Adhesion and Autoadhesion Measurements of Micronized Particles of Pharmaceutical Powders to Compacted Powder Surfaces

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Micronized samples of lactose monohydrate and salmeterol xinafoate have been used to study the adhesion of micronized particles to compacted powder surfaces. After an initial increase in median adhesion force with increased press-on force no further increase in median adhesion force can be achieved. Thus application of larger press-on forces eventually appears to result in a maximum plastic deformation of the micronized particles. This is in contrast to previous experiments using particles of the same materials in a size range between 20 and 120 μm, where an increase in press-on force always led to an increase in median adhesion force.

The adhesion of micronized lactose monohydrate particles to salmeterol xinafoate surfaces is numerically higher than the adhesion of micronized salmeterol xinafoate particles to lactose monohydrate surfaces, although theoretically the same two materials are adhered to each other. This effect could be due to differences in the surface roughness of the compacted surfaces. Hence, if a true estimate of adhesion is required from adhesion studies of any two materials, either material should be used as particulate and as compacted powder material. Otherwise a careful consideration of the practical conditions which are to be modelled has to be made to choose the most appropriate system.

The relative autoadhesion force of micronized lactose monohydrate particles could have been predicted from the results obtained using larger particles. This is valid with small limitations also for the relative autoadhesion force of salmeterol xinafoate. The relative adhesion force of salmeterol xinafoate particles to compacted lactose monohydrate surfaces appears independent of particles size even into micronized size range if particles with similar morphology are compared.

Key words adhesion; autoadhesion; centrifuge technique; micronized particle; particle morphology; surface roughness

The adhesion force of salmeterol xinafoate particles of various sizes to compacted lactose monohydrate surfaces has been reported previously.[1] Furthermore autoadhesion measurements of lactose monohydrate and salmeterol xinafoate particles of similar size had been undertaken.[2] For these experiments a centrifuge technique described in detail earlier[3] had been employed, and the adhesion distributions were measured using different preliminary press-on forces to enhance the contact between the particles and the surfaces. It had been found for both materials that the ratio of the median adhesion and autoadhesion force determined and the press-on force applied is proportional to the size of the adhered or autoadhered particles. Hence it might be possible to estimate the median adhesion and autoadhesion force of micronized particles from results obtained using larger particles. This would be advantageously because measurements on micronized particles require not only a powerful centrifuge technique,[4] but also a very powerful microscope and light source to identify the particles remained adhered or autoadhered to the surface after a spin-off force to detach the particles had been applied. Micronized particles are usually agglomerated, and the deposition of single micronized particles on top of a surface is another problem which may cause difficulties.

Several points appear to restrict the idea of predicting the median adhesion and autoadhesion force of micronized particles from measurements on macro-particles:

1. Kendall *et al.*[5] proved that micronized particles form strong agglomerates, and the size of these agglomerates depends among other things on the surface free energy of the powder. The agglomerates behave like macro-particles, but to what extent the single micronized particles are similar to the macro-particles is unknown.

2. Micronization can change the surface free energy of a material.[6] Adhesion is very much related to the surface free energy of the materials in contact,[7] and therefore any change in surface free energy should be reflected in a change of the adhesion properties.

3. Already for large particles, a difference in the median adhesion force between salmeterol xinafoate and lactose monohydrate was found if either lactose monohydrate or salmeterol xinafoate had been used to form the compacted powder substrate surface.[8] This difference can be due to a difference in surface roughness of the compacted surfaces, where lactose monohydrate surfaces are usually quite rough and salmeterol xinafoate surfaces are comparable to for example aluminium or polyethylene surfaces. Having micronized particles, these differences in surface roughness could influence the results even more, because the size is now so small, that the particles can be positioned either at the top of the asperities or in the valleys between the asperities of the compacted surface. The former usually leads to a reduction in adhesion strength, while the latter is reflected in an increased adhesion strength.[9]

On the other hand, substance properties such as its elastic and plastic behaviour are as important as surface roughness or surface free energy.[10,11] The elastic and plastic properties of the particles and compacted surfaces have not been changed, and in cases where these properties dominate in the adhesion and autoadhesion process, a prediction of the median adhesion and autoadhesion force of the micronized particles from macro-particles could be possible.

Hence the autoadhesion and adhesion of particles of

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two model pharmaceutical powders, a drug (salmeterol xinafoate) and an excipient (lactose monohydrate) in their micronized form has been investigated, and a comparison to the macro-particle tests has been made.

Experimental

Materials Micronized salmeterol xinafoate (Glaxo Research & Development, Ware, UK) and micronized lactose monohydrate (Lactochem, Saltney, UK) have been used as model particles in the adhesion and autoadhesion experiments. To prepare the compacted surfaces normal powders of the above materials and microcrystalline cellulose (Avicel PH101, FMC Corporation, Philadelphia, U.S.A.) have been used.

Methods Bilayer surfaces of salmeterol xinafoate were prepared from 360 mg microcrystalline cellulose and 50 mg salmeterol xinafoate (top layer) using a compaction pressure of 80 MPa whereas the lactose monohydrate sandwich surfaces were made from 330 mg microcrystalline cellulose and 100 mg lactose monohydrate (top layer) using 80 MPa compaction pressure. The amount microcrystalline cellulose was weighed, poured into a 12.77 mm diameter punch and die system and the powder surface was levelled horizontally using first a spatula and then a 12.77 mm punch surface without application of any measurable pressure. It is assumed that the density of the powder bed did not exceed the maximum powder density at this stage. The amount of drug or lactose monohydrate was weighed and spread on top of the microcrystalline cellulose powder layer. Again care was taken to distribute the powder equally. The upper punch was fitted and the punch and die system was placed between the two platens of an Universal Testing Machine (Instron, Model TT, High Wykcombe, UK). The necessary compaction pressure was applied using a crosshead speed of $0.05\,mms^{-1}$. The punch and die system was dissembled, and the compacts were stored in petri dishes at 35% relative humidity of the air at 20 °C for at least 4 weeks, the top layer facing the air. Due to expansion processes after compression the compacts have the following dimensions: diameter 12.9 mm, height 2.95 mm. The top layer is approximately 400 μm thick.

A special sieve-brush technique has been developed which produces free settling single micronized particles, if the powders have been stored under dry conditions (*e.g.* in a desiccator over silica gel). Six surfaces were dusted for each experiment ("adhesion samples"). Usually some agglomerates are also deposited on top of the surfaces. These were removed using a mild air stream. The brush and sieve were cleaned with alcohol and acetone after use.

The particle size of the micronized powders ranges between 0.2 and 5 μm. Particles smaller than 3 μm cannot clearly be distinguished from the surface roughness of the compacts with great certainty using an optical microscope. Hence only particles in the size range of 3 to 5 μm have been counted in the adhesion experiments. Such particles have an average particle mass of 5.11×10^{-2} ng (lactose monohydrate) or 4.29×10^{-2} ng (salmeterol xinafoate), if sphericity is assumed, and using the experimental powder densities of $1.525\,gcm^{-3}$ and $1.280\,gcm^{-3}$ for lactose monohydrate and salmeterol xinafoate, respectively.

The adhesion and autoadhesion force measurements were undertaken by means of an Ultracentrifuge (Centrikon T-1080, Kontron Instruments, Milan, Italy) using a vertical rotor and a set of specially designed adapters.[12] After deposition of the micronized particles on top of the active layer of the compacted surfaces a press-on force was applied, the magnitude of which can be calculated from the particle mass, the radial distance of the particles from the centre point of the rotor and the square of the rotor speed. The initial number of particles in the central area of the surfaces was determined by manually counting them using an image analysis system (Seescan Solitaire 512, Seescan, Cambridge, UK). Several spin-off forces were applied and the number of particles remained adhering was counted, unless the number of particles was either less than 15% of the initial particle number, or the active surface split from the carrier surface and destroyed the adhesion sample. The resulting adhesion and autoadhesion force distributions were used to calculate the median adhesion and autoadhesion force and the interquartile range for the reasons previously described.[2] The median force is the value at which 50% of the initial number of particles are detached. The interquartile range is the difference between the force values, where 75% and 25% of the particles are detached.

Results

Four test series have been undertaken to investigate the autoadhesion and adhesion properties of micronized salmeterol xinafoate and lactose monohydrate to compacted surfaces. In Fig. 1a—d the adhesion and autoadhesion force distributions are plotted as log-probability graphs. Tables 1 and 2 summarize the results in form of distribution shape independent characteristics of the adhesion and autoadhesion force distributions, median adhesion and autoadhesion force and interquartile range, because the adhesion and autoadhesion force distributions (log-probability graphs) are nonlinear.

The compacted surfaces of lactose monohydrate resist a centrifugal speed of 23000 to 25000 rpm, before the active layer becomes detached from the microcrystalline cellulose carrier layer. This is nearly twice the acceleration rate of the compacts used in previous studies[1,2] and demonstrates that the sandwich technique introduced in this paper does not only save large amounts of active material, but also allows the use of such compacts in an ultracentrifuge at high centrifugal speeds. The compacted bilayer surfaces with salmeterol xinafoate as active layer did not show any sign of wear or destruction during the experiments, and the two layers did not split apart.

Discussion

The autoadhesion experiments of lactose monohydrate show that after a steady increase in median autoadhesion force for lower press-on forces a press-on force of 14.25×10^{-12} N only insignificantly increases the autoadhesion strength compared to the next lower press-on force of 11.41×10^{-12} N (see Table 1). This suggests that a press-on force of 11.41×10^{-12} N is sufficient to cause maximal plastic deformation of the micronized lactose monohydrate particles. Any further increase in press-on force results in elastic deformation only and hence does not increase the contact area and the resulting autoadhesion force between the particles and the surfaces.

In the case of micronized salmeterol xinafoate particles autoadhered to compacted surfaces a maximum of plastic deformation is reached at the press-on force of 10.74×10^{-12} N. There is a drop in median autoadhesion force at the highest press-on force, and the difference between this value and the preceding median autoadhesion force is statistically significant ($t = 2.88$, $t_{10;P=0.05} = 2.23$), and can therefore not be caused by variations of the material properties. The drop in median autoadhesion force at the highest press-on force could be due to fracture phenomena of the asperities of the particles,[13] which are in contact with the surface. Fracture of either or both the particles and the surface can result in little fragments which could be positioned between the surfaces of the contiguous bodies. It has been shown that the presence of fine particles or protuberances at the surface of adhered particles of a size between 25 and 60 μm reduces the median adhesion force of these particles to a flat surface significantly.[14]

The autoadhesion force of salmeterol xinafoate is clearly higher than the autoadhesion force of lactose monohydrate unless the high press-on force applied causes particulate fracture. In practice that means that very high forces *e.g.* during mixing should be avoided.

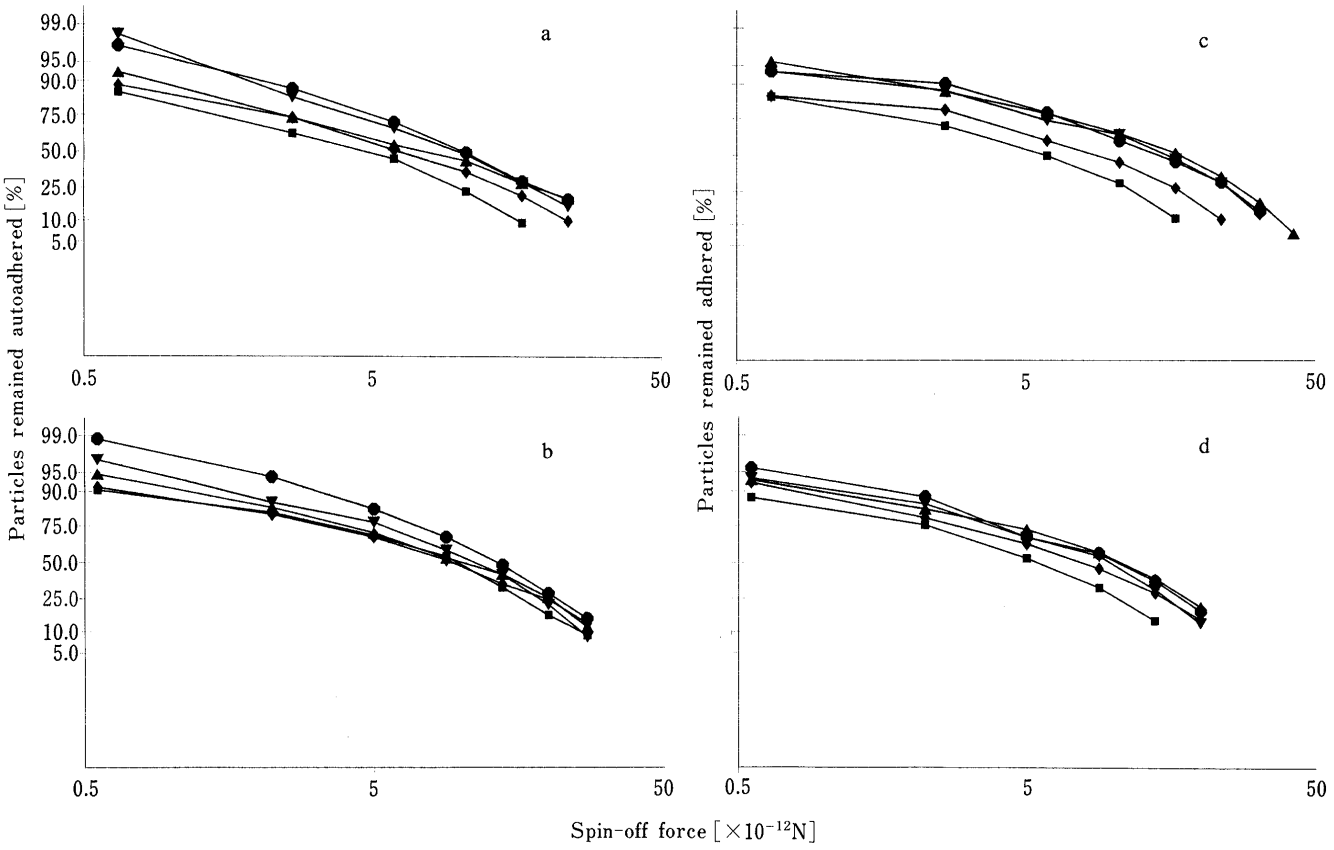

Fig. 1. log-Probability Graphs of the Autoadhesion Force Distributions of Lactose Monohydrate (a) and Salmeterol Xinafoate (b) and the Adhesion Force Distributions of Micronized Particles of Lactose Monohydrate on Salmeterol Xinafoate Disks (c) and Salmeterol Xinafoate on Lactose Monohydrate Disks (d)

The press-on force applied increases in the order of ◆, ■, ▲, ●, ▼ (for force values refer to Tables 1 and 2).

Table 1. Median Autoadhesion Force (F_{ad}) and Interquartile Range (IQR) for Lactose Monohydrate and Salmeterol Xinafoate at Different Press-on Forces (F_{on})

Substance	F_{on} [$\times 10^{-12}$ N]	F_{ad} [$\times 10^{-12}$ N]	IQR [$\times 10^{-12}$ N]
Lactose monohydrate	4.78	5.09±1.13	8.63±1.08
	6.67	6.55±1.14	12.38±1.02
	8.88	7.98±0.40	16.16±2.80
	11.41	10.56±0.56	14.18±2.53
	14.25	11.28±3.28	13.90±1.95
Salmeterol xinafoate	4.77	9.74±0.77	12.54±2.64
	6.50	9.47±1.55	16.28±1.92
	8.48	10.78±3.42	15.74±2.39
	10.74	13.26±0.83	15.07±4.35
	14.62	11.12±1.62	13.77±2.47

Values are the mean and standard deviation of 6 adhesion samples.

The adhesion between lactose monohydrate and salmeterol xinafoate can be studied in two ways: first using salmeterol xinafoate as compacted surface and lactose monohydrate particles in micronized form, and secondly vice versa. The main difference in these experiments is in the surface roughness of the compacted powder surfaces. Surface roughness can increase or decrease the adhesion force between particles and a surface depending on the position of the particles.[9] Particles attached to the top of asperities have less contact, but particles deposited into a valley between the asperities are virtually trapped, and the application of a press-on force may push them even deeper into the valley. Hence the ratio between particle size, in some cases (*e.g.* needle shape) particle shape and distance between the asperities can cause increase or decrease of the adhesion force obtained on a rough surface compared to an ideally smooth surface. When measured by surface profilometry the compacted lactose monohydrate surfaces are about 10 times rougher than compacted salmeterol xinafoate surfaces.[8] A comparison between the median adhesion forces of the two possible particle-surface systems will therefore say something about the position of the particles on the surfaces used.

The use of micronized lactose monohydrate particles adhered to salmeterol xinafoate surfaces shows first an increase in adhesion strength with increased press-on force, but after a maximum force reached at a press-on force of 11.41×10^{-12} N, the median adhesion force drops and then remains relatively constant (see Table 2). Again it means that the plastic deformation of the lactose monohydrate particles cannot be increased further, and the drop could be due to the brittle character of lactose monohydrate.[15] Comparing the interquartile range in these experiments with those obtained in the autoadhesion studies of lactose monohydrate, the comparatively large values suggest that the adhesion of the particles to salmeterol xinafoate is more variable than the autoadhesion. However, the difference in variability could also simply be the result of differences in the surface roughness of the compacted powder surfaces. Compacted salmeterol

Table 2. Median Adhesion Force (F_{ad}) and IQR for Lactose Monohydrate Particles Adhered to Compacted Salmeterol Xinafoate Surfaces and Salmeterol Xinafoate Particles Adhered to Compacted Lactose Monohydrate Surfaces at Different Press-on Forces (F_{on})

Particles	F_{on} [$\times 10^{-12}$ N]	F_{ad} [$\times 10^{-12}$ N]	IQR [$\times 10^{-12}$ N]
Lactose monohydrate	6.67	6.00±1.52	10.08±0.66
	8.88	8.64±1.78	13.66±1.07
	11.41	17.09±1.65	22.07±2.20
	14.25	14.55±3.86	19.35±2.97
	17.41	15.80±2.38	20.47±1.93
Salmeterol xinafoate	6.50	5.46±0.93	8.51±0.89
	8.48	7.83±1.33	12.69±2.20
	10.74	10.78±1.34	13.86±1.11
	14.62	10.50±1.22	12.80±0.92
	17.53	9.85±0.44	11.80±0.79

Values are the mean and standard deviation of 6 adhesion samples.

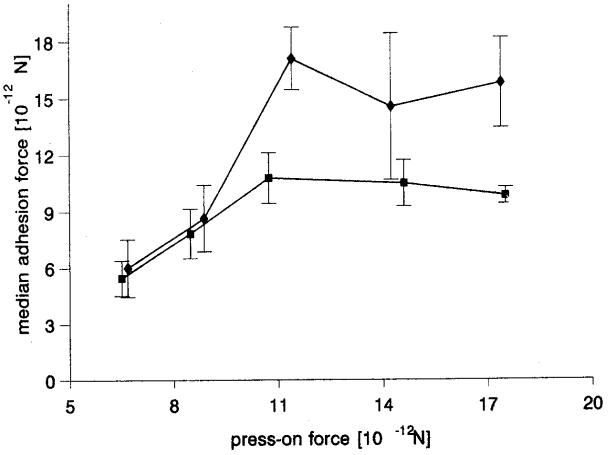

Fig. 2. Comparison of the Adhesion Forces of ■ Lactose Monohydrate Particles Adhered to Salmeterol Xinafoate Surfaces and ◆ Salmeterol Xinafoate Particles to Lactose Monohydrate Surfaces

Arithmetic mean ± standard deviation.

xinafoate surfaces are less rough than compacted lactose monohydrate surfaces, and hence the surface roughness effect on the adhesion process is less dominant for lactose monohydrate particles adhered to compacted salmeterol xinafoate surfaces.

The adhesion force between micronized salmeterol xinafoate particles and compacted lactose monohydrate surfaces (see Table 2) is clearly different than the force values obtained when the two materials are the other way round. Figure 2 compares the increase in adhesion force as a function of press-on force for both test systems. At low press-on forces the resulting median adhesion forces are similar, but in the upper range of press-on forces, lactose monohydrate particles are more strongly adhered to salmeterol xinafoate surfaces than salmeterol xinafoate particles to lactose monohydrate surfaces. If the adhesion forces were different at any press-on force, the conclusion would be that the salmeterol xinafoate particles are attached to the top of the asperities of the lactose monohydrate surfaces only, and hence due to smaller contact area the adhesion force would be lower. However, the phenomenon that at lower press-on forces both systems led to similar adhesion strength suggests, that this is not the case. Probably both salmeterol xinafoate particles and

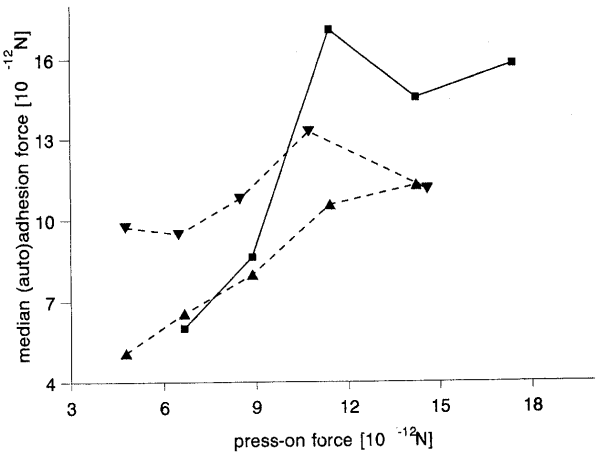

Fig. 3. Comparison between Autoadhesion Forces of ▲ Lactose Monohydrate and ▼ Salmeterol Xinafoate and ■ Adhesion Forces between These Two Materials

lactose monohydrate particles are stuck in the valleys between the asperities because of their very small particle size. Regarding microroughness measurements, the rugosity R_a (2.01 μm and 0.30 μm for lactose monohydrate and salmeterol xinafoate surfaces, respectively[8]) is usually proportional to the distance between asperity tips, *i.e.* the larger the value of R_a, the deeper are the valleys and the larger the distance between asperity tips. Therefore, the width between single asperities of the lactose monohydrate surfaces is much greater than that of the salmeterol xinafoate surfaces. Higher press-on forces deform particles, and they are pushed further down into the valleys between the asperities. In the case of the lactose monohydrate particles this means that they are mechanically trapped due to the narrowness between the asperities of the compacted salmeterol xinafoate surfaces. This would also explain the increased variability of the adhesion forces which occur in this system. The variability of the adhesion forces of salmeterol xinafoate particles to lactose monohydrate surfaces is similar to the variability of the autoadhesion forces obtained for salmeterol xinafoate.

In Fig. 3 the median autoadhesion forces for both micronized materials and the median adhesion force of lactose monohydrate particles to compacted salmeterol xinafoate surfaces have been drawn as functions of press-on force. At higher press-on forces the adhesion process would dominate over the autoadhesion, which would be advantageous for example in mixing, where homogeneity is required. However, using the adhesion experiments of salmeterol xinafoate particles adhered to compacted lactose monohydrate surfaces instead, the forces were similar at the highest press-on force. Hence the two models—adhesion of salmeterol xinafoate particles onto compacted lactose monohydrate surfaces, and adhesion of lactose monohydrate particles onto compacted salmeterol xinafoate surfaces—give different answers. Therefore, it is necessary to decide which model reflects better the practical situations, such as interparticulate contact during mixing. Salmeterol xinafoate particles have a spiky, irregular surface structure. From this particle structure it can be derived that, during for example mixing of micronized salmeterol xinafoate with

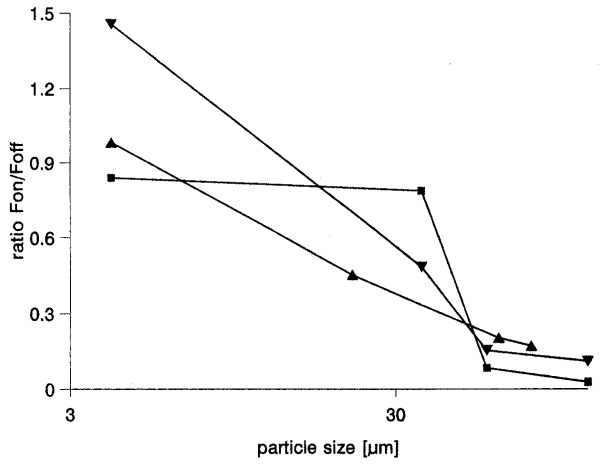

Fig. 4. Comparison of the Relative Adhesion and Autoadhesion Forces (Ratio F_{ad}/F_{on}) of Lactose Monohydrate and Salmeterol Xinafoate at an Acceleration Rate of About $14000 \times g$ Forces

▲, lactose monohydrate (autoadhesion); ▼, salmeterol xinafoate (autoadhesion); ■, salmeterol xinafoate particles adhered to compacted lactose monohydrate surfaces.

micronized lactose monohydrate, mechanical effects will lead to the positioning of lactose particles in the gaps of the rough surface of the salmeterol xinafoate particles, which finally leads to adhesion between the two components. Hence during mixing of the two components, salmeterol xinafoate particles are the substrate to which the lactose monohydrate particles become adhered. Therefore, the model to use lactose monohydrate particles adhered to compacted salmeterol xinafoate surfaces appears to provide a better reflection of practical processes.

In Fig. 4 the relationship between the adhesion and autoadhesion experiments reported earlier[1,2] using larger particle sizes to the results obtained using micronized particles is illustrated. However, this can only be done at similar acceleration rates (g forces). Due to the differences in the rotor design the centrifuges used previously and currently do not match in terms of their acceleration rates at similar centrifugal speeds. However, an acceleration rate of about $14000 \times g$ has been used for the larger particles ($12000\,\text{rpm} = 14416 \times g$) and for the micronized particles ($13000\,\text{rpm} = 13875 \times g$). From the graph it can be seen that in the case of lactose monohydrate particles a prediction of the autoadhesion force of the micronized particles can be achieved using the log-linear relationship between the relative autoadhesion force and the particle size. This is, with some restrictions, also valid for the autoadhesion of salmeterol xinafoate particles. The larger particle fractions 'b' (57 μm) and 'c' (116 μm) are different in their morphology to micronized salmeterol xinafoate or to particle fraction 'a' (36 μm).[2] The results of the autoadhesion experiments using particle size fraction 'c' were different to those of particle size 'a' and 'b'. This is also reflected in the relationship shown in Fig. 4. The relative adhesion force of salmeterol xinafoate particles to compacted lactose monohydrate surfaces appears to be independent of particle size, if the morphology of the particles is similar.

It can be concluded that using larger particle sizes offers certain possibilities of predicting the relative adhesion and autoadhesion strength of micronized particles to compacted powder surfaces. The main restriction appears to be the requirement for an identical particle morphology. The advantage of using larger particles is that the preparation of adhesion and autoadhesion samples is much easier, and that the imaging technique does not require more sophisticated microscopical and lightening facilities.

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