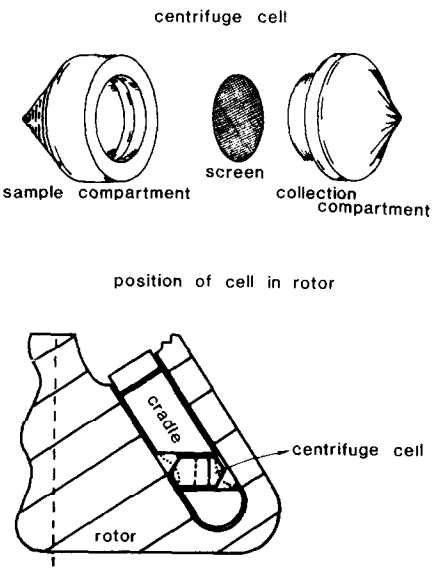

Fig. 1. Design of the centrifuge cell. (Cell length 3.3 cm; external diameter 2.3 cm.)

Materials

Glass beads (500 μm, Selby Scientific, Australia) coated with hydroxypropyl methylcellulose phthalate (HPMCP, Type HP-55, Shin-Etsu Chemical Co., Japan) were used as the carrier material. The coating process was carried out using an air suspension technique (Uni-Glatt; laboratory unit, Glatt GmbH, F.R.G.). The coating solution was 5% w/v HPMCP in equal volumes of dichloromethane and methanol (3 litres/kg beads). Coating conditions were as follows: inlet air temperature 50°C, coating solution application rate 20–30 ml · min^{-1}, and outlet air temperature 25–30°C. The finished coating beads were ovendried at 50°C for 24 h to eliminate residual solvent, then stored over silica gel (R.H. < 10%).

TABLE 1

Physical properties of drug and carrier materials

Materials	Density [a] ($g \cdot cm^{-3}$)	Mean particle size (μm) [b]	S.D. of size distribution
coated beads	2.15	500	–
sulphapyridine fraction I	1.35	15.47	0.89
fraction II		27.21	1.07
sulphamerazine fraction I	1.29	14.54	1.19
fraction II		17.74	1.35
succinylsulphathiazole	1.43	23.43	1.60
phenacetin	1.20	< 45	–
ascorbic acid	1.70	< 45	–

[a] Average of three determinations.
[b] Volume mean diameter.

The following 5 drug compounds were used to form the interactive mixtures: sulphapyridine, sulphamerazine, succinylsulphathiazole (Sigma Chemical Co., U.S.A.), ascorbic acid (David Craig, Australia) and phenacetin (Evan Medica, U.K.). All drug compounds were also stored under dry conditions over silica gel (R.H. < 10%). Some of the physical properties of these materials are shown in Table 1.

Methods

Particle size classification. Sulphapyridine and sulphamerazine were classified into two different size ranges (20 and 45 μm). The others were screened to 45 μm. These size fractions of drug powder were prepared using the oscillating air column method of sieving (Sonic Sifter, model L3P, ATM, U.S.A.) fitted with micromesh sieves and a horizontal pulse accessory (model L3-N8).

Particle size analysis. Particle size distributions of the drug materials were determined by two methods: (a) the size distributions of sulphapyridine, sulphamerazine, succinylsulphathiazole powders were determined by a laser diffraction technique (Malvern 2600/3600, Malvern Instruments, U.K.) using water as the suspending medium; and (b) the size distributions of ascorbic acid and phenacetin powders were determined by a microscopic technique using a research microscope (Olympus BH2, Japan) with appropriate stage and eyepiece micrometers. Liquid paraffin was used as the dispersion medium and about 300 particles were measured.

Particle density determination. Particle density of all materials was determined by liquid displacement using a pycnometric bottle (50 ml, Crown, U.K.). Water was used for the density determinations of the coated carrier beads, sulphapyridine, sulphamerazine, succinylsulphathiazole and phenacetin; and chloroform was used for the ascorbic acid powder.

Preparation of interactive mixture. Carriers and drug powders were equilibrated in an environmental chamber (Thermoline Scientific Equipment, Australia) at a controlled relative humidity of $26 \pm 1\%$ and temperature of $25.0 \pm 0.5°C$ for 24 h. The formation of the interactive system was also performed 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 rpm for 10 min. The glass jar was positioned at an angle of 42° to the vertical; this position provided optimum blending conditions. Samples between 60 and 150 mg were immediately taken for adhesion measurements. The homogeneity of interactive mixes was determined using fifteen 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 performed by scanning electron photomicrography (Phillip, model 505 SEM, U.K.).

Adhesion measurement. Adhesion measurements were performed by means of a IEC B-20A high-speed refrigerated centrifuge with a fixed rotor, type 870 (Damon/IEC Division, U.S.A.) which allowed rotation speed up to 19,000 rpm. 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 rpm. The rotor was accelerated to the desired speed which was maintained for 30 s before deacceleration.

Analysis of drug. The amount of drug detached after each consecutive centrifugation step and the drug retained on the carrier was 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, U.K.). Beer's law calibration curves for all the drug materials over the concentration range 0.002–0.020 $mg \cdot ml^{-1}$ 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

Principle of centrifuge technique

The principle of the adhesion measurement by the centrifuge technique involves the induced centrifugal force detaching the particle from the substrate. The detachment force applied to the particle is directed outwards from the centre of rotation through the centre of gravity of the particle. The force (F) acting on the particle is given by Eqn. 1 according to Newton's second law (Halliday and Resnick, 1966).

$$F = m(a + g) \tag{1}$$

where m is the mass of the particle, a is the centrifugal acceleration, g is the acceleration due to the earth's gravity. Centrifugal acceleration is dependent on the angular velocity (ω) and the distance between centre of the particle and the axis of rotation (ℓ): i.e.

$$a = \omega^2 \cdot \ell \tag{2}$$

$$\omega = 2\pi \cdot S \tag{3}$$

where S is the centrifugal speed. Therefore, Eqn. 1 can be rewritten when $\omega^2 \cdot \ell \gg g$:

$$F_{det} = m \cdot \omega^2 \cdot \ell \tag{4}$$

where F_{det} is the detachment force, and ω is the angular velocity at which the particle leaves the substrate. The force acting on the particle during centrifuging is related to the particle weight, the angular velocity and the distance between the centre of the particle and the axis of rotation. According to Eqn. 4, the detachment force can be rewritten in terms of density and particle size:

$$F_{det} = \pi \cdot d^3 \cdot \rho \cdot \omega^2 \cdot \ell/6 \tag{5}$$

where d is the diameter of the drug particle and ρ is the particle density. Therefore, drug materials of the same size but of different density will experience a different force acting on them at the same speed of centrifuging. High density drug particles adhering to the carrier with the same attractive force as low density particles of the same size can be dislodged at a lower centrifugal speed.

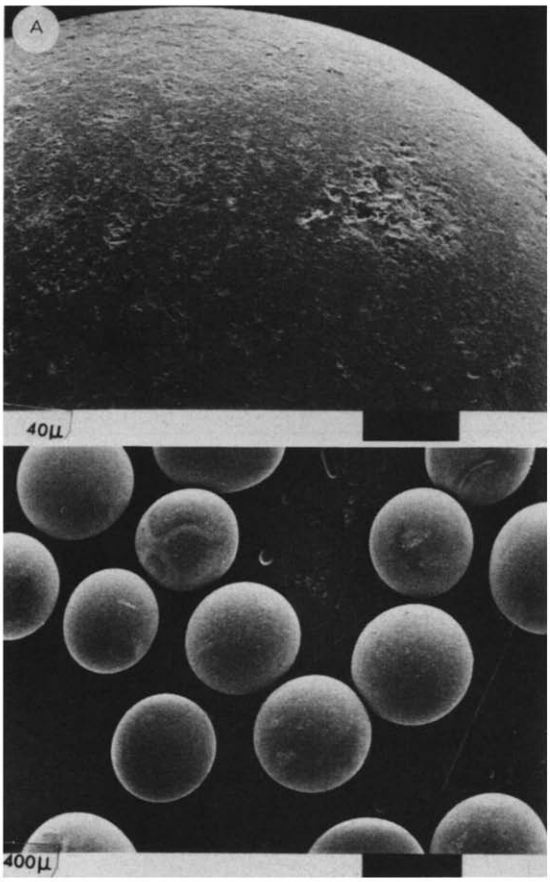

Fig. 2. Scanning electron photomicrographs of the glass beads (A), the glass beads coated with HPMCP (B), and the interactive mixture of coated carrier and sulphapyridine (C) (0.9%; fraction II).

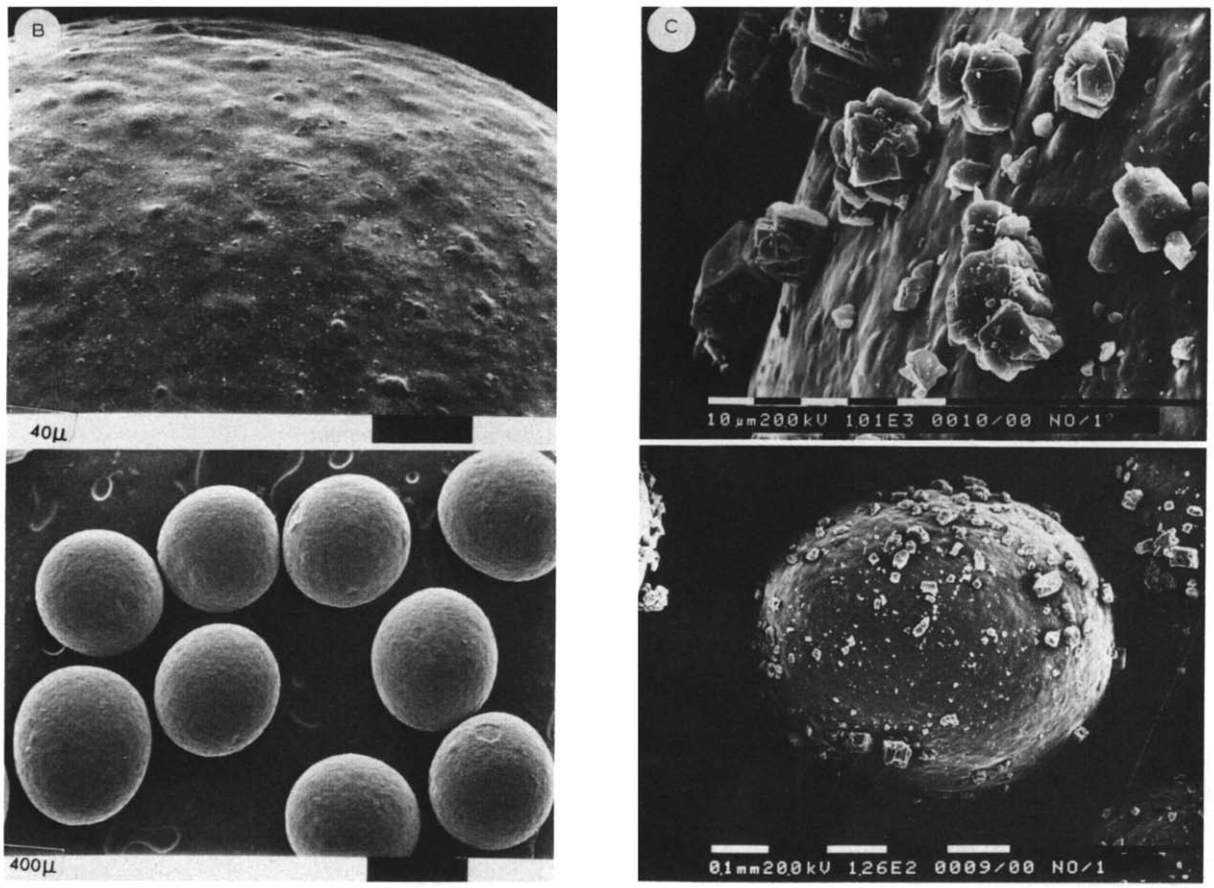

Fig. 2 continued.

Interactive systems

Electron photomicrographs of the glass bead surface prior to and after coating with HPMCP are depicted in Fig. 2. The glass beads have identical spherical shapes but possess surface irregularities (Fig. 2A). Fig. 2B shows a satisfactorily uniform, dust-free coating of HPMCP on the glass beads. The advantages of the coated glass beads in this study were as follows.

(a) The physicochemical properties of the surfaces brought into contact primarily determine the degree of their interactions. Coating the beads therefore eliminated the non-uniformity of the glass surface of the carrier. Accordingly, to avoid surface variation of the carriers used, only the coated beads from the same batch were used throughout one phase of the investigation.

(b) As the carrier was spherical, the direction of the centrifugal force applied on the carrier surface was uniform regardless of changes in the orientation of the carrier.

(c) The carrier's regular surface minimized the effect of surface asperities which could prevent drug particle detachment by mechanical interlocking.

(d) The uniformly sized, spherical carriers centrifuged against the screen formed a high porosity packing which facilitated the removal of the detached drug particles into the collection compartment of the centrifuge cell.

(e) Adhesion between the coated substrate and many drugs was strong enough to prevent accidental dislodgement during normal handling but allowed a high proportion of particles to be detached under the centrifuging conditions used in the study.

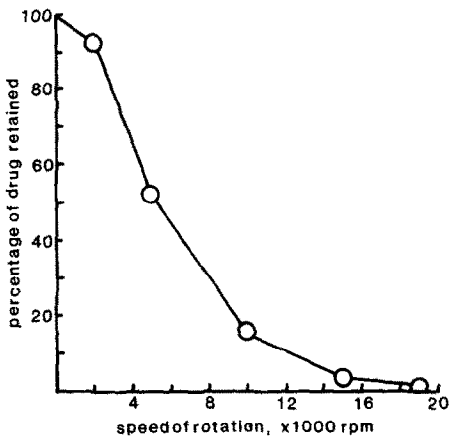

Fig. 3. Adhesion profile of the sulphapyridine-coated carrier interactive system (0.9%; fraction II).

The adhesion characteristics of the drug particles on the carrier surface were examined and confirmed by scanning electron photomicrograph. The sulphapyridine powder was distributed on the carrier surface as a monolayer of particles (Fig. 2C). No substantial agglomerates were formed; however, a few tiny drug particles adsorbed on the coarser ones were observed. This tendency is not an unusual occurrence in bulk powders since the adhering particles are difficult to dislodge by the forces generated during normal processing (Jones and Pilpel, 1965).

Adhesion measurement

Adhesion profiles typical of that shown in Fig.

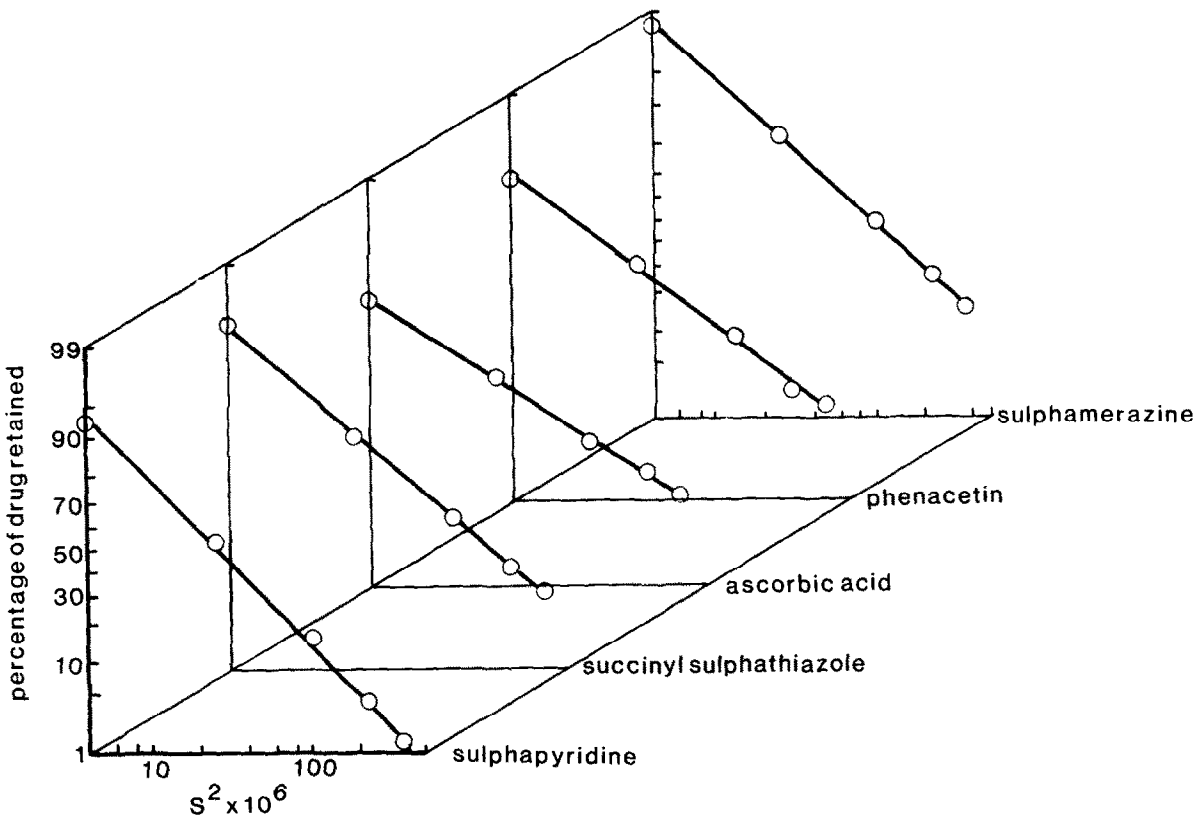

Fig. 4. Logarithmic probability plots of percentage of drug retained on the carrier against the square of the centrifugation speed for the drugs used in the study.
sulphapyridine 1.3%, $S_{50} = 5044$ rpm, $\sigma = 3.5$
sulphamerazine 0.7%, $S_{50} = 9162$ rpm, $\sigma = 4.0$
succinylsulphathiazole 0.9%, $S_{50} = 6438$ rpm, $\sigma = 4.2$
phenactin 0.3%, $S_{50} = 6577$ rpm, $\sigma = 5.3$
ascorbic acid 0.9%, $S_{50} = 5245$ rpm, $\sigma = 7.3$

3 were obtained when the percentage of drug retained on the carrier was plotted against the speed of rotation for all the drugs studied and for all conditions. This profile showed the adhesive tendency of a 1.30% sulphapyridine interactive mix (fraction II) which was determined immediately after blending for 10 min. Almost all of the drug was detached (1.3% of drug remained on carrier) when the speed of centrifuging reached 19,000 rpm.

The adhesion profiles were found to follow a log normal distribution function. Linearization of the adhesion profiles was achieved when they were represented on logarithmic probability coordinates by plotting the values of the logarithm of the square of the rotor speed (S^2) on abscissa and the percentage of drugs retained on the probability ordinate. All the drug-carrier interactive systems under all the conditions studied in this investigation produced linear adhesion profiles; some of these profiles are represented in Fig. 4. Such linearization of the data allowed the determination of the average speed of detachment, S_{50} (the speed at which 50% of the drug was detached) and the standard deviation (σ) of the adhesion distribution. The standard deviation of adhesion was calculated from the relation, $\sigma = S_{16}^2/S_{50}^2$, where S_{16} is the speed at which 16% of the drug was retained on the carrier.

The parameters S_{50} and σ can be used to evaluate the adhesion tendency of drug particles to carriers. The parameter S_{50} characterizes the adhesion tendency of the drug particles, the greater the S_{50} value, the higher the degree of interaction between drug powder and carrier. The σ value measures the scatter of minimum and maximum rotor speed required to detach the drug particles.

Change in shape of the adhesion profile was not observed in this experiment as was reported in a previous study (Staniforth et al., 1981). In that investigation, the shape of the adhesion profile which exhibited two distinct phases was influenced by the concentration of powder in the mixes. The initial phase showed rapid loss of drug powder from the mixture which was explained by the loss of free or weakly bound particles, or maybe by the break up of the carrier transferring the drug through the screen. In the present study, all the adhesion profiles showed log normal behaviour and were not influenced by the change in drug concentrations and particle size distributions.

Most studies on adhesion have been carried out using monosize adherent particles (Krupp, 1967; Zimon, 1982). In the particle–plane surface system, all particles are subjected to an acceleration force in a direction normal to the substrate. Therefore, the adhesion force possessed the same magnitude but was opposite in direction to the detachment force. As all particles leaving the substrate at each consecutive rotor speed are uniform in size, the detachment force can be directly calculated by multiplication of the particle mass and the relative centrifugal forces. However, the calculation of the detachment force is more complicated when polydisperse adherent particles are used, since it is difficult to determine the particle size distribution of the particle detached at each speed of centrifugation.

The adhesive system employed in this study was composed of drug particles interacting with carrier beads and not with a plane substrate. The drug particles at a different location on the carrier surface will experience centrifugal forces in different directions relative to the normal. The dependence of the magnitude of the force to remove particle on the direction of the applied force have been demonstrated experimentally with a particle–plane system by varying the so-called zenith angle, i.e. the angle between the directions of the applied force and normal to the plane (St. John and Montgomery, 1971). The detachment force at some zenith angles was less than one-hundredth of that required for a normal detachment. Therefore, drug particles with the same adhesive force and size but located at different positions on the carrier will require different forces of detachment. The magnitude of the force which detaches the particle from the carrier, other than normal to its surface, will not be identical with its adhesive force. In addition, since there are experimental difficulties in defining the exact particle sizes detached at each centrifuging speed, the estimation of the true adhesive force between drug particle and carrier is not possible. Consequently, the relative centrifugal force in the arbitrary form of rotor speed squared (S^2) rather than the directly ex-

pressed detachment force was used to assess the degree of adhesion.

Monosize particles, even under identical conditions of interaction with the substrate, will possess an adhesion force distribution resulting from several causes, for example, variation in the interfacial geometry, surface roughness, energy non-homogeneity of the contiguous surface, irregular particle shape, contamination causing non-homogeneity of surface, local variation in substrate hardness, and difference in surface electrical charge (Derjaguin and Zimon, 1961; Krupp, 1967; Loffler, 1968; Zimon and Ronginskii, 1974). In the case of polydisperse adherents, the adhesion distribution is also affected by the size distribution characteristics, the coarser particle will be removed with greater ease than the fine adherents at a given detachment force. The examination of the size distribution of polydisperse particles deposited on a plane substrate initially and after centrifugations showed an orderly shift to smaller size distributions with the greater rotor speeds applied (Kordecki and Orr, 1960; Corn and Stein, 1965). Size selective detachment was also found in the drug–carrier interactive system examined in this study. The particle size of sulphapyridine (fraction II) which remained on the carrier after centrifugation at low and high rotor speeds was observed by microscope. Large particles of the sulphapyridine were observed in the sulphapyridine powder and the interactive mixture spun at 2000 rpm (i.e. particles up to 25–30 μm were seen in photomicrographs of the substrate surface). These particles progressively disappeared from the interactive mixture at higher rotation speeds, e.g. at 15,000 rpm, particles up to 5–10 μm were observed while, at 19,000 rpm, the particle size did not exceed 5 μm.

Little information was available in the previous literature on the factors inherent in the experimental procedure that affect the adhesion profile (Donald, 1968; Staniforth et al., 1981). The following experiments were performed to test the effects of centrifuge cell loading and time of centrifugation after reaching the desired rotor speeds on the detachment rate of drug particles. S_{50} values for a sulphapyridine interactive system (fraction I) were determined at different cell loading of 60, 100 and 150 mg (Fig. 5). Adhesion measurements of 5 individual mixes containing the same level of drug concentration were observed at each sample size. No significant effect of the sample cell loadings between 60 and 150 mg was found (statistically tested by analysis of covariance, $P = 0.05$). Generally, nominal sample cell loadings of 100 mg were used for adhesion measurements throughout the studies.

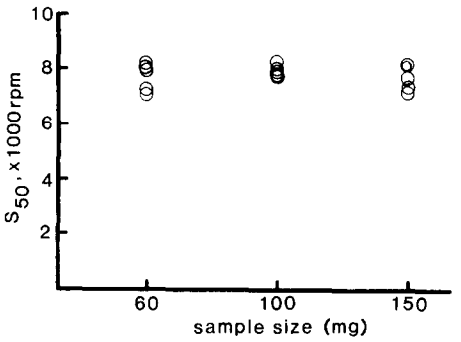

Fig. 5. The effect of cell loading on the S_{50} of a sulphapyridine–carrier interactive system (0.9%; fraction I).

The effect of centrifugation times was investigated by comparing the S_{50} of sulphapyridine interactive mixes (fraction II) determined at 30 and 60 s of centrifugation at each speed. Five replicate adhesion measurement of the individual mixes were determined (Fig. 6). No significant difference of S_{50} determined at 30 and 60 s of centrifuging times was observed (statistically tested by analysis of covariance, $P = 0.05$). The S_{50} val-

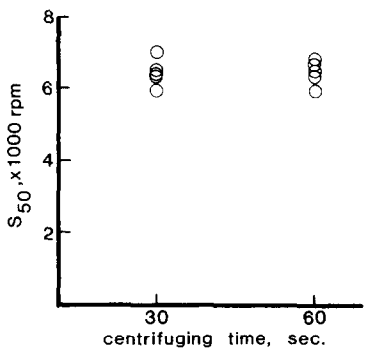

Fig. 6. The effect of centrifugation time on the S_{50} of a sulphapyridine–carrier interactive system (0.9%; fraction II).

ues determined at the different centrifugation times were also in good agreement at all level of drug concentrations in the mixes. The results indicated that 30 s of centrifugation was adequate to allow the detached drug particles to be displaced from the sample compartment to the collection compartment. However, centrifugation time and sample cell loading might depend on the configuration of centrifuge cell and the design of the adhesive system under investigation, and would need to be evaluated for a particular system.

The results of replicate adhesion measurements were consistent and reproducible. Constant experimental conditions in particular during the blending process were essential to reproduce the adhesion characteristics of the drug powders. The scatter of repeated measurements was consistent with previous studies (Zimon, 1982). The change in orientation of interactive units during consecutive centrifugations did not significantly affect the results of the adhesion measurements.

Conclusions

Previous investigations of particle adhesions by similar centrifugal techniques have not interpreted the experimental data beyond the basic adhesion profile shown in Fig. 3. The linearization of the data using logarithmic probability profiles allowed a more precise determination of the S_{50} which can be used as a parameter to assess the adhesive nature of drug powders. The standard deviation of the adhesion distribution (σ), determined from the linearized plot, can be used also to characterize the adhesive nature of the drug powder. The good consistency and reproducibility of the adhesion measurements was probably due to the use of a model adhesive system and the constant experimental procedure employed throughout the study. The use of the model interactive systems in this investigation has eliminated most of the carrier variables (such as shape factor, surface asperities, and non-uniform surface properties) which have complicated the interpretation of previous drug adhesion profiles. A knowledge of the behaviour of these ideal systems will therefore provide a basis for future investigations of more complex and realistic carrier systems.

The major disadvantage of the particle–bead system was that the precise determination of the adhesive force was complex due to the polydisperse drug powder, the size selective particle detachment and the varying zenith angles of the centrifugal force.

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