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Variations in the adhesion force between a drug and carrier particles as a result of changes in the relative humidity of the air

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Abstract

The influence of the press-on force applied and the relative humidity of the air during storage of adhesion samples made from lactose monohydrate surfaces (as a model carrier) and salmeterol xinafoate (as a model drug) particles has been studied using the centrifuge technique. Capillary forces were observed for samples which were subjected to a relative humidity of 75 or 95%. The resulting strong adhesion forces between drug and carrier particles cannot be reduced by a restorage of the samples at a low relative humidity. An equilibrium value of the capillary force was reached within 72 h. Experiments where particles adhered to compacted powder surfaces lead to the same conclusions as experiments where the particles adhered to carrier particles. Model calculations have shown that it is possible to establish a relationship between adhesion forces and the interfacial energy of the materials in contact. If a minimisation of the adhesion strength is sought, the interfacial energies between the surfaces should be as small as possible when Lifshitz-van der Waals' forces are the main adhesion force component, whereas in the case when capillary forces dominate the adhesion process, the interfacial energy between the contiguous surfaces should be large. © 1997 Elsevier Science B.V.

Keywords: Adhesion force; Air relative humidity; Adhesion samples; Storage; Salmeterol xinafoate; Lactose monohydrate surfaces; Dry powder aerosols

1. Introduction

Adhesion between powder particles or particles and surfaces plays a key role in the understanding of powder flow and powder mixing. The formula-

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tion and manufacture of dry powder aerosols is only one example, where the knowledge of adhesion (contact of different materials) and autoadhesion (contact between surfaces of the same material) forces is useful to guarantee an optimal formulation and to prevent disturbances during the production.

The total force of adhesion is known to be a summation value of several additive force components (Stewart, 1986), e.g.

$$F_{ad} = F_{vdw} + F_c + F_e + F_{es} \tag{1}$$

where F_{ad} is the force of adhesion, F_{vdw} is the Lifshitz-van der Waals' force, F_c is the capillary force, F_e is the electrical force, and F_{es} is the electrostatic (Coulomb) force. The value of F_e is a constant for two materials in contact, and F_e cannot arise if moisture is present in the gap between the contiguous surfaces (Zimon, 1982). An electrostatic force F_{es} only participates, if the particles and/or surfaces have been actively charged (Deryaguin et al., 1968, 1978). The magnitude of the Lifshitz-van der Waals' force F_{vdw} can be varied by an external load applied (Lam and Newton, 1993). If the centrifuge method (Böhme et al., 1962) is used to assess adhesion forces, the external load is the press-on force applied before assessing the detachment forces. An increase in press-on force leads to an increase in area of contact due to either plastic (Demejo et al., 1988) or elastic deformation (Pashley et al., 1984) of the adhered particles and the surfaces. A reduction in the distance of separation between the particles has also been observed (Podczeck et al., 1994). The capillary force F_c has been identified as the force which dominates over any other force component, once the relative humidity of the air has reached a value of 65 to 75% (Böhme et al., 1967; Ketkar and Keller, 1975; Zimon, 1982).

In this paper, the influence of the relative humidity of the air on the adhesion force between a drug, salmeterol xinafoate, and a carrier excipient, lactose monohydrate, has been studied as a model system. According to Rumpf (1977), electrostatic forces (F_{es}), which arise due to the contact potential of contiguous bodies, are 10 times smaller than Lifshitz-van der Waals' forces (F_{vdw}), and electrostatic forces due to excess charges are also at least 10 times smaller than F_{vdw}. Also, the use of a press-on force to enhance the true area of contact between particles and surfaces increases the F_{vdw} by a factor of about 5. Hence, the ratio between F_{vdw} and F_{es} is about $F_{vdw} \approx 50 \times F_{es}$. Thus, electrostatic forces are too small to influence significantly the adhesion forces measured after application of an external force. Taking this into account and considering the electrical forces to remain constant during the experiments, Eq. (1) can be reduced to the following:

$$F_{ad} = F_{vdw} + F_c \tag{2}$$

The assessment of the order of magnitude between F_{vdw} and F_c, the reversibility of the capillary forces and the ability to link the force components to the distance of separation z_0 between the contiguous bodies, the interfacial energy $\Delta\gamma$ and the reduced Young's modulus at the contact points between particles and surfaces is the aim of the study.

Rumpf (1977) defined the Lifshitz-van der Waals' forces between a spherical particle and a flat surface as follows:

$$F_{vdw} = \frac{\hbar\omega r}{8\pi z_0^2} \tag{3}$$

where $\hbar\omega$ = Lifshitz constant, r = radius of the particle, and z_0 = distance of separation. The Lifshitz constant for an autoadhesion or adhesion contact can be obtained using dielectric spectroscopy (Böhme et al., 1967; Krupp, 1967; Osborne-Lee, 1988). The equation does not take into account a rough surface and therefore deviations of experimental values from the theoretical forces occur. At equally applied press-on forces, however, the true area of contact between the particle and the surface is a constant (Persson, 1993), and relative comparisons with other adhesion force components such as the capillary force appear reasonable.

Adhesion forces also depend on the interfacial energy between the two surfaces in contact (Johnson et al., 1971; Deryaguin et al., 1975) and on the elastic properties of the surfaces contact, i.e. the reduced Young's modulus at the contact point between the contiguous bodies (Johnson, 1976).

The surface roughness does not only influence the Lifshitz-van der Waals' force, but also the contact angle between, e.g. water and the surface (Zografi and Johnson, 1984), and therefore the magnitude of the capillary forces (Gillespie and Settineri, 1967; O'Brien and Hermann, 1973). The surface roughness decreases the contact angle measured and therefore the capillary force should increase if O'Brien and Hermann (1973) theory is considered. However, The significance of this effect in real measurements, where the experimental error from the contact angle measurements and the adhesion force measurements has to be taken into account, is unknown.

2. Materials and methods

One particle size fraction of salmeterol xinafoate (Glaxo Research and Development, Ware, UK) was produced by air jet sieving (Alpine, Augsburg, D). The average particle mass of this particle size fraction was determined using an autobalance (AD-4, Perkin-Elmer, Connecticut, USA), whereas the average particle size of the fraction was defined by means of an Image Analyzer (Seescan Solitaire 512, Cambridge, UK), fitted with a CCD-4 black/white camera (Rengo Co. Ltd. Toyohashi, Japan) and an Olympus BH-2 microscope (Olympus Co., Tokyo, Japan). Five accurately weighed samples were suspended in liquid paraffin (BDH, Poole, UK), and the particles were counted with the image analyzer. The particle mass was found to be 64.0 ± 8.2 ng and the mean particle size (Feret's diameter, average of 1000 particles) 35.9 μm.

Flat powder surfaces of 10 mm diameter and 3 mm height were produced by compaction of 300.0 mg of lactose monohydrate (Lactochem, UK) using an Universal Testing Instrument (Instron, Model TT, High Wykcombe, UK) at a compaction pressure of about 70 MPa and a dwell time of 3 min. Large carrier particles of lactose monohydrate (average Feret's diameter 194 ± 59 μm, image analysis) were produced by manual sieving.

Particles were sprinkled onto the compacted powder surfaces (adhesion samples for particle-on-surface experiments) using a sieve technique to guarantee an agglomeration-free deposition of single particles on top of the surfaces. The preparation of the adhesion samples for particle-on-particle experiments is more difficult and has been described in detail by Podczeck (1995). For both techniques the adhesion samples were stored under different relative air humidity conditions until the adhesion measurement took place. A difference in relative humidity of the air was simulated with desiccators, which contained different saturated salt solutions. In this way, a relative humidity of the air of 5% (sodium hydroxide), 35% (calcium chloride), 55% (magnesium nitrate), 75% (sodium chloride) and 95% (potassium nitrate) was achieved.

The adhesion tests were performed using a centrifuge technique described earlier (Lam and Newton, 1991; Podczeck et al., 1994). The samples were sealed in an air-tight adhesion cell, which has been described in the previous publications, during the determination of the adhesion force, thus eliminating any gross change in humidity. The press-on force to increase the contact between the particles and the substrate surfaces was varied between 1.00×10^{-9} and 10.00×10^{-9} N. The spin-off force necessary to detach the particles adhered was varied between 0.063×10^{-9} and 14.13×10^{-9} N (particle-on-surface experiments) or 20.35×10^{-9} N (particle-on-particle experiments) according to the limitations of the centrifuge used (MSE High Speed Ultracentrifuge, Fisons Instruments, Crawley, UK). The particles remained adhering were counted using the image analyzer described above in a manual mode. The surfaces were illuminated with a cold light beam applied parallel to the surface (Cold light, Olympus Co., Hamburg, D). The median adhesion force and the interquartile range of the adhesion distributions were calculated for the reasons discussed by Podczeck et al. (1994). Results are the arithmetic mean and standard deviation of six replicates.

To test the influence of the relative humidity of the air on the adhesion force and the reversibility of the effects three consecutive storage periods were defined. First the compacted powder surfaces were stored at a defined level of relative humidity (prestorage). The period of prestorage does not apply to particle-on-particle experiments, because the technique requires the carrier and the substrate particles to be stored over silica gel. After the end of the prestorage period the powder particles were sprinkled onto the disks and the resulting adhesion samples were stored at a defined level of relative humidity (first storage period). Adhesion samples for particle-on-particle experiments were subjected to the first storage period immediately after preparation. After this storage period was finished the samples were immediately transferred into a further container providing the relative humidity of the second storage period, where the samples were kept until the experimental determination of the adhesion force took place. During the storage and experiment, the room temperature was maintained at 20 ± 2°C and the relative humidity ranged between 30 and 40%.

The experiments were organised in a centre of gravity design (Podczeck, 1995). The influence of press-on force, prestorage of the compacted surfaces, first storage humidity and second storage humidity of the adhesion samples were used as main factors of the design (Table 1). Surface points were added to test possible interactions between the first and second storage humidity. The storage time of the adhesion samples at the first or second storage condition was 72 h, whereas the prestorage of the compacted surfaces was at least 6 weeks. The press-on force was applied after the second storage time was completed, and the determination of the adhesion force followed immediately. The experiments were completed as quickly as possible, because the laboratory conditions could not be exactly controlled in terms of relative humidity of the air. The experiments were randomised to exclude systematic errors due to individual variations.

3. Results and discussion

In a previous work (Podczeck, 1995), the adhesion between salmeterol xinafoate particles and lactose monohydrate surfaces was assessed using two different strategies: first the use of compacted lactose monohydrate surfaces, and secondly the use of large lactose monohydrate carrier particles. Compacted powder surfaces are very different to particulate surfaces, and especially the higher level of porosity will influence the effect of relative humidity on the adhesion forces. Furthermore, contact angle measurements to assess the surface free energy of a powder, if undertaken on compacted surfaces, do not necessarily provide a thermodynamically correct estimate because of possible heterogeneity of the compact surface and crystal deformations during compaction (Buckton and Newton, 1986). However, the common pharmaceutical methods for contact angle measurements, the sessile drop technique (Ohm and Lippold, 1985) and the Wilhelmy plate method,

Table 1
Centre of gravity design to study the influence of the press-on force (F_{on}) and the relative humidity of the air in the prestorage period (PR), first (S1) and second storage period (S2) on the adhesion of salmeterol xinafoate particles to compacted lactose monohydrate surfaces and salmeterol xinafoate particles to lactose monohydrate particles

Experiment	F_{on} [$\times 10^{-9}$ N]	PR[n] [%]	S1 [%]	S2 [%]
1	1.0	35	55	55
2	2.5	35	55	55
3*	5.0	35	55	55
4	7.5	35	55	55
5	10.0	35	55	55
6	5.0	5	55	55
7	5.0	55	55	55
8	5.0	35	5	55
9	5.0	35	35	55
10	5.0	35	75	55
11	5.0	35	95	55
12	5.0	35	55	5
13	5.0	35	55	35
14	5.0	35	55	75
15	5.0	35	55	95
16[s]	5.0	35	5	5
17[s]	5.0	35	5	95
18[s]	5.0	35	95	95
19[s]	5.0	35	95	5

* Centre of gravity.
[s] Surface point (interaction term).
[n] Not studied in particle-on-particle experiments.

Table 2
Median adhesion force (F_{ad}) and interquartile range (IQR) of the adhesion force distributions observed on salmeterol xinafoate particles adhered to compacted lactose monohydrate surfaces and salmeterol xinafoate particles adhered to lactose monohydrate particles

Experiment	Factor	Particle-on-surface		Particle-on-particle	
		F_{ad} [$\times 10^{-9}$ N]	IQR [$\times 10^{-9}$ N]	F_{ad} [$\times 10^{-9}$ N]	IQR [$\times 10^{-9}$ N]
1	F_{on}	1.03 ± 0.07	1.53 ± 0.05	0.34 ± 0.05	0.63 ± 0.07
2	F_{on}	1.57 ± 0.40	2.85 ± 0.31	0.58 ± 0.14	0.91 ± 0.13
3	F_{on}	3.04 ± 0.20	4.86 ± 0.42	0.72 ± 0.14	1.07 ± 0.20
4	F_{on}	3.34 ± 0.28	6.54 ± 0.88	1.24 ± 0.06	1.44 ± 0.12
5	F_{on}	3.83 ± 0.51	7.43 ± 0.55	1.78 ± 0.31	1.95 ± 0.25
6	PR	4.18 ± 1.92	7.36 ± 2.28	n.d.	n.d.
7	PR	4.34 ± 0.42	7.16 ± 0.55	n.d.	n.d.
8	S1	2.19 ± 0.42	3.30 ± 0.16	0.86 ± 0.12	1.09 ± 0.13
9	S1	1.96 ± 0.30	3.94 ± 0.39	0.75 ± 0.07	1.05 ± 0.18
10	S1	7.39 ± 2.07	12.47 ± 0.89	3.76 ± 0.63	6.05 ± 0.82
11	S1	(38.73 ± 20.1)	(75.16 ± 35.5)	9.50 ± 1.26	14.42 ± 0.94
12	S2	2.56 ± 0.43	4.09 ± 0.15	0.60 ± 0.09	0.74 ± 0.12
13	S2	1.16 ± 0.17	2.05 ± 0.23	0.89 ± 0.16	1.09 ± 0.09
14	S2	14.22 ± 3.11	(22.35 ± 6.09)	4.78 ± 1.12	10.56 ± 0.94
15	S2	(12.10 ± 2.49)	(20.39 ± 2.92)	6.27 ± 0.91	13.73 ± 1.75
16	S1/S2	0.32 ± 0.08	0.96 ± 0.13	0.51 ± 0.09	0.72 ± 0.14
17	S1/S2	7.17 ± 0.76	12.20 ± 0.92	8.89 ± 1.28	14.80 ± 0.94
18	S1/S2	9.35 ± 3.11	(17.18 ± 3.15)	8.58 ± 1.15	15.02 ± 1.49
19	S1/S2	11.40 ± 3.09	(25.73 ± 11.0)	6.55 ± 1.39	14.19 ± 0.98

For factor levels refer to Table 1.
Values in brackets are extrapolations from the log-probability graphs.
n.d., values not determined.

require compacts, and alternative methods of liquid penetration into loose powder beds (Studebaker and Snow, 1955) are regarded to be very inaccurate per se (Gissinger and Stamm, 1980). Hence, the influence of relative humidity of the air on the adhesion between two powder materials could be different for particles adhered to compacted powder surfaces (particle-on-surface experiments) and particles adhered to carrier particles (particle-on-particle experiments).

In Table 2 the results for particle-on-surface and particle-on-particle experiments are summarized listing the median adhesion force and the interquartile range of the adhesion force distributions. Fig. 1 shows the adhesion force distributions of the particle-on-surface experiments obtained for a variation of the relative humidity in the first storage period. Up to a relative humidity level of 55% the adhesion force distributions are not visibly affected indicating that no capillary force is involved. However, at the higher relative humidity levels of 75% and 95% the adhesion force distributions are distorted towards higher force values, and the terminal portion of the adhesion force distributions appears to be more dependent on the relative humidity level. This might be due to water condensation into the pores of the compacted powder surfaces leading to a hydrostatic force. Fig. 2 compares the adhesion force distributions of the particle-on-surface experiments if the relative humidity in the second storage period was varied. Again a higher level of relative humidity increases the adhesion force, affecting the terminal portion of the adhesion

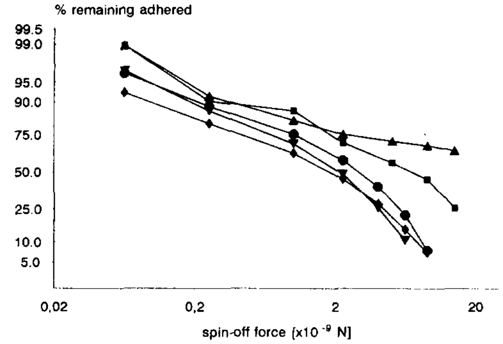

Fig. 1. The influence of the first storage period S1 on the adhesion force distributions of salmeterol xinafoate sticking to compacted lactose monohydrate surfaces (log-probability graphs). (▼) S1 = 5%; (◆) S1 = 35%; (●) S1 = 55%; (■) S1 = 75%; (▲) S1 = 95%.

force distributions to a greater extent. Here, an increase in relative humidity from 5% to 35% already alters the adhesion properties. However, because the adhesion force distributions obtained for 35% and 55% relative humidity of the air are similar, this is probably a plasticizing effect due to adsorbed water. The experiments to study the interaction between the first and second storage period clearly show that, in the case of salmeterol xinafoate particles adhered to compacted lactose surfaces, the effect of excessive relative humidity of the air is not reversible, at least not by just storing the adhesion samples at a very low relative humidity of the air such as 5%. Padmadisastra et al. (1994) found that a high relative humidity can cause solid bridges between pharmaceutical powder particles in adhesion contact, and therefore adhesion forces once built cannot be lowered by drying the samples. However, in the present experiments lactose monohydrate is water soluble, but the drug is water insoluble. The vapour pressure of the water might be reduced due to the contact between salmeterol xinafoate and lactose monohydrate, and therefore a restorage at a low relative humidity could not lead to the evaporation of the water, and the capillary force was manifested.

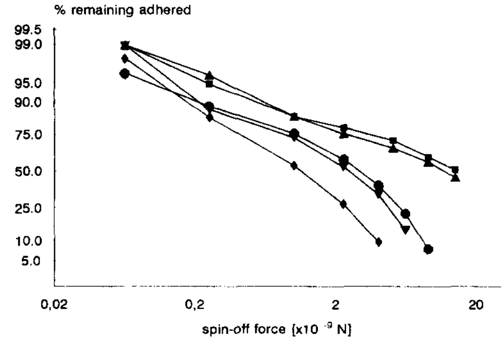

Fig. 2. The influence of the second storage period S2 on the adhesion force distributions of salmeterol xinafoate sticking to compacted lactose monohydrate surfaces (log-probability graphs). (▼) S2 = 5%; (◆) S2 = 35%; (●) S2 = 55%; (■) S2 = 75%; (▲) S2 = 95%.

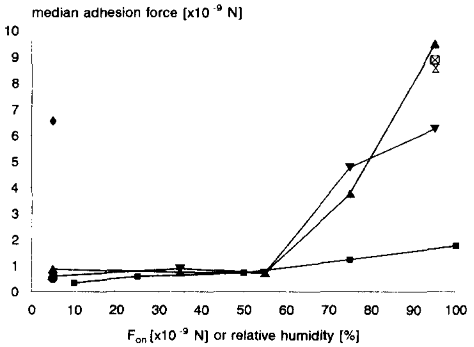

Fig. 3. The influence of the press-on force (F_{on}) and the relative humidity of the air in the first (S1) and second (S2) storage period on the median adhesion force of salmeterol xinafoate sticking to lactose monohydrate particles. (▲) S1; (▼) S2; (■) F_{on}; (●) S1 = S2 = 5%; (☒) S1 = 5%/S2 = 95%; (⧗) S1 = S2 = 95%; (◆) S1 = 95%/S2 = 5%.

In principle, the influence of the relative humidity of the air in the first and second storage period on the adhesion of salmeterol xinafoate to lactose monohydrate particles (particle-on-particle experiments) is similar to the effects found in the particle-on-surface experiments (see Table 2). The median adhesion forces as functions of the relative humidity of the air and the press-on force are summarized in Fig. 3. Similarly to the particle-on-surface experiments the adhesion force (capillary force) build up during the first storage period cannot be reduced during the second storage period, and the relative humidity of the first storage period has a higher effect on the adhesion force measured than the second storage period. The last point suggests that the formation of capillary forces does not take more time than one storage period, hence maximal 72 h. This is confirmed by the two interaction experiments (1: S1 = 5%, S2 = 95%; 2: S1 = S2 = 95%), which lead to similar adhesion forces.

The critical level of humidity for storage of interactive mixtures of salmeterol xinafoate adhered to lactose monohydrate appears to be 55% according to these experiments. Higher humidity levels will cause any dosage form that relies on the detachment of the drug from the carrier particles, as for example in dry powder inhalations, to be non-functional. The results agree with the findings reported by Prime et al. (1996), and with those reported by Brindley et al. (1995) for the dry powder aerosol Serevent®, which contains an interactive mixture of these two materials.

Fig. 4 compares the effects which the main factors (press-on force, relative humidity in the first and second storage period, prestorage of the compacted powder surfaces) had on the adhesion forces, measured both in particle-on-surface and in particle-on-particle experiments, based on Analysis of Variance (ANOVA). The press-on force has only a minor effect on the adhesion forces and an application of force, e.g. during mixing will not be able to overcome strong adhesion forces due to a high relative humidity during manufacture. The effects of the factors tested are generally smaller in particle-on-particle experiments than in particle-on-surface experiments.

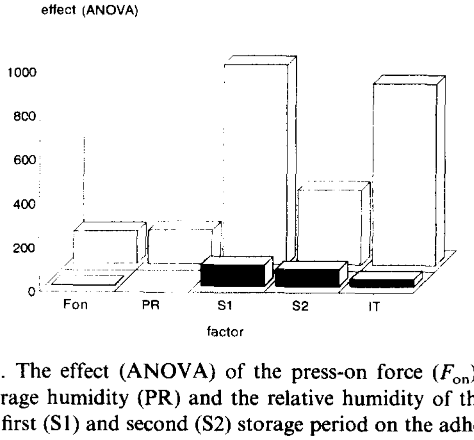

Fig. 4. The effect (ANOVA) of the press-on force (F_{on}), the prestorage humidity (PR) and the relative humidity of the air in the first (S1) and second (S2) storage period on the adhesion of salmeterol xinafoate to lactose monohydrate in particle-on-particle (front bars) or particle-on-surface experiments. IT, interaction term between S1 and S2.

Previous investigations to study only the influence of press-on force have also shown that the adhesion force in particle-on-particle experiments was always smaller than in particle-on-surface experiments (Podczeck et al., 1994). However, in the case of the influence of the relative humidity of the air on the adhesion properties, the general conclusions are identical, and therefore the use of only one of the two techniques—particle-on-particle or particle-on-surface measurements—is adequate. As particle-on-surface are the easier measurements to make, this would be the procedure recommended to establish the influence of humidity.

For low dose drugs such as salmeterol xinafoate, capillary forces between the carrier excipient particles can dominate the performance of the powder mixture. Hence, autoadhesion studies for lactose monohydrate have been reported (Podczeck et al., 1996). It was found that capillary forces were high but reversible after subsequent storage in a low humidity environment. The autoadhesion force of salmeterol xinafoate was not effected by changes in relative humidity of the air (Podczeck et al., 1996).

To find out the reasons for the different response of the systems (autoadhesion of lactose monohydrate, salmeterol xinafoate; adhesion between the two substances) to a change in relative humidity of the air, physical parameters characterizing the two substances in contact must be considered. Table 3 lists the physical parameters which potentially need to be taken into account. The interfacial energy has been calculated from the surface free energy values of lactose monohydrate and salmeterol xinafoate which have been previously reported (Podczeck et al., 1995), and the values of the reduced Young's moduli have also been calculated from the Young's moduli of the individual substances (Podczeck et al., 1995). To calculate the distance of separation, it was necessary to estimate the Lifshitz constant. For the autoadhesion of the two test materials this has already been reported (Podczeck et al., 1994) using low frequency dielectric spectroscopy. For the assessment of adhesion, the constant could be derived by joint integration of the real dielectric functions. The Lifshitz constant for the adhesion

Table 3
Physical parameters characterizing the autoadhesion contact of lactose monohydrate and salmeterol xinafoate, and the adhesion contact between salmeterol xinafoate and lactose monohydrate

	Autoadhesion lactose monohydrate[a]	Autoadhesion salmeterol xinafoate[a]	Adhesion particles-on-surfaces	Adhesion particles-on-particles
$\Delta\gamma$ [mJ m^{-2}]	147.2	109.6	127.0	127.0
E^* [GPa]	13.35	5.85	8.14	8.14
z_0 [nm]	66 ± 9	38 ± 2	34 ± 8	61 ± 5
F_{max} [$\times 10^{-9}$ N]	32.1	3.1	38.7	9.5
F_{vdw} [$\times 10^{-9}$ N]	1.0	2.2	2.8	0.8
F_c [$\times 10^{-9}$ N]	31.1	(0.9)	35.9	8.7
P_{max} [Pa]	10.36	0.76	9.45	2.32

[a] Data based on results reported earlier (Podczeck et al., 1995).
$\Delta\gamma$, interfacial energy.
E^*, reduced Young's modulus at the contact points between two surfaces.
z_0, distance of separation between contiguous bodies.
F_{vdw}, Lifshitz-van der Waals' force.
F_c, capillary force.
F_{max}, maximal adhesion force obtained;
P_{max}, apparent maximal adhesion pressure obtained.

between lactose monohydrate and salmeterol xinafoate is 3.943×10^{-18} J. The distance of separation between the adhered particles and the surfaces used can be calculated from Eq. (3) (see Section 1) as a mean value of those measurements at a press-on force of 5×10^{-9} N which did not involve capillary forces. The maximal force measured was taken from Table 2, and the Lifshitz-van der Waals' force was calculated as a mean force value of all experiments which did not involve storage at a higher relative humidity than 55% at any stage, and where the press-on force applied was 5×10^{-9} N. The difference between maximum adhesion/autoadhesion force obtained and calculated Lifshitz-van der Waals' force is considered to be the capillary force. An apparent maximum adhesion/autoadhesion pressure was also calculated because the lactose monohydrate and salmeterol xinafoate particles are not of similar weight or size. This calculation implies that the maximum force obtained is mainly a result of capillary forces and therefore the area of contact could be approximated by the visible area of the two-dimensional particle images, which was 3099 μm^2 and 4095 μm^2 for lactose monohydrate and salmeterol xinafoate particles, respectively, determined using image analysis.

The difference in the adhesion forces obtained from either particle-on-surface or particle-on-particle experiments can clearly be explained by the differences in the distance of separation z_0 (see Table 3). The Lifshitz-van der Waals' forces F_{vdw} are also related to the interfacial energy $\Delta\gamma$. Fig. 5 shows the linear relationship between F_{vdw} and the ratio $\Delta\gamma/z_0$. Therefore, an adhesion force due to Lifshitz-van der Waals' forces can be reduced either by reducing the interfacial energy of the solids in contact, which would involve crystallographic or chemical modifications of the powders,

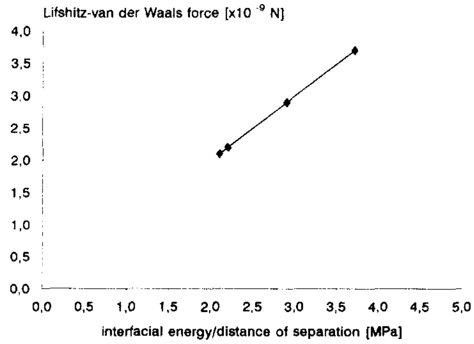

Fig. 5. Lifshitz-van der Waals' forces as a function of the ratio between interfacial energy $\Delta\gamma$ and distance of separation z_0 [$F_{vdw} = f(\Delta\gamma/z_0)$].

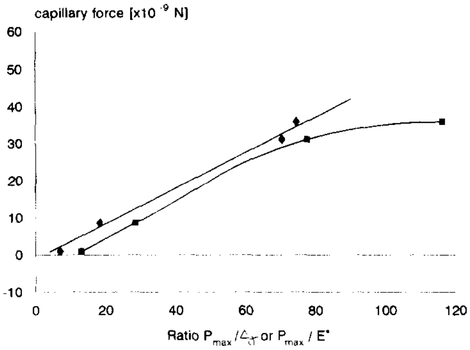

Fig. 6. Capillary forces as a function of (◆) the ratio of adhesion pressure $P_{\max}$ to interfacial energy $\Delta\gamma$ [$F_c = f(P_{\max}/\Delta\gamma)$] and (■) the ratio of $P_{\max}$ to reduced Young's modulus E^* [$F_c = f(P_{\max}/E^*)$].

or by applying only low forces during any powder handling processes.

Fig. 6 shows the relationships between the estimated capillary force F_c and the ratio of either maximum adhesion pressure $P_{\max}$ to interfacial energy $\Delta\gamma$, or $P_{\max}$ to reduced Young's modulus E^*. The linearity of F_c as a function of $P_{\max}/\Delta\gamma$ suggests that a large interfacial energy might be an advantage if capillary forces are to be reduced. The hyperbolic shape of $F_c = f(P_{\max}/E^*)$ however implies that the elastic properties of the materials in contact make a smaller contribution to the magnitude of capillary forces. This is not surprising, because moisture can act as plasticiser and also can convert elastic into plastic deformations. This suggests that the strength of adhesion/autoadhesion forces is clearly related to surface energy properties of the materials in contact, but an exact prediction of the change of capillary forces due to a variation in relative humidity of the air is not possible on basis of the results presented in this paper and in the previous work (Podczeck et al., 1996).

4. Conclusions

The study has clearly identified that strong capillary forces which developed during storage of samples of salmeterol xinafoate and lactose monohydrate at relative humidities of 75% and above cannot be reduced by restoring the samples at low relative humidities. This phenomenon was observed when the drug was adhered to compacted lactose monohydrate surfaces and when adhered to lactose monohydrate particles. Hence the former type of experiments, which are easier to perform, can be used to study the influence of storage conditions on drug-carrier mixtures. A relationship was observed between adhesion forces and the interfacial energy of the materials in contact. This suggests that for systems to have a minimum adhesion strength, the interfacial energies should be small for systems involving Lifshitz-van der Waals' forces, i.e. dry conditions, but should be large for systems involving capillary forces, i.e. high relative humidity.

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