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Correlation between total adhesion and charge decay of a model interactive system during storage

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Summary

The effect of storage at 33% relative humidity on the degree of particle adhesion of model drug–carrier interactive systems was studied. A centrifuge method was used to determine total particle adhesion characterized by the S_{50} value while the electrostatic particular detachment charge was measured with an air stream Faraday cage. All interactive systems showed decreases in the extent of interaction during storage over 23 days with the type of drug–carrier system influencing the rate of adhesive change. Good correlation was obtained between the total adhesion and the electrostatic charge produced on particle detachment. A theoretical model was developed which allowed the estimation of the non-electrical interactive force contribution of each drug system.

Introduction

Interactive systems are formed when micronized drug particles are physically adsorbed onto the surface of larger carrier particles (Hersey, 1975). Drug–carrier adhesion is caused by electrical including contact potential and coulombic, capillary, molecular and interfacial including salt bridge and sintering interactions (Zimon, 1982; Krupp, 1967; Polke, 1970; Rumpf, 1972). Changes in the degree of interaction between the drug and carrier particles can occur during processing and subsequent storage. Powder particles under dynamic conditions during processing often become triboelectrically charged as the result of continuous frictional contacts and collisions with various surfaces which possess suitable triboelectric properties (Bailey, 1984). Electrostatic interactions of pharmaceutical powders have been well recognized, e.g. during fluidization or mixing processes at low ambient humidity (Roshchin and Avakyan, 1979; Thiel and Stephenson, 1982), or during triboelectrification by pneumatic processing to produce more interactive powders (Staniforth and Rees, 1982a; Staniforth, 1982). In addition, many workers have applied the method of charging particulate solids by electrons or ions using corona discharges to induce electrostatic interaction in powder mixtures (Tucker and Suh, 1976; Enstad, 1981a and b; Staniforth and Rees, 1982b). Capillary interactions depend on the environmental moisture content and the ability to form liquid

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bridges; such interactions can change with storage time depending on conditions. Interfacial reactions rely on special circumstances and will usually build up over a period of time.

The ability of interactive systems, therefore, to modify the degree of adhesion during processing and storage will influence the segregation characteristics of the drug in the mixture in particular the tendency of constituent segregation. The purpose of this study is to observe the relationship between the total adhesiveness of a model interactive system and the electrostatic charge on the drug particles.

Experimental

The carrier consisted of glass beads (500 μm; Selby Scientific, Australia) coated with hydroxypropylmethylcellulose phthalate (HP-55, Shin-Etsu Chemical Co., Japan) using an air suspension technique (Uni-Glatt laboratory unit, Glatt GmbH, F.R.G.). The adherent drugs were sulphapyridine (Sigma Chemical Co., USA; $d_v =$ 27.2 μm), sulphamerazine (Sigma Chemical Co., USA; $d_v = 17.7$ μm) and succinylsulphathiazole (Sigma Chemical Co., USA; $d_v = 23.4$ μm). All materials were equilibrated in an environmental chamber (Thermoline Scientific Equipment; Australia) at a controlled relative humidity of $33.0 \pm 1.0\%$ and temperature of $25.0 \pm 0.5\,^{\circ}$C for 24 h. The interactive mixtures (10 g) were prepared in an environmental chamber under the same conditions by blending for 15 min using a method previously described (Kulvanich and Stewart, 1987a). The interactive mixtures were stored in dessicators at 25.0 °C and at 33% relative humidity maintained by a saturated magnesium chloride solution.

The size fractions of drug powder were prepared using the oscillating air column method of sieving (Sonic Sifter, model L3P, ATM Corp., U.S.A.) fitted with micromesh sieves and a horizontal pulse accessory (model L3-N8). The particle size distributions of sulphapyridine, sulphamerazine, and succinylsulphathiazole powders were determined by a laser diffraction technique (Malvern 2600/3600, Malvern Instruments, U.K.) using water as the suspending medium.

Total adhesion was determined using a specially designed aluminium centrifuge cell which consisted of a sample and collection compartment separated by a replaceable screen (250 μm) and was held in position within the centrifuge rotor so that the screen was normal to the axis of rotation (Kulvanich and Stewart, 1987a). 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 decceleration. 100 mg samples were taken for each adhesion measurement.

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, 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.

Electrostatic charge measurements were performed using the air stream Faraday cage (Kulvanich and Stewart, 1987b). The average charge-to-mass ratios were determined with 1.5 g of interactive mixture at an air flow velocity of 7.2 $m \cdot s^{-1}$.

Results and Discussion

The centrifuge method allowed the determination of the adhesion profile which was a logarithmic normal function when the percent of drug

remaining on the carrier was regressed against the square of the speed of rotation (Kulvanich and Stewart, 1987a). The profile could be characterized by the S_{50}, i.e. the speed required to dislodge 50% of adherent particles, and σ, i.e. the geometric standard deviation of the adhesive distribution. In these experiments the total degree of adhesion of the drug particles in the interactive systems was measured by the S_{50} parameter.

The air stream Faraday cage (Kulvanich and Stewart, 1987b) determined the degree of the static electrification of the interactive mixture which was calculated as the average charge-to-mass ratio or tribo (T) in MC/g of adherent powder, i.e. $T = Q/m$, where Q was charge magnitude measured and m was the mass of powder detached. The concentration of powder detached ($C\%$) was expressed as $100m/w$, where w is the weight of mixture after powder detachment.

The relationship between the S_{50} and tribo parameters of a sulphapyridine, succinylsulphathiazole and sulphamerazine interactive mix at various storage times is presented in Tables 1–3. Observation of the data showed that: (1) the initial degree of interaction of the sulphamerazine onto the polymer-coated carrier as shown by the S_{50} values is markedly greater than the other interactive mixtures; (2) all the interactive mixtures showed a decrease in the total adhesion and average charge to mass ratio with time; and (3) the rate of total adhesion and electrostatic charge decay was different in the three mixtures.

The concentrations of powder specified in the total adhesion measurement column represent the total concentration of adhered powder in the mixtures, i.e. all the adhered drug powder was removed during the centrifugation process. However, in the charge measurement column, the concentrations shown represent the amount of drug powder removed from the cage during the air streaming charge measurements, i.e. some powder interacted with the Faraday cage after detachment from the carrier (Kulvanich and Stewart, 1987b).

For the sulphapyridine interactive mixture, the drug concentration in the mix was estimated from the percentage of powder in the sample taken from a freshly prepared mix for total adhesion measurement (at time zero in the table) and was 0.93%. The corresponding powder concentration calculated from the amount detached during charge measurement was 0.74% which indicated that a proportion of the powder was not removed from the cage by the air drag force. The tribo of the freshly prepared mix therefore was underestimated and would be higher than 8.56 $\mu C^{v}.g^{-1}$ since this value did not include the very highly triboelectrically charged particles which were not removed from the cage. However, after the mixture was stored for 1 day and charge decay had commenced, almost all the powder could be detached (0.89%). The percentage of powder in the samples which were taken from the sulphapyridine mix for total adhesion measurement on day 23 was significantly low (0.71%). This was possibly

TABLE 1

The comparison of S_{50} and tribo properties of sulphapyridine powder (fraction II)–carrier interactive mix during storage at 33% R.H. and 25°C

Storage time (day)	Adhesion measurement		Charge measurement	
	S_{50} (rpm)	Concentration (%) [a]	Tribo ($C \cdot g^{-1}$)	Concentration (%) [b]
0	8100	0.93	8.56 [c]	0.74
1	5450	0.91	6.57	0.89
2	3850	0.87	4.10	0.96
4	2150	0.88	3.06	0.96
6	2600	0.87	2.17	0.94
23	1250	0.71	0.77	0.96

[a] Concentration of sulphapyridine powder in the sample taken for adhesion determination.
[b] Concentration of sulphapyridine powder detached during charge determination.
[c] Underestimated tribo as partial powder detached.

TABLE 2

The comparison of S_{50} and tribo properties of succinyl sulphathiazole powder–carrier interactive mix during storage kept at 33% R.H. and 25 °C

Storage time	Adhesion measurement		Charge measurement	
	S_{50} (rpm)	Concentration (%) [a]	Tribo ($C \cdot g^{-1}$)	Concentration (%) [b]
0	7050	0.78	6.50	0.81
1.5 h	6900	0.74	6.30	0.72
4.0 h	6400	0.77	2.87	0.83
1 day	5500	0.71	0.90	0.80
11 days	5250	0.75	0.79	0.80

[a] Concentration of succinyl sulphathiazole in the sample taken for adhesion measurement.
[b] Concentration of succinyl sulphathiazole powder detached from sample mix during charge measurement.

caused by the dislodgement of weakly bound particles during removal of the small samples for measurement.

The observations on the succinyl sulphathiazole mix showed that all the powder could be detached during charge measurement of the freshly prepared mix as the powder concentration was of the same order as that observed in the sample for adhesion measurement (Table 2). In contrast, highly triboelectrified powder systems were produced for the sulphamerazine interactive mixture and complete drug removal did not occur in the early storage period (Table 3).

Observation of all the mixtures showed a relationship between total adhesion and charge decay in the interactive system. For the sulphapyridine mixture, the charge decay was relatively rapid with the average charge-to-mass ratio decreasing to less than 10% of its initial value after 23 days storage; total adhesion also decreases to about 15% of its initial value. The succinylsulphathiazole mixture showed a rapid decrease of S_{50} and tribo properties during the first day, with little further decrease being detected during further storage for 11 days.

The sulphamerazine powder mix also showed the same trend in the decrease of S_{50} and tribo values (Table 3). As sulphamerazine possessed a slow rate of charge decay, the mix was transferred from 33% R.H. to 75% R.H. at day 17 in order to accelerate the charge decay rate. The corresponding decrease in tribo and S_{50} at day 19 reflected the increased charge decay in the higher humidity conditions. Lower drug powder concentrations were determined from samples for the total adhesion measurement reinforcing the strong resis-

TABLE 3

The comparison of S_{50} and tribo properties of sulphamerazine powder–carrier interactive mix during storage at 33% R.H. and 25 °C.

Storage time (day)	Adhesion measurement		Charge measurement	
	S_{50} (rpm)	Concentration (%) [a]	Tribo ($C \cdot g^{-1}$)	Concentration (%) [b]
0	12450	0.71	7.88 [c]	0.58
1	12800	0.65	8.65 [c]	0.57
17	9400	0.73	6.89	0.66
19 [d]	7400	0.69	4.30	0.66

[a] Concentration of sulphamerazine powder in the sample taken for adhesion measurement.
[b] Concentration of sulphamerazine powder detached from sample mix during charge determination.
[c] Underestimated tribos as partial powder detached.
[d] Sample taken from the mix which was transferred from 33% to 75% R.H. at day 17.

tance to detachment of the sulphamerazine from the polymer-coated carrier. This effect might be particle size related with the powders containing the smaller particles being more resistant to removal by the detachment forces. Particle size analyses confirmed that the sulphamerazine contained a higher percentage of fine powder than the other drugs, i.e. sulphamerazine possesses 22.0% of particles by weight less than 10.1 μm compared with 12.4% and 3.5% less for succinylsulphathiazole and sulphapyridine, respectively. While some correlation existed between lower particle size and reduced detachment, consideration needs to be given to the intensity of the interactive forces. The effects observed also could be explained wholly or partly by a higher intrinsic degree of adhesion between the sulphamerazine particles and the carrier.

Four types of forces are primarily important in the adhesion of small particles to surfaces; molecular forces, electrostatic forces, capillary force due to formation of liquid bridge, and interfacial forces including salt bridge formation, mechanical interlocking of particles and sintering effects. The capillary force will be relatively ineffective under dry condition or at low relative humidity (i.e. 33%). The force components assisting particle adhesion at low to medium relative humidity will be as follows (Aleinikova et al., 1968; Krupp, 1967; Derjaguin et al., 1977):

$$F_{AD} = F_{NEL} + F_{EL}$$

where F_{NEL} is the non-electrical force component and includes the molecular force, salt bridge formation, mechanical interlocking, etc. and F_{EL} is the electrical force component which consists of interactive forces caused by the electrical double-layer at the contact points (F_c) and the coulombic interaction of the electrical charge distributed over the particle surface due to previous electrifications (F_{IM}).

During storage of the interactive systems studied, both the total adhesion and the average charge-to-mass ratio decreased. Correlation of the total adhesive force and the electrical forces quantitatively is not possible. For example, accurate estimations of the total adhesive force using the centrifuge technique is hindered by lack of knowledge of the particles size distribution removed from the carrier at each centrifuging time and by particle orientation effects during detachment (Kulvanich and Stewart, 1987a). In addition, calculation of the electrical forces requires a knowledge of the drug–carrier separation distances and areas of contact. The following theoretical treatment of the force components in these interactive systems can be achieved using the mathematical expressions derived for each of the force components (Zimon, 1982):

$$F_{AD} = F_{NEL} + F_{IM} + F_C$$

$$d^3\pi\rho\omega^2 l/6 = F_{NEL} + Q^2/x^2 + 2\pi Q^2/A$$

$$\omega^2 = 6F_{NEL}/d^3\pi\rho l + \left[6/x^2\pi d^3\rho l + 12/Ad^3\rho l\right]Q^2$$

where d is the adhered particle diameter, ρ is the particle density, ω is the angular rotating velocity, l is the distance between the particle carrier interface and the axis of rotation during centrifugation, Q is the charge on the particle, x is the distance between the centres of the charges during coulombic interaction between the charged particle and its image, and A is the contact area between the particle and substrate during contact electrification.

The square of the rotational speed is therefore related to the square of the charge of the drug powder. The physical meaning of the charge Q in the derived equation is different for the image and contact force interaction. Q is the charge on the particle during Coulombic interaction between the precharged particle and a neutral surface and is the charge developed when a particle is detached from a surface after interaction by contact electrification. In the air stream Faraday cage both these charges will be measured and the parameter Q can be represented by the average charge-to-mass ratio. Since the interactive systems contain a distribution of adherent particle sizes and since the intrinsic adhesive force is also distributed in intensity, the detachment of particles cannot be reflected by a single angular velocity. In the developed centrifuge method the "average" detachment velocity is represented by the S_{50} value. Such a value can be

used to compare the degree of interaction in mixtures provided the standard deviation of the forces in the system remains constant.

Fig. 1 shows the correlation between the square of the S_{50} and the square of the average charge-to-mass ratio. Several observations can be made.

(1) Good correlation existed between the S_{50} as a measure of total adhesion and the square of the average charge-to-mass ratio for the interactive mixtures shown, i.e. the correlation coefficients for the sulphapyridine and succinylsulphathiazole interactive mixtures were 0.98 and 0.93 with significance at the 99% and 95% level, respectively

(2) The intercept value is a complex function involving the non-electrical force component, particle size and density and is different for the two interactive mixes, i.e. 3.08×10^7 and 1.74×10^6 for the succinylsulphathiazole and sulphapyridine interactive mixtures, respectively. Since the sulphapyridine and succinylsulphathiazole possess similar densities (1.35 and 1.43 $g \cdot cm^{-3}$, respectively) and similar particle size distributions (volume mean diameter of 27.2 μm, S.D. = 1.1 μm; and 23.4 μm, S.D. = 1.6 μm, respectively), the different intercept values for the two mixes reflect different non-electrical degrees of interaction. The succinylsulphathiazole therefore probably has a greater molecular interaction with the polymer-coated carrier than the sulphapyridine since the degree of capillary interaction and other surface forces would be expected to be low in the humidity conditions of the study.

(3) Changes in the slope of the regression will be a function of the particle density and size distribution, the area of contact between the drug particles and the carrier surface and the distance between particle centre and its image at the interface. The slightly differing slopes obtained in Fig. 1 (i.e. 4.52×10^5 and 6.54×10^5 for the succinylsulphathiazole and sulphapyridine interactive mixtures, respectively) reflect the contributions of these parameters in the two mixes. While the particle size and density are similar for the drug powders and will not influence the slope significantly, small particle size differences will affect x^2, and the particle shape and orientation at the surface, the deformation characteristics of the powder and the degree of impact during mixing will affect the area of contact.

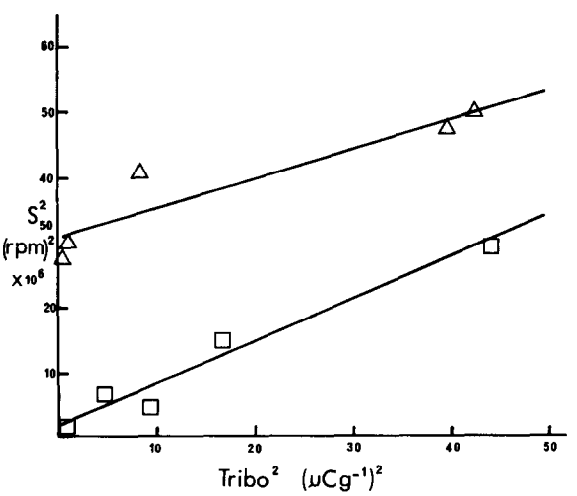

Fig. 1. Correlation between the square of the S_{50} and the square of the average charge-to-mass ratio for the sulphapyridine (□) and succinylsulphathiazole (△) interactive mixtures. ———, linear least -squares regression.

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