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Influence of carrier moisture adsorption capacity on the degree of adhesion of interactive mixtures

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Abstract

The interaction of sulphathiazole and succinylsulphathiazole with Compactrol®, TabBase®, Emdex® and lactose granules was studied. Carriers with a high capacity to adsorb moisture caused a significant increase in the adhesion when the mixtures were stored under high humidity conditions. The effect was attributed to capillary interaction following liquid bridge formation between the drug and carrier surfaces. Oven drying of the moist mixtures further increased the degree of adhesion probably due to solid bridge formation.

Key words: Interactive mixing; Particle adhesion; Capillary interaction; Solid bridging; Crystal bridge

Interactive or ordered mixtures contain fine drug particles adhered to pharmaceutical carriers (Hersey, 1975). Particle adhesion involves several different mechanisms including (a) electrical interactions which comprise contact potential forces due to the difference in work function between contiguous uncharged dissimilar materials and Coulombic forces due to the interaction of charged materials with a surface, and (b) non-electrical interactions which include intermolecular forces occurring between closely contacted surfaces due to Van der Waals forces, capillary forces caused by the formation of liquid bridges between surfaces and solid bridging between surfaces occurring by melting and crystallization processes (Rumpf, 1961; Krupp, 1967; Zimon, 1982; Stewart, 1986). At any time the total adhesion force (F) in an interactive mixture will consist of a number of force components (Stewart, 1986):

$$F = F_c + F_e + F_{im} + F_m + F_s$$

where F_c, F_e, F_{im}, F_m and F_s are the capillary, contact potential, Coulombic, intermolecular and solid bridging interactive force components, respectively. The relative contribution of these components to the total adhesion in a particulate system will depend on material related, environmental and processing factors. The capacity of a carrier to adsorb moisture therefore would be expected to have a marked influence on the degree of drug particle interaction. For example,

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carriers which possess high moisture levels would be expected to facilitate interaction by capillary and solid bridge adhesion with electrical adhesion being less dominent due to charge decay (Kulvanich and Stewart, 1987b). This communication reports on adhesion of two sulphonamides to pharmaceutical carriers with differing moisture adsorption capacity.

Sulphathiazole and succinylsulphathiazole (Sigma, U.S.A.) were used as the adherent drugs. Emdex® (Dextrose; Mendell, U.S.A.), TabBase® (Dextrose), Compactrol® (Calcium sulphate dihydrate; Mendell, U.S.A.) and lactose granules were used as carriers. The lactose granules were formulated with 2% PVP as a binder, prepared by wet granulation in Erweka laboratory scale equipment using the PVP in solution as the granulating agent and dried overnight at 50°C. Particle size drug fractions were classified using a Sonic Sifter, model L3P (ATM Corp., U.S.A.) and micro mesh sieves. Particle size fractions of the carriers were classified using a Pascal sieve shaker (Pascal, U.K.) and Endecott Test Sieves. All classification procedures were carried out at 22 ± 1°C and 50% relative humidity (RH). Drugs and carriers were stored in a desiccator containing silica gel. Other chemicals used were analytical grade and all chemicals were used as supplied from the manufacturers.

10 g of a 1% sulphonamide (45–53 μm) interactive mixture with each carrier (250–425 μm) was prepared in a glass jar rotated at 25 rpm for 15 min on a friability tester (Erweka, Germany). The jar was positioned at an angle of 40° to the vertical; this position provided optimum blending conditions. The formation of an interactive system in which the drug particles adhered to the carrier surface and in which few unattached drug particles were observed was verified by scanning electron microscopy using a Philips, model 505 SEM (Philips, U.K.). Homogeneity of the mixture was determined using 20 × 50 mg samples and the coefficient of variation of the mixtures was less than ±3% indicating satisfactory mixing (Cook and Hersey, 1974; Crooks and Ho, 1976).

A specially designed aluminium centrifuge cell consisting of a sample and collection compartment separated by a replaceable screen (150 μm) was held in position within the centrifuge rotor so that the screen was normal to the axis of rotation (Kulvanich and Stewart, 1987a). The percentage of drug retained on the carrier was determined after centrifuging at 20000 rpm for 30 s in a microprocessor-controlled, high speed centrifuge (International Equipment Co., U.S.A.) with a 895 rotor. The temperature in the centrifuge chamber was 20°C and the interactive mixture sample size was accurately known (40–70 mg). The amount of sulphonamide detached after centrifugation and the sulphonamide retained on the carrier were assayed spectrophotometrically. The sulphonamides were extracted into 0.1 M NaOH and the absorbance measured at the wavelength of maximum absorption on a Pye Unicam PU8600 (U.K.) ultraviolet visible spectrophotometer (i.e., 255 nm for both sulphathiazole and succinylsulphathiazole). Spectra were determined using a double beam Varian DMS 100S (U.S.A.) ultraviolet visible spectrophotometer. Beer's law standard curves were prepared at the wavelength of maximum absorbance using four concentrations and four replicates over the concentration range 0.25–5.0 mg%. There was no significant deviation from linearity and the sulphonamide concentrations were obtained by inverse prediction (Williams, 1959). Dissolved carriers did not interfere with the absorbance measurement of the sulphonamides. The coefficient of variation of the assay was ±1.3% ($n = 20$) for all drugs and extraction methods were validated.

Saturated salt solutions were used to maintain constant relative humidity conditions inside small desiccators incubated at 20 ± 1°C (Winston and Bates, 1960). The following saturated salt solutions were used: potassium nitrate (95%), potassium chloride (85%), sodium chloride (75%), ammonium nitrate (63%) and magnesium chloride (32%). Relative humidity was monitored within the desiccator using a Humidity Probe (Hanna Instruments, Italy) with variability being < 3%. The moisture content of the carriers was determined by drying the sample at 100°C to constant weight.

The moisture sorption characteristics of the pharmaceutical direct compression vehicles suitable for use as carriers in interactive systems

Table 1
Moisture uptake by interactive system carriers

Carrier	RH (%)	Percent moisture uptake [a]				
		1	2	4 (days)	7	10
Lactose granules	32	−0.15	−0.13	−0.14	−0.16	−0.16
	63	0.21	0.32	0.40	0.40	0.40
	75	0.43	0.68	0.84	0.87	0.87
	95	1.55	2.06	2.66	2.29	2.29
Emdex®	32	−0.49	−0.54	−0.56	−0.58	−0.58
	63	0.28	0.38	0.39	0.35	0.32
	75	0.60	0.89	1.22	1.33	1.33
	95	6.24	8.23	11.68	17.48	17.48
Tab Base®	32	0.23	0.31	0.19	0.18	0.18
	63	1.17	1.21	1.17	1.14	1.14
	75	1.48	1.63	1.88	1.96	1.96
	95	3.44	4.91	7.53	12.3	12.3

[a] Moisture uptake determined by weight differences.

were studied (Table 1). The carriers were stored at constant temperature (20 ± 1°C) over a range of relative humidity conditions from 32 to 95% for a 10 day period. Emdex® and TabBase® showed the greatest propensity for moisture sorption with equilibrium moisture uptakes at 95% RH of 17.5 and 12.3%, respectively. The uptake under other relative humidity conditions was not great and equilibrium moisture contents were achieved after 7 days. Compactrol® did not sorb significant amounts of moisture at any relative humidity condition, i.e., less than 0.006%.

The degree of adhesion of the sulphonamides to the carriers, measured by the percent retained after centrifugation at 20000 rpm, was determined after the preparation of the interactive mixtures (Table 2). The initial adhesion represents the interaction between drug and carrier particles stored in a drying cabinet over silica gel and would essentially be comprised of electrical and intermolecular interactive force components (Zimon, 1982). The type of drug and carrier influenced the initial degree of interaction substantially with the percent remaining varying between 52.4 and 79.5% for these systems. Succinylsulphathiazole was adhered more strongly than sulphathiazole. Emdex® and TabBase® produced greater adhesion than Compactrol® and lactose granules. Different compounds are known to possess differing adhesion properties for the same carrier surface, e.g., contact potential and intermolecular interactive forces will be influenced by the drug's chemistry and processing conditions, while the extent of capillary interaction will depend on contact angle and equilibrium moisture content (Zimon, 1982). The mixtures were stored for 3 days at 95% relative humidity and the adhesion again measured. The results shown in Table 2 demonstrate that Compactrol mixtures showed little change in adhesion. Capillary interaction in this system was expected to be low due to the poor water sorption capacity of this carrier, i.e., at 95% RH the moisture uptake was negligible. Little evidence existed for decreased adhe-

Table 2
The degree of adhesion of sulphathiazole and succinylsulphathiazole (1%, 45–53 μm) in interactive mixtures with Compactrol®, lactose granules, Emdex® and TabBase® (250–425 μm)

Drug	Condition	Percent retained [a]			
		Compactrol®	Lactose	Emdex®	TabBase®
Sulphathiazole	day 1 [b]	52.4	62.6	71.3	63.4
	day 3 [c]	55.3	67.1	91.4	79.2
	dried [d]	53.5	60.8	98.5	85.7
Succinyl-sulphathiazole	day 1	67.6	65.7	79.5	67.4
	day 3	66.0	87.4	87.1	77.3
	dried	60.1	86.8	97.5	84.8

[a] Percent retained on carrier at 20000 rpm.
[b] Percent retained determined on the same day of preparation of the interactive system.
[c] Percent retained determined after 3 days of storage at 95% RH.
[d] Percent retained determined after 3 days of storage at 95% RH followed by drying at 100°C.

sion due to charge decay on storage. However, previous studies (Kulvanich and Stewart, 1988) using succinylsulphathiazole adhered onto a model polymer coated carrier demonstrated that charge decay occurred rapidly after preparation (within 2 h) when stored under high humidity conditions and then remained constant over a 14 day period. The adhesion measurement was performed during the first day but several hours after preparation of the interactive system, and this could account for the observed behaviour. Both TabBase® and Emdex® showed significant increases in adhesion during high humidity storage. These results are most attributed to the development of capillary interaction as the moisture content increased during storage. Increased adhesion occurred in all TabBase® and Emdex® systems despite the probable decrease in electrical interaction due to charge decay (Kulvanich and Stewart, 1987b).

After 3 days storage at high humidity the interactive mixtures were oven dried at 100°C and the degree of adhesion again measured (Table 2). Compactrol® interactive systems showed little change in adhesion; however, both the Emdex® and TabBase® interactive systems with high affinity for moisture displayed increased adhesion over the initial mixture and the mixture stored at high humidity. The percent remaining for the Emdex® and TabBase® interactive systems was high, i.e., between 84.8 and 98.5%, indicating that strong adhesion had occurred. It as unlikely that the strong interaction was due to increased electrical adhesion as previous interaction in these dried systems after mixing was not high and triboelectrification (increased charging) due to increased particle contacts was unlikely during tray drying. The increased adhesion signifies possible solid bridge formation between the drug and the moisture soluble carrier. The formation of solid bridges in these interactive mixtures could occur by dissolution of the water-soluble carriers in the liquid bridge with the subsequent crystallization of the carriers causing strong bonding during the drying process. A scanning electron microscope examination of the dried interactive mixtures was undertaken but these studies were not helpful in identifying solid bridge formation or recrystallisation of the dissolved carrier. Further studies are necessary to confirm the above hypothesis. However, the strength of the interaction is indicative of permanent bonding. The development of this technology to optimize solid bridging in the formation of interactive systems may have useful applications in the delivery of drugs.

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2. References

Cook, P. and Hersey, J.A., Powder mixing in the tabletting of fenfluramine hydrochloride; evaluation of a mixer. *J. Pharm. Pharmacol.*, 26 (1974) 298–303.

Crooks, M.J. and Ho, R., Ordered mixing in direct compression of tablets. *Powder Technol.*, 14 (1976) 161–167.

Hersey, J.A., Ordered mixing: A new concept in powder mixing practice. *Powder Technol.*, 11 (1975) 41–44.

Krupp, H., Particle adhesion: theory and experiment. *Adv. Colloid Interface Sci.*, 1 (1967) 119–239.

Kulvanich, P. and Stewart, P.J., Correlation between total adhesion and charge decay of a model interactive system during storage. *Int. J. Pharm.*, 39 (1987b) 51–57.

Kulvanich, P. and Stewart, P.J., Influence of relative humidity on the adhesive properties of a model interactive system. *J. Pharm. Pharmacol.*, 40 (1988) 453–458.

Kulvanich, P. and Stewart, P.J., Fundamental considerations in the measurement of adhesional forces between particles using the centrifuge method. *Int. J. Pharm.*, 35 (1987a) 111–120.

Rumpf, H., The strength of granules and agglomerates. In Knepper, W.A. (Ed.), *Agglomeration*, Interscience, New York, 1961, pp. 379–418.

Stewart, P.J., Particle interaction in pharmaceutical systems. *Pharm. Int.*, 7 (1986) 146–149.

Williams, E.J., *Regression Analysis*, Wiley, New York, 1959, p. 90.

Winston, P.W. and Bates, D.H., Saturated solutions for the control of humidity in biological research. *Ecology*, 41 (1960) 232–237.

Zimon, A.D., *Adhesion of Dust and Powder*, 2nd Edn, Consultants Bureau, New York, 1982, pp. 93–144.