ELSEVIER International Journal of Pharmaceutics 145 (1996) 221–229

international journal of pharmaceutics

The influence of constant and changing relative humidity of the air on the autoadhesion force between pharmaceutical powder particles

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Received 22 August 1996; accepted 11 October 1996

Abstract

The influence of the press-on force applied and the relative humidity of the air during the storage of autoadhesion samples made from lactose monohydrate or salmeterol xinafoate has been studied using the centrifuge technique. Capillary forces can be obtained for lactose monohydrate if subjected to a relative humidity of 75% or more. The resulting strong autoadhesion forces are reversible by subsequently storing the autoadhesion samples at a low humidity environment. The strength of the capillary forces depends on the storage time, and to reach an equilibrium level requires more than 72 h. For the less polar salmeterol xinafoate the performance of capillary forces could not be proved with certainty. It appears that a very small increase in autoadhesion force at higher relative humidity levels is more likely caused by adsorbed water acting as a plasticizer. Model calculations of capillary forces did not prove successful in predicting the autoadhesion force of the materials if stored at a high relative humidity of the air. The knowledge of the surface free energy and its polar component gave a better basis for a prediction. Copyright © 1996 Elsevier Science B.V.

Keywords: Autoadhesion; Capillary forces; Lactose monohydrate; Powder particles; Press-on force; Relative humidity; Salmeterol xinafoate; Surface free energy

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1. Introduction

The development of dry powder aerosols involves the knowledge of the adhesion properties between the drug substance and carrier excipient particles as well as the adhesion properties between the particulate materials and the inhaler device material. The adhesion of the powder to the inhaler device material should be as minimal as possible, whereas the adhesion strength be-

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PII S0378-5173(96)04774-6

tween the drug substance and carrier excipient material has to be balanced to guarantee first the transport of drug-carrier agglomerates out of the inhaler device into the upper respiratory tract, and secondly the separation of the drug particles, which must reach the lung, from the carrier particles, which are usually swallowed. The adhesion force between the particulate materials is therefore of special interest. For dry powder inhalations a low dose drug is usually mixed with a carrier excipient (drug to carrier ratio 1:50 to 1:500). Hence a large quantity of carrier particles are in direct contact to each other. Although often referred to as 'cohesion' in the pharmaceutical literature, this phenomenon is correctly called autoadhesion, because the particles are not at an atomic distance from each other, nor do they form a single solid body (Zimon, 1982). There are also dry powder inhalations reported for high dose drugs, where little or no carrier excipient is necessary. In these cases drug particles are in autoadhesion contact (Wong et al., 1995).

The aim of the present work was to study the extent of capillary forces and their dependence on the relative humidity of the air using two pharmaceutical substances, salmeterol xinafoate and lactose monohydrate, in autoadhesion contact. Both chemicals are possible components in dry powder inhalations. They have been chosen, because they differ in their surface properties such as surface roughness, surface free energy and wettability. The experimental force values shall be compared with theoretical capillary forces and Lifshitz-van der Waals forces calculated. The experiments were based on a statistical design which allowed the reversibility of autoadhesion forces due to humidity of the air to be assessed.

Generally, adhesion and autoadhesion forces between contiguous bodies are due to Lifshitz-van der Waals, capillary, electrical and electrostatic (Coulomb) forces (Rumpf, 1977), but the dominance of one or several factors over the other(s) depends on the environmental conditions during the experiments and on the physico-chemical properties of the materials in contact. The experimental determination of electrostatic forces requires special equipment to charge the particles and/or surfaces and to measure a possible charge decay, as described by Deryaguin et al. (1968, 1978). Electrostatic forces are at least ten times smaller than Lifshitz-van der Waals forces (Rumpf, 1977), and through moisture a charge leakage will occur. The role of electrostatic forces in adhesion is thus to contribute to the deposition and agglomeration of particles, but once adhesion contact has been formed, other forces are responsible for the adhesion strength (Visser, 1995). In a dry environment, electrical forces arise during the contact of surfaces, but they are constant for the contact of two defined materials (Zimon, 1982). Also these forces are at least ten times smaller than Lifshitz-van der Waals forces (Rumpf, 1977), and in the presence of moisture in the gap between the contiguous bodies they cannot exist (Zimon, 1982). Lifshitz-van der Waals forces act between contiguous bodies up to a distance of separation of 100 nm (Rumpf, 1977) and depend on the radius of contact, the Lifshitz constant and the distance of separation (Krupp, 1967). Capillary forces arise from moisture in the gap between the contiguous bodies. Hydrophillic, porous materials often contain moisture trapped in the pores, which is able to build up liquid bridges to adhered/autoadhered surfaces (Schubert, 1974). A second source of capillary forces is moisture which condenses in the gap between the contiguous bodies. Such condensation starts at a relative humidity of the air of about 50%. Below this value no such capillary forces exist (Zimon, 1982), and above a relative humidity of the air of 65–75% (Zimon, 1982; Ketkar and Keller, 1975) capillary forces dominate the adhesion/autoadhesion strength. The extent of capillary forces due to moisture condensation depends on the geometry of the gap between the contiguous bodies and on the properties of the materials in contact such as surface free energy, wettability and surface roughness (Massimilla and Donsì, 1976). However, moisture condensation may also cause a change in the electrical conductivity of a material (Kulvanich and Stewart, 1988), or may act as a plasticizer (Iida et al., 1992) and hence increase the adhesion/autoadhesion force via increasing the contact area between the contiguous bodies due to enhanced plastic deformability.

2. Theory

Several theories are reported in the literature to calculate capillary forces acting between a particle and a flat surface. All of them consider the particles to be spherical. Therefore, their use to predict capillary forces for common pharmaceutical powders is limited. However, such calculations still give a rough estimate of the order of magnitude of the forces. (Note that powder particles and a surface made from an identical material can have different surface properties, i.e. different contact angles (Buckton and Newton, 1986). Hence the equations cited below might be used for adhesion and autoadhesion contact).

A very simple calculation method of capillary forces has been developed by O'Brien and Hermann (1973):

$$F_c = 2\pi r\sigma(\cos\theta_1 + \cos\theta_2) \tag{1}$$

where F_c is the capillary force, r is the radius of the spherical particle adhered, θ_1 and θ_2 are the contact angles between the two bodies in contact and a liquid, σ is the surface tension of the liquid. In the case that the influence of the relative air humidity is to be studied, the contact angles between the two powder materials and water are needed. However, this equation requires an ideal sphere being in contact with a plate like surface. It does not allow the possible adjustment of the differences in the menisci and hence the contact area between the liquid and the particle in the contact zone, which will vary depending on the liquid vapour pressure.

The surface tension of the liquid will increase the force acting between the contiguous bodies. These so-called surface tension forces ($F_{c,1}$) can be calculated as

$$F_{c,1} = 2\pi a_0\sigma \tag{2}$$

where a_0 is the radius of the meniscus. The meniscus formed along the surfaces will also reduce the liquid pressure. The liquid pressure ($F_{c,2}$) can be expressed as

$$F_{c,2} = \pi a_0^2 P_c \tag{3}$$

where P_c is the capillary pressure. Therefore the capillary force (F_c) can be calculated from (Zimon, 1982):

$$F_c = F_{c,1} - F_{c,2} = 2\pi a_0\sigma - \pi a_0^2 P_c \tag{4}$$

Gillespie and Settineri (1967) described a method of calculating the radius of the liquid meniscus (a_o):

$$a_0 = r\sin\alpha + \frac{r(1-\cos\alpha)\cos(\theta+\alpha)}{1+\sin(\theta+\alpha)} \tag{5}$$

where θ is the contact angle between the adhered particle and the liquid, α is the angle between the perpendicular from the centre of gravity of the particle and the connecting line between the centre of gravity of the particle and the outer surface of the meniscus.

The capillary pressure (P_c) is an index for the difference in pressure, which exists between two bulk phases that are separated by a curved surface and in a state of equilibrium (Zimon, 1982). The two bulk phases are not the particle and the substrate surface, but the liquid bridge between the contiguous bodies and the air, whereas the curved surface stays for the particulate materials in contact. The calculation of the capillary pressure is different for adhesion and autoadhesion. Metskevich and Nerpin (1967) derived the following equation to estimate the capillary pressure for a particle and a plane surface in contact, which have different wetting properties:

$$P_c = \frac{\sigma}{r}\left(\frac{\cos(2+\theta_1) + \cos\theta_2}{1-\cos\alpha}\right) \tag{6}$$

where θ_1 is the contact angle for the particle and θ_2 is the contact angle for the substrate surface. Zimon (1982) quotes the following equation for the case that $\theta_1 = \theta_2$:

$$P_c = \frac{\sigma}{r}\left(\frac{r}{a_0} - \frac{\cos(\theta+\alpha)}{1-\cos\alpha}\right) \tag{7}$$

For autoadhesion contacts, where the contact angle θ between the condensed water and the surface is small, and the radius of the meniscus a_0 does not reach the full particle radius, Fisher and Israelachvili (1981) proposed a simpler equation to calculate the capillary force:

$$F_c = 4\pi r\sigma\cos\theta + 4\pi r\gamma_{sl} \tag{8}$$

where σ is the surface tension of the condensed liquid (e.g. water), and γ_{sl} is the solid–liquid interfacial free energy. Luckham (1989) proved this equation to be valid in experiments using a force microscope.

A direct comparison between the capillary forces calculated and experimental adhesion forces is not immediately possible, because first the adhesion force measured for particles which are larger than the distances between the asperities of the contact surface is usually smaller than the calculated value due to a reduced true area of contact because of the surface roughness (Corn, 1961). Secondly, at a higher relative air humidity the gap between the contiguous bodies will be filled with water, and in the equilibrium state this gap, which is then equivalent to the liquid film thickness, has an equilibrium value (T). This separation distance will lower the adhesion force between the particle and the surface by generating a disjoining pressure (F_{disj}) (Zimon, 1982):

$$F_{\mathrm{ad}} = F_{\mathrm{c}} - F_{\mathrm{disj}} \tag{9}$$

where F_{ad} is the force of adhesion, and $F_{\mathrm{disj}} \propto T$.

3. Materials and methods

One particle size fraction of salmeterol xinafoate (Glaxo Research and Development, Ware, UK) and lactose monohydrate (Lactochem, UK) were produced by air jet sieving (Alpine, Augsburg, D). The average particle mass of these particle size fractions was determined using an autobalance (AD-4, Perkin-Elmer, CT, USA), whereas the average particle size of the fractions was defined by means of an Image Analyzer (Seescan Solitaire 512, Cambridge, UK), fitted with a CCD-4 black/white camera (Rengo, Toyohashi, Japan) and an Olympus BH-2 microscope (Olympus, Tokyo, Japan). Five accurately weighed samples were suspended in liquid paraffin (salmeterol xinafoate) or triacetin (lactose monohydrate) (BDH, Poole, UK), and the particles were counted with the image analyzer. The particle masses are 64.0 ± 8.2 and 80.8 ± 3.9 ng for salmeterol xinafoate and lactose monohydrate, respectively. The mean particle size (Feret's diameter, average of 1000 particles) is 35.9 and 62.3 mm, for salmeterol xinafoate and lactose monohydrate, respectively.

Flat powder surfaces of 10 mm diameter and 3 mm height were produced by compaction of 300.0 mg of lactose monohydrate or 240.0 mg salmeterol xinafoate 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.

Particles were sprinkled onto the powder surfaces using a sieve technique to guarantee an agglomeration free deposition of single particles on top of the surfaces. To study the autoadhesion properties, salmeterol xinafoate particles were deposited onto salmeterol xinafoate surfaces, and lactose monohydrate particles were deposited onto lactose monohydrate surfaces. These autoadhesion samples were stored under different relative humidity of the air conditions until the autoadhesion 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 autoadhesion tests were performed using a centrifuge technique described earlier (Podczeck et al., 1994; Lam and Newton, 1991). 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 autoadhered was varied between 0.063×10^{-9} and 14.13×10^{-9} N according to the limitations of the centrifuge used (MSE High Speed Ultracentrifuge, Fisons Instruments, Crawley, UK). The particles remained autoadhering were counted using the image analyzer described above. The surfaces were illuminated with a cold light beam applied parallel to the surface (Cold light, Olympus, Hamburg, D). The median autoadhesion force and the interquartile range of the autoadhesion distributions were calculated. Results are the arithmetic mean and standard deviation of six replicates.

To test the influence of the relative humidity of the air on the autoadhesion 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). After the end of this storage period the powder particles were sprinkled onto the disks and the resulting autoadhesion samples were stored at a defined level of relative humidity (first storage period). 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 autoadhesion force took place.

The experiments were organised in a centre of gravity design (Podczeck, 1986). The influence of press-on force (F_{on}), prestorage of the compacted surfaces (PR), first storage humidity (S1) and second storage humidity (S2) of the autoadhesion 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 autoadhesion samples at the first or second storage condition was 72 h, whereas the prestorage of the compacted surfaces was at least 6 weeks. This time appears to be sufficient, because Zimon (1982) could show that an equilibrium capillary force has already been built up after 30 min. The press-on force was applied after the second storage time was completed, and the determination of the autoadhesion force followed immediately. The experiments were completed as quickly as possible, because the humidity conditions in the laboratory could not be controlled. The experiments were randomised to exclude systematic errors due to individual variations.

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 autoadhesion of lactose monohydrate particles to compacted lactose monohydrate surfaces and salmeterol xinafoate particles to compacted salmeterol xinafoate particles

Experiment	F_{on} ($\times 10^{-9}$ N)	PR (%)	S1 (%)	S2 (%)
1	1.0	35	55	55
2	2.5	35	55	55
3[a]	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[b]	5.0	35	5	5
17[b]	5.0	35	5	95
18[b]	5.0	35	95	95
19[b]	5.0	35	95	5

[a] Centre of gravity.
[b] Surface point (interaction term).

4. Results and discussion

Although a variation in press-on force was included in the statistical design, the main purpose of the study was to assess the influence of the relative humidity of the air on the autoadhesion properties of lactose monohydrate and salmeterol xinafoate. The effects due to variation in relative humidity can be compared with those which are a result of the variation in press-on force. In this way a judgement as to whether or not problems with increased autoadhesion due to increased relative humidity of the air can be overcome by application of more force (e.g. high shear mixing) is possible. In any case, analysis of variance (ANOVA) was used to confirm the significance or absence of an effect.

Table 2 summarizes the autoadhesion results both for lactose monohydrate particles autoadhered to compacted lactose monohydrate surfaces and salmeterol xinafoate particles autoadhered to compacted salmeterol xinafoate surfaces. For lactose monohydrate ANOVA for the median autoadhesion force and the interquartile range showed that the press-on force and the relative humidity of the air in the prestorage period have no significant effect on the autoadhesion properties of this carrier excipient. However, the relative humidity of the air in the first and second storage

Table 2

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

Experiment	Factor	Lactose monohydrate		Salmeterol xinafoate	
		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}	0.41 ± 0.14	0.71 ± 0.12	1.25 ± 0.06	1.66 ± 0.28
2	F_{on}	0.83 ± 0.10	0.92 ± 0.06	1.05 ± 0.17	1.74 ± 0.10
3	F_{on}	1.29 ± 0.23	1.62 ± 0.30	2.05 ± 0.35	2.50 ± 0.32
4	F_{on}	1.51 ± 0.17	1.71 ± 0.30	3.19 ± 3.40	3.63 ± 0.55
5	F_{on}	1.69 ± 0.37	1.86 ± 0.45	3.40 ± 0.29	3.93 ± 0.53
6	PR	1.13 ± 0.19	1.35 ± 0.14	2.09 ± 0.23	2.68 ± 0.12
7	PR	1.27 ± 0.28	1.51 ± 0.11	2.87 ± 0.42	3.06 ± 0.36
8	S1	0.88 ± 0.09	0.88 ± 0.12	2.27 ± 0.15	2.85 ± 0.41
9	S1	1.21 ± 0.15	1.19 ± 0.13	2.48 ± 0.29	2.91 ± 0.53
10	S1	1.66 ± 0.38	2.74 ± 0.13	1.85 ± 0.18	2.49 ± 0.28
11	S1	5.56 ± 1.75	(19.30 ± 2.12)	2.14 ± 0.11	2.73 ± 0.29
12	S2	0.64 ± 0.07	0.85 ± 0.11	2.04 ± 0.28	2.45 ± 0.53
13	S2	0.81 ± 0.14	1.10 ± 0.09	2.07 ± 0.19	2.42 ± 0.08
14	S2	2.84 ± 0.64	3.67 ± 0.70	2.30 ± 0.34	2.71 ± 0.48
15	S2	(19.69 ± 2.04)	(21.68 ± 4.55)	3.13 ± 0.22	3.46 ± 0.29
16	S1/S2	0.57 ± 0.12	0.70 ± 0.14	2.02 ± 0.04	2.70 ± 0.59
17	S1/S2	3.67 ± 0.88	10.22 ± 0.56	1.90 ± 0.23	2.20 ± 0.09
18	S1/S2	(32.07 ± 6.09)	(30.74 ± 8.40)	1.97 ± 0.11	2.12 ± 0.29
19	S1/S2	9.56 ± 2.14	(21.62 ± 2.40)	1.97 ± 0.10	2.57 ± 0.23

For factor levels refer to Table 1.

Values in brackets are extrapolations from the log-probability graphs.

period and their interaction are highly significant factors (all $p < 0.0001$). Fig. 1 illustrates the effect of the first storage period on the autoadhesion properties of lactose monohydrate. Up to a relative humidity of 55% the increase in autoadhesion force appears to be rather small confirming that a limiting relative humidity of 65% has to be applied to ensure an effect (Zimon, 1982; Ketkar and Keller, 1975). A relative humidity of 75% and more increases the autoadhesion force of lactose monohydrate significantly.

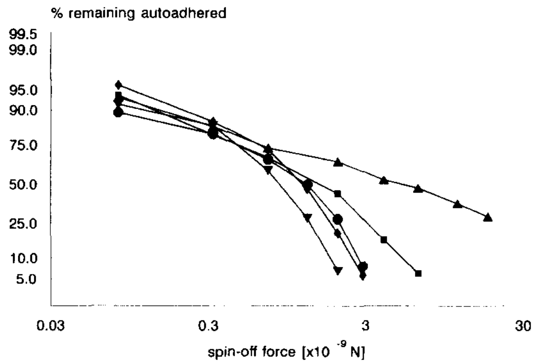

Fig. 1. The influence of the first storage period S1 on the autoadhesion force distributions of lactose monohydrate (log-probability graphs). ▼, S1 = 5%; ◆, S1 = 35%; ●, S1 = 55%; ■, S1 = 75%; ▲, S1 = 95%.

However, the change in relative humidity mainly influences the autoadhesion distributions at their lower end. Usually, the lower spin-off forces remove larger particles and those particles which are positioned on top of asperities. In such cases, the contact zone between particle and surface is open to the environment, and an evaporation of the condensed water during the second storage period appears possible. Experiments undertaken by Padmadisastra et al. (1994a,b) have suggested that for hydrophillic excipients such evaporation might cause a growth of solid bridges and therefore very high adhesion forces, because the excipient could have partly dissolved. The

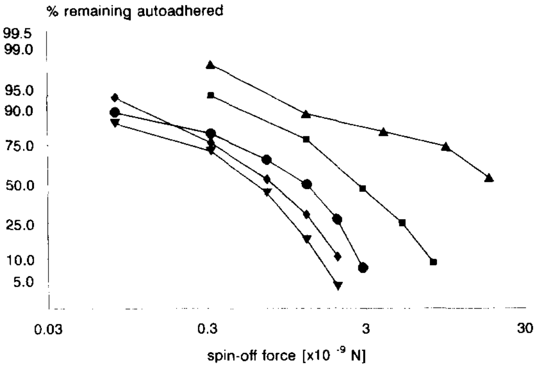

Fig. 2. The influence of the second storage period S2 on the autoadhesion force distributions of lactose monohydrate (log-probability graphs). ▼, S2 = 5%; ◆, S2 = 35%; ●, S2 = 55%; ■, S2 = 75%; ▲, S2 = 95%.

findings in this paper contradict these results, but the protocol of the experiments is very different to that used by Padmadisastra et al. (1994a,b), who prepared interactive mixtures between excipient granules and drug substances, which were then stored at 95% relative humidity. After 3 days they determined the percentage particles remaining adhered at 20 000 rpm with specially designed centrifuge cells. However, the use of a powder bed does not guarantee that all adhered drug particles face the periphery of the rotor and the outer surface of the powder bed, and the majority of the adhered particles will be mechanically trapped. A direct comparison with the results reported here is therefore not advisable.

Fig. 2 compares the autoadhesion force distributions for lactose monohydrate for the experiments where the relative humidity of the air was changed in the second storage period. Again the critical level of relative humidity appears to be above the test value of 55%. The whole autoadhesion profiles are altered when a relative humidity of 75 or 95% was used. Especially interesting are the results for the interaction between first and second storage period (Table 2). A restorage of the autoadhesion samples after a first relative storage humidity of 95% at a relative storage humidity of 5% reduces the median force of autoadhesion down to a tenth of the median autoadhesion force if the samples were stored at 95% relative humidity of the air only. However, the results also show that the median force of autoadhesion for lactose monohydrate is a highly time dependent property, because the storage at 95% relative humidity over the first and second period leads to a threefold higher median autoadhesion force than the storage at 5% (first period) in combination with a storage at 95% (second period). This is in contrast to Zimon (1982), who found that the maximum capillary force has been built up after 30 min. There is no significant difference between the median autoadhesion force if the samples were stored at 5% relative humidity only and the median adhesion force for samples which were first stored at 55% and then at 5% relative humidity of the air. However, a storage at 5% followed by a storage at 55% relative humidity of the air increases the median autoadhesion force significantly ($F = 25.63$, $p < 0.0001$). The higher humidity level in the second storage period leads to a moisture absorption which causes a softening of the surfaces and hence an increased plasticity.

Fig. 3 compares the autoadhesion force distributions for salmeterol xinafoate changing the relative humidity of the air in the first storage period. The graphs suggest that there is no real dependence of the autoadhesion properties, although the ANOVA proved the differences to be significant ($F = 5.38$, $p = 0.001$). From Table 2 it can be seen that there is an increase and decrease in the median autohesion force values consistent with the effect being non-existent. The significance

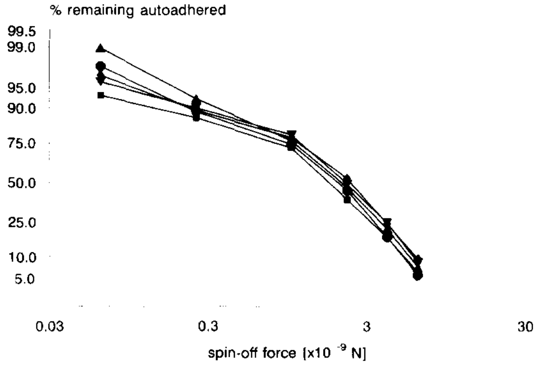

Fig. 3. The influence of the first storage period S1 on the autoadhesion force distributions of salmeterol xinafoate (log-probability graphs). ▼, S1 = 5%; ◆, S1 = 35%; ●, S1 = 55%; ■, S1 = 75%; ▲, S1 = 95%.

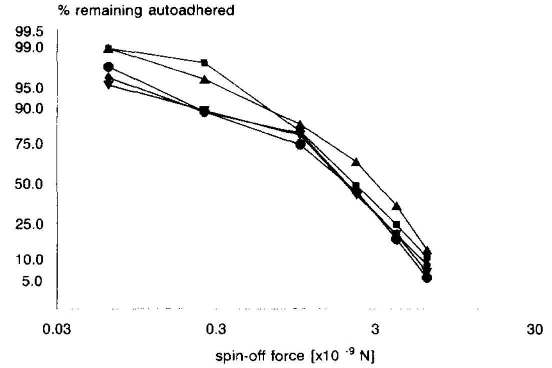

Fig. 4. The influence of the second storage period S2 on the autoadhesion force distributions of salmeterol xinafoate (log-probability graphs). ▼, S2 = 5%; ◆, S2 = 35%; ●, S2 = 55%; ■, S2 = 75%; ▲, S2 = 95%.

in the ANOVA is therefore a result of the low variability of the measurements. Fig. 4 shows the autoadhesion force distributions if the relative humidity in the second storage period was changed. The autoadhesion force increases slightly above a relative humidity of 55% suggesting the performance of capillary forces. However, the median autoadhesion forces for the interaction between relative humidity of the first and second storage period are not significantly different, which contradicts the results obtained from the variations in the second storage period. Therefore, the increase in median autoadhesion force (see Fig. 4) cannot be explained by the existence of capillary forces, but by a plasticising effect of the moisture adsorbed. The significant effect of the variation in relative humidity of the air in the prestorage period (see Table 2; $F = 9.60$, $p < 0.0001$) appears to confirm this theory, because the humidity levels tested are all below the critical level of 65%. In the case of the autoadhesion of salmeterol xinafoate particles to compacted salmeterol xinafoate surfaces the press-on force is the controlling variable (see Table 2; $F = 65.21$, $p < 0.0001$), which can overcome any of the effects discussed above.

Fig. 5 compares lactose monohydrate and salmeterol xinafoate in terms of the effects of the factors and interaction tested. Both materials behave very different. One reason for this could be their different surface free energy. Chawla (1993) reported a surface free energy of 73.56 mJ/m^2 for lactose monohydrate, where 76.9% are due to polarity. Podczeck et al. (1995) found that salmeterol xinafoate is less polar (32.4%) and the total surface free energy is also less (54.79 mJ/m^2). The smaller polarity value appears to be mainly responsible for the limited effect the relative humidity of the air has on the autoadhesion properties of salmeterol xinafoate. This finding correlates with a report by Jashnani and Byron (1996), who found that hydrophobic powders are less sensitive to a high storage humidity than hydrophillic powders with respect to their emptying and aerosolisation properties from dry powder inhalations.

Finally the calculation of a theoretical capillary force using Eqs. (7) and (8) was attempted. A problem arose with Eq. (7), because the angle α (the angle between the perpendicular of the centre of gravity of a particle and the outer meniscus of the liquid film) is unknown. However, numerical interpolation showed that an angle below 70° (lactose monohydrate) or 60° (salmeterol xinafoate) results in negative force values. Using Eq. (7), the theoretical capillary force between lactose monohydrate particles and a flat lactose monohydrate surface is therefore about 1.2×10^{-5} N ($\alpha = 70°$), whereas for salmeterol xinafoate a theoretical capillary force of 6.6×10^{-7} N ($\alpha = 60°$) was estimated. Both force values are huge compared with the experimental autoadhesion forces

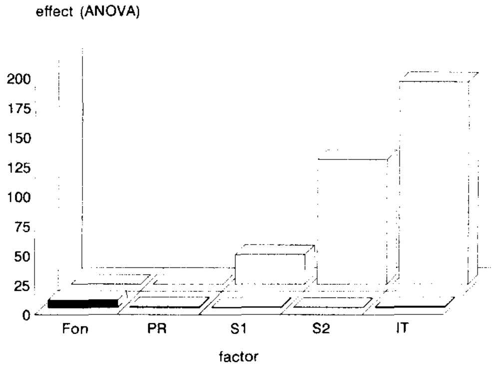

Fig. 5. The effect (ANOVA) of the press-on force (F_{on}), the prestorage humidity (PR) and the relative humidity of the air in the first (S1) and second (S2) storage period on the autoadhesion of salmeterol xinafoate (front bars) and lactose monohydrate; IT, interaction term between S1 and S2.

observed at a high relative humidity of the air. Using Eq. (8), the theoretical capillary forces are 2.9×10^{-8} and 1.2×10^{-8} N for lactose monohydrate and salmeterol xinafoate, respectively. These values appear more reasonable, although still suggesting a large disjoining pressure due to a large gap between the particles and the surface, which is filled with water. However, the clear difference between the two substances tested (see Fig. 5) is better reflected in the theoretical capillary force values, which are based on Eq. (7). Hence, the tendency to observe capillary forces for a material can be obtained using calculations of a theoretical capillary force, but the magnitude of such forces cannot be estimated. Therefore, the measurement of surface free energy values, which also characterized the tendency of capillary forces to exists, appears a better way to predict the autoadhesion properties of a material if subjected to a high level of relative humidity of the air.

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