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Assessment of the mode of adherence and the deformation characteristics of micronized particles adhering to various surfaces

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Abstract

A method of calculating the mode of adherence and the characterization of separation (ductile or brittle) of particles adhered to various surfaces has been described. The adhesion force of micronized particles of a drug to nominally flat surfaces has been measured using the centrifuge technique. The mode of adherence and the character of deformation of the adhesion contact was calculated from the experimental values using the model described by Maugis and Pollock (1984). In all cases the character of deformation of the adhesion contact was fully plastic. However, the mode of adherence varied for different surfaces. If either the drug or excipient was autoadhered to a compacted drug or excipient powder surface, the mode of adherence was found to be brittle separation, whereas the adhesion of the drug to compacted lactose monohydrate powder surfaces followed the ductile rupture mode over the whole range of external forces applied. Using surfaces with lower surface free energy (aluminium, polyhydroxymethylene), the mode of adherence for the drug was ductile rupture, whereas a higher surface free energy of the surface material (polyvinylchloride, polyethylene) resulted in brittle separation. The existence of ductile rupture indicates that the drug might be lost on surfaces during powder processing and handling. Thus the choice of material to which the drug has contact needs to be made very carefully. Copyright © 1996 Elsevier Science B.V.

Keywords: Adhesion; Centrifuge technique; Deformation mechanism; Mode of adherence; Powder technology

1. Introduction

During powder processing and handling individual particles are in contact with each other and with the surface of any equipment used. The nature and degree of interaction between the par-

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ticles and between particles and surfaces determines the properties of the powder bulk, e.g. during mixing or powder flow. The major mechanisms of interaction to be considered are adhesion and friction.

The presence of adhesion between powder particles and solid surfaces may be deliberate and advantageous, for example using an inert excipient as carrier for micronized drug particles (interactive mixture). However, powder adhesion may also present a problem, for example during particle size reduction by micronization, when excessive adhesion can cause blockage of the micronizer.

In the pharmaceutical literature, major attention was drawn to the adhesion between particles during mixing. Hersey (1975) proposed that adhesion between particles could improve the homogeneity of powder mixtures. According to his theory of mixing, a mixture where adhesion occurs mainly between a fine powder component and a coarse grade excipient is called 'ordered'. However, the author did not complement his theory with measurements of adhesion forces acting between these particles. Yip and Hersey (1977) compared a theoretical degree of homogeneity of binary mixtures of micronized salicylic acid or fine grade crystal violet and coarse grade sucrose with practical mixing results. They found that the mixtures were nearly perfectly homogeneous, as confirmed by a calculation of the homogeneity index derived by Buslik (1973). They concluded that adhesion interactions between the particles had led to an ordered mixture. Egermann (1983) introduced the term 'interactive', which defines more closely the phenomena occurring in such mixtures, to replace 'ordered' in the literature.

Measurements of adhesion forces in a powder bulk were undertaken by Schmidt and Walter (1994) using an electronic tensiometer. They were able to explain the formation of supersaturated interactive mixtures in contrast to simple interactive mixtures by means of adhesion and autoadhesion measurements. The major drawback of their method is its limited ability to measure adhesion forces of micronized materials, and that all force values are characteristics of the powder bulk rather than of single particles.

In processes such as capsule filling or tabletting, the contact with the powder leads successively to a coating of e.g. punches, dies and nozzles due to adhesion. This powder film can have a strong, often negative effect on the performance of tablet presses, or it can improve the tabletting properties of a powder mixture due to lubrication. Powders with little adhesion tendency to dosator nozzle walls of capsule filling machines were found to result in an even capsule filling performance, and the texture of the dosator nozzle walls, for example a scratched rough surface, appeared less critical (Tan and Newton, 1990). However, substances with large adhesion tendency such as lactose gave unsatisfactory filling results, especially when the surface of the nozzles was worn (Jolliffe and Newton, 1983). To study these phenomena in a more simplified manner, Booth and Newton (1987) used a centrifuge technique to measure the adhesion force between powder particles and lubricated or unlubricated surfaces.

While all above papers consider the occurrence of adhesion forces between particles and particles to surfaces and have tried to quantify them, none of the papers considered the possibility that a detachment of particles from the surface to which they are sticking might be incomplete, i.e. small amounts of the drug particle are left on the surface. Such a detachment mechanism would have consequences in terms of drug loss or contamination during powder processing and handling, for example due to drug remaining on vessel walls, tubes, or on carrier particles as used in interactive powder mixtures.

Maugis and Pollock (1984) described a model based on the Johnson–Kendall–Roberts-theory ('JKR-theory', 1971), which allows the assessment of the mode of adherence of small particles to surfaces. Adhesion forces can be measured during loading or unloading, and the model describes primarily the force of adhesion during separation between a particle and a surface, thus a phenomenon of crack propagation. While finally the proposed mode of adherence describes this separation mechanism in terms of its fracture mechanics, its determination is based on the calculation of the underlying forces of adhesion. Hence, in the physical literature the terminology 'mode of adherence' is used instead of, for example, 'mode of separation' or 'mode of failure', and in this paper the terminology is maintained for reasons of consistency with the physical literature. Adhesion forces in the sense of unloading can be obtained by the centrifuge technique (Beams et al., 1955; Böhme et al., 1962), and such data can be processed using the above concept. However, the model and the derived implications are only applicable to dosage forms and processes with dominant single particle–particle or particle–surface contact, such as powder particles during mixing, flow through a hopper or pipe, or filling processes where no or only low compression forces are applied. The basic JKR-theory is only valid for 'conditions of light loading' (Johnson et al., 1971), which excludes its use for example to explain strength in tablets or dry granulated powders.

Three modes of adherence can be distinguished.

1. Ductile rupture (F_d-mode). If a particle is detached from a surface following the F_d-mode, surface damage occurs. This means that either small parts of the particle are left on the surface or vice versa, depending on the mechanical properties of particle and surface. Ductile rupture cannot occur if an external load applied to cause adhesion of the particle resulted in only elastic deformation of the adhesion contact.
2. Brittle separation at a contact radius equal to the contact radius achieved using an external load (F_m-mode). Following this mode the detachment of the adhered particle from the surface causes no surface damage and thus would be preferable. The F_m-mode can practically only exist after elasto-plastic deformation of the adhesion contact.
3. Brittle separation at a contact radius smaller than the contact radius achieved using an external load (F_b-mode). If the particle detachment from the surface follows the F_b-mode, again no surface damage will occur. Thus the difference between the F_m and the F_b-mode is of a physical nature, but the practical consequences in terms of drug loss are similar.

To calculate the mode of adherence and the nature of deformation, additionally to the adhesion force measured (F_{ad}) after application of a defined press-on force (F_{on}), the value of Young's modulus of elasticity (E), yield strength (Y) and work of adhesion ($\Delta\gamma$) of the materials in contact are required. While E and Y are tabulated for many metals and plastics, they can also be experimentally evaluated, for example for powdered materials by means of beam bending (Church and Kennerley, 1983). In the case of adhesion, the reduced Young's modulus (E^*) at the contact points between the two surfaces (Timoshenko and Goodier, 1970):

$$\frac{1}{E^*} = \left(\frac{1 - \nu_1^2}{E_1}\right) + \left(\frac{1 - \nu_2^2}{E_2}\right) \tag{1}$$

has to be used instead of E to assure consistency with Griffith's theory (Griffith, 1921) of crack propagation (Maugis, 1995), while the yield strength of the softer material is used. (The values of ν_1 and ν_2 in Eq. (1) are the Poisson's ratios for the two materials in contact, and E_1 and E_2 are the values of the Young's moduli of these materials. Eq. (1) also holds, if the adhesion between particles of the same material, i.e. autoadhesion, is considered (Horn et al., 1987)).Applying the centrifuge technique to measure F_{ad} for a defined F_{on}, the area of contact A between particles and a surface can be calculated as described by Podczeck et al. (1996a):

$$A = \pi\left(0.5\frac{F_{ad}F_{on}}{E^*\pi\Delta\gamma}\right)^{2/3} \tag{2}$$

The radius of contact a is related to A by:

$$a = \left(\frac{A}{\pi}\right)^{1/2} \tag{3}$$

Assuming that ν is for pharmaceutical powders on average 0.3 (Roberts et al., 1991), a constant K related to the deformability of the adhesion contact can be calculated (Johnson et al., 1971):

$$\frac{1}{K} = \frac{3}{4}\left(\frac{1 - \nu_1^2}{E_1} + \frac{1 - \nu_2^2}{E_2}\right) = \frac{3}{4}\frac{1}{E^*} \tag{4}$$

The model of Maugis and Pollock (1984) then consists of the following steps:

1. All force values and the values of $\Delta\gamma$ and a will be normalized (the normalized values carry the superscript '*' and are dimensionless):

$$F^* = F\frac{12\pi Y^3}{\Delta\gamma^2 K^2} \quad (5)$$

where F is either F_{ad} or F_{on};

$$a^* = \frac{aK}{rY} \quad (6)$$

where r is the particle radius;

$$\Delta\gamma^* = \frac{\Delta\gamma K^2}{rY^3} \quad (7)$$

and the normalized force of ductile rupture, F_d^*, is calculated from:

$$F_d^* = -\left(\frac{6\pi a^*}{\Delta\gamma^*}\right)^2 \quad (8)$$

The value of the F_d^*-force of adhesion does not depend on the deformation mechanism. Hence, Eq. (8) is applicable for the following three types of deformation.

2. Adhesion force following elastic deformation:

$$F_b^* = -\frac{18\pi}{\Delta\gamma^*} \quad (9)$$

where F_b^* is the normalized force of brittle separation at a smaller radius of contact than reached after application of a defined press-on force.

3. Adhesion force following elasto-plastic deformation:

$$F_m^* = -\left(\frac{6\pi a^*}{\Delta\gamma^*}\right)^{3/2}(2-\phi) \quad (10)$$

$$F_b^* = -\left(\frac{6\pi a^*}{\Delta\gamma^*}\right)^{3/2}\frac{1}{\phi} \quad (11)$$

with the criterion ϕ defined as:

$$\phi = \frac{\left(\frac{6\pi a^*}{\Delta\gamma^*}\right)^{1/2}(1.1 + 0.58\ \ln[0.29a^*])}{3} \quad (12)$$

where F_m^* is the normalized force of brittle separation at the contact area reached after application of a defined press-on force.

4. Adhesion force following fully plastic deformation:Only the value of ϕ in Eqs. (10) and (11) will be changed to:

$$\phi = \left(\frac{6\pi a^*}{\Delta\gamma^*}\right)^{1/2} \quad (13)$$

The following rules must be obeyed if the mode of adherence and the nature of deformation are to be assessed:

1. The absolute value of the smallest adhesion force calculated (Eqs. (8)–(11) and (13)) indicates the mode of adherence present, thus if for example under fully plastic deformation conditions the 3 adhesion force values are in the order $|F_b^*| < |F_m^*| < |F_d^*|$, then the F_b-mode characterizes the detachment process.

2. After purely elastic loading, only brittle separation at a smaller than the true radius of contact at maximum load can exist. Thus, the comparison of $|F_b^*| > |F_d^*|$ indicates that the press-on force has caused at least elasto-plastic deformation.

3. Fully plastic deformation can be identified by comparing ϕ (Eq. (13)) with $F_b^*(F_b^* = -\phi^2)$ or $F_d^*(F_d^* = -\phi^4)$.

4. The F_b-mode can only exist when $\phi \geq 1$, and accordingly the F_m-mode will be valid only for $\phi \leq 1$. The 2 models of brittleness are equivalent at $\phi = 1$. In practice, the F_m-mode exists only in the range of elasto-plastic deformations (Maugis and Pollock, 1984).

The above model is restricted to adhesion of particles to surfaces without occurrence of viscoelastic deformation or creep. The occurrence of creep is unlikely under the experimental conditions of the centrifuge technique, which will be applied in this paper. The influence of viscoelastic phenomena on the adhesion forces and shape of the contact area between particles and surfaces cannot be completely excluded. However, viscoelasticity is a time dependent process, which involves for example a time span of 10^{10} h for rubber (Greenwood and Johnson, 1981), whereas the contact of powders with surfaces during powder handling, e.g. mixing, flow, inhalation, is a dynamic process with short contact times. Elasticity and hardness are related mechanical properties of solids, and thus a change in hardness over time could be used to estimate the change of E from its initial value to a value representing a fully relaxed system. However, for pharmaceutical powders such measurements have only been undertaken on compacts with considerable porosity (Hiestand, 1995) using a large indenter, and the steep slope of functions of hardness against porosity demonstrate the invalidity of these values to represent the particulate properties themselves. Measurements on single crystals as carried out by Duncan-Hewitt and Weatherley (1989) would thus be more appropriate, but extremely long indentation times would be required leading to erroneous results (Duncan-Hewitt, 1995). To date it is therefore not known which time span would be involved in the viscoelastic deformation of pharmaceutical powder particles, and a reliable way of determination has not yet been found. Hence, it will be assumed that the model described above is to date the only sufficient way to describe situations occurring during powder handling.

The aim of the present work was to assess the mode of adherence and the character of deformation for micronized particles adhered to various surfaces using the centrifuge technique (Podczeck and Newton, 1995). Changes in mode of adherence or deformation mechanism would indicate a preference in use of certain surface materials for example for containers, hoppers or other powder processing and handling equipment.

2. Materials and methods

Micronized powders of an excipient, lactose monohydrate (Lactochem, Saltney, UK), and a drug, Salmeterol Xinafoate (Glaxo R and D, Ware, UK), have been used as particles adhered to surfaces made from aluminium, polyethylene, polyhydroxymethylene and polyvinylchloride in the form of disks (all supplied by Glaxo R and D, Ware, UK). Additionally, model surfaces were prepared from ordinary lactose monohydrate and drug as described by Podczeck and Newton (1995). Particulate powder surfaces have been prepared as described previously (Podczeck et al., 1995a). In the following text, those experiments which involved the use of the compacted powder surfaces or plastic/aluminium disks will be called 'particle-on-surface' experiments, whereas those experiments which were based on the use of particulate surfaces will be called 'particle-on-particle' experiments.

The average particle mass of the micronized powders was calculated from the experimental powder densities, assuming sphericity. The true powder density was assessed experimentally using micronized powders in a Beckman air pycnometer (Model 930, Beckman Instruments, USA).

Adhesion and autoadhesion samples were prepared depositing particles of either the drug or lactose monohydrate on top of the particulate or compacted powder surfaces, and the plastic or aluminium disks. The powders had been stored over silica gel. A special sieve-brush technique has been developed which produces free settling single particles. Six surfaces were dusted for each experiment. The occurrence of single particles deposited on top of the surfaces used was checked microscopically for every disk. Agglomerates were removed from the surfaces using a mild air stream. The brush and sieve were carefully cleaned after each use.

The experimental set-up and procedure of the centrifuge technique has been described in detail by Podczeck and Newton (1995). The maximum centrifugal speed necessary was maintained exactly for 1 min. Two centrifugal forces applied have to be differentiated:

(a) the press-on force, which is applied to increase the contact between particles and surfaces; the dusted surfaces are positioned in direction of the rotor axis, so that the centrifugal force vector passes first the particles and then the surfaces;

(b) the spin-off force, which is applied to detach the particles adhered to the surfaces; the dusted surfaces are positioned in direction of the outside of the rotor head, so that the centrifugal force vector passes first the surfaces and then the particles.

The number of particles initially adhered to the surfaces (central area of 7 mm diameter) was determined after the press-on force had been applied using an image analyzer (Seescan Solitaire 512, Cambridge, UK), which is attached to a microscope (Olympus BH-2, Tokyo, Japan), in a manual mode. The surfaces had to be illuminated using a cold light source (High Light 3002, Olympus, Hamburg, Germany), which was attached parallel to the surface, 1.5 cm from the periphery. The two light beams were placed at 180° to each other to minimize the formation of shadows. The initial number of particles was about 500 per surface, and six surfaces were used parallel in each experiment. A spin-off force was applied, and the number of particles that remained adhered was determined. An adhesion force distribution was obtained by successively increasing the spin-off force after each counting. The median adhesion force, which is the force value were 50% of the particles are detached, and the interquartile range, which is the difference of the force values necessary to detach 75 and 25% of the particles initially adhered, was calculated from each individual adhesion force distribution. In this way, a quantitative characterization of the average adhesion force and its variability was possible without making any assumption about the nature of the underlying distribution function. All results reported are the mean and standard deviation of the median adhesion force values only using six replicates.

Measurements to determine the surface free energy of the aluminium and plastic surfaces have been undertaken by means of the sessile drop technique. Prior to the experiments, the surfaces were cleaned in an ultrasonic bath using ethanol or distilled water to match the chemical properties of the materials. No attempt was made to remove possible oxide layers, because this would not match the use of these materials in industry. The surfaces were positioned in front of an image camera (CCD-4 miniature video camera, Rengo, Toyohashi, Japan), which was equipped with a zoom lens (18-108/2.5, Olympus, Hamburg, Germany) and connected to the image analyzer described above. The advancing contact angle against liquids was measured adapting the technique described by Timmons and Zisman (1966). A fine copper wire was used to deposit a droplet of reproducible size on top of the surface, the image was taken and the contact angle determined from width and height of the drop. Successively, more liquid was added from the wire, and the contact angle was measured each time until a constant value was obtained, which is regarded to be the advancing contact angle. Three liquids of different polarity have been used: distilled water, glycerol (BDH, Poole, UK) and diiodomethane (Aldrich, Fillingham, UK). The results are the mean values of six replicates.

Experiments to obtain the surface free energy of salmeterol xinafoate and lactose monohydrate were undertaken using the Wilhelmy plate technique. Beams of 20 × 20 × 1 mm were produced using a Specac 15 000 hydraulic press (Specac, Kent, UK). Drug (500 mg) or lactose monohydrate (1.2 g) were compacted at a pressure of 94 MPa, using a dwell time of 3 min for lactose monohydrate. The beam porosity did not exceed 15%. The beams were stored at a relative humidity of 35% until the measurements took place. Contact angles were measured using the beams as plates in the dynamic contact angle analyzer (DCA-312, Cahn Instruments, Ceritos, CA, USA). The plate speed was 100 ± 0.1 μm s^{-1}. Six replicate measurements were performed for each of the three test liquids stated above.

3. Results and discussion

Table 1 lists the physical properties of the materials used in the study. Young's modulus E and the yield strength Y are physical constants of a material and variations in reference data are due to imperfect measurement methods. The use of manufacturer's data provided with the plastic materials studied therefore reflects a reasonable estimate of the materials' properties. For powders, however, the assessment of these values is more complicated. For the drug, the same batches of material as previously described (Podczeck et al., 1995a) have been used, and thus reference values are provided. Due to a lack of material of micronized and ordinary lactose monohydrate, which were specially made batches for Glaxo Research and Development Ltd. UK, also literature data had to be sought. The value of E of a material can be assessed from its chemical structure (Roberts et al., 1991), and hence this value was used, assuming that it matches closest the true physical property of the material. The value of Y for lactose monohydrate was chosen from a slow compaction experiment (Roberts and Rowe, 1987), because the increase in press-on force up to its maximum using the centrifuge technique takes several min and is therefore also a slow process. For equivalent particle sizes and slow com-

Table 1
Physical properties of the materials used

Material	Description	Y (MPa)	E (GPa)	γ_s (mJ m^{-2})
Salmeterol	Micronized	19.7[a]	10.65[b]	52.6
(Xinafoate)	Ordinary powder	19.7	10.65	54.8
Lactose	Micronized	150.1[c]	24.29[d]	73.6
(Monohydrate)	Ordinary powder	150.1	24.29	55.3
Polyhydroxymethylene		3.7[e]	3.50[e]	32.8
Polyvinylchloride		21.2[e]	0.50[e]	49.6
Polyethylene		16.3[e]	1.20[e]	41.3
Aluminium		76.4[e]	70.60[e]	38.2

Y, yield strength, E, Young's modulus; γ_s, surface free energy.

[a] Taken from Podczeck et al. (1996a).

[b] Taken from Podczeck et al. (1994).

[c] Taken from Roberts and Rowe (1987).

[d] Taken from Roberts et al. (1991).

[e] Manufacturer's data (all surface materials have been used as supplied to match their use in industry. Thus, an influence of surface oxidation on the γ_s values cannot be excluded).

paction, the Y values reported in the literature are similar (see e.g. Roberts and Rowe, 1987; Fell and Newton, 1971), and hence the value given in Table 1 appears to be a reasonable estimate of the physical property of the material. The values for the surface free energy (γ_s) listed in Table 1 are all experimental values, and for example the comparison of the γ_s value for lactose monohydrate (ordinary powder) with literature data (Sheridan et al., 1995: 53.9–55.5 mJ m^{-2} for different sources) proves that the method used provided reliable estimates of this surface property.

From the values of the Young's modulus E (Table 1) the reduced Young's modulus can be calculated on basis of Eq. (1), and the work of adhesion $\Delta\gamma$ when a particle comes into adhesion contact with a surface can be calculated as described by Adamson (1982). The yield strength Y necessary to calculate the mode of adherence is always the value of the material that has the lower value of Y. Thus sometimes Y is taken from the particular material and sometimes from the material forming the surface.

From Table 1 it can be seen that the surface materials to which the drug particles were adhered varied in their elasticity from very stiff (aluminium) to highly elastic (polyvinylchloride, polyethylene). The yield strength of the surface materials varied by a factor of about 40 in their extremes. However, the variation in surface free energy γ_s is, if compared to Maugis and Pollock's theoretical approach (factor of about 1000 between minimum and maximum threshold considered), only small with a difference of only 40.8 mJ m^{-2} between the largest and smallest value of γ_s. However, the materials chosen reflect common surface materials in pharmaceutical powder processing and handling, and the drugs are usually all low energy substances with a γ_s below 100 mJ m^{-2}. Thus the study undertaken reflects typical situations.

Table 2 summarizes the results of the adhesion experiments listing the press-on force and correspondent median adhesion force for each experiment. In addition to the adhesion of the drug to surface materials from plastics or aluminium, the adhesion to an excipient was studied using lactose monohydrate as a model, and the autoadhesion of the drug was also investigated. For comparison, the autoadhesion of the excipient was also tested. While the autoadhesion of the drug is only slightly higher than the autoadhesion of the excipient, the adhesion between drug and excipient is clearly higher suggesting that the manufacture of interactive mixtures on the basis of these two material is possible. However, it should be noted that the adhesion forces measured in particle-on-surface experiments using compacted lactose

Table 2
Experimental results of the adhesion force measurements

Number	Particles	Surface	F_{on} ($\times 10^{-12}$N)	F_{ad}($\times 10^{-12}$N)
1	Salmeterol	Salmeterol	4.77	9.74 ± 0.77
			6.50	9.47 ± 1.55
			8.48	10.78 ± 3.42
			10.74	13.26 ± 0.83
			14.62	11.12 ± 1.62
2	Lactose	Lactose	4.78	5.09 ± 1.13
			6.67	6.55 ± 1.14
			8.88	7.98 ± 0.40
			11.41	10.56 ± 0.56
			14.25	11.28 ± 3.28
3	Lactose	Salmeterol	6.67	6.00 ± 1.52
			8.88	8.64 ± 1.78
			11.41	17.09 ± 1.65
			14.25	14.55 ± 3.86
			17.41	15.80 ± 2.38
4	Salmeterol	Lactose	6.50	5.46 ± 0.93
			8.48	7.83 ± 1.33
			10.74	10.78 ± 1.34
			14.62	10.50 ± 1.22
			17.53	9.85 ± 0.44
5	Salmeterol	Lactose (particles)	6.50	8.22 ± 1.96
			8.48	10.98 ± 2.36
			10.74	19.26 ± 0.87
			14.62	21.75 ± 1.49
			17.53	19.71 ± 2.37
6	Salmeterol	Polyhydroxymethylene	6.50	1.65 ± 0.46
			8.48	2.04 ± 0.33
			10.74	3.54 ± 0.51
			14.62	2.67 ± 0.36
			17.53	2.45 ± 0.24
7	Salmeterol	Polyvinylchloride	6.50	4.54 ± 0.94
			8.48	31.42 ± 5.45
			10.74	43.19 ± 9.20
			14.62	58.02 ± 8.36
			17.53	37.23 ± 6.66
8	Salmeterol	Polyethylene	6.50	3.92 ± 0.70
			8.48	18.81 ± 4.77
			10.74	38.13 ± 2.85
			14.62	29.11 ± 4.55
			17.53	28.27 ± 4.22
9	Salmeterol	Aluminium	6.50	28.14 ± 9.97
			8.48	44.40 ± 7.00
			10.74	38.47 ± 9.18
			14.62	28.30 ± 3.98
			17.53	40.69 ± 9.07

F_{on}, press-on force; F_{ad}, median adhesion force (arithmetic mean ± S.D. of six replicates); experimental data previously reported by Podczeck et al., 1995b (sets 1-4); Podczeck et al., 1996b (sets 5-9).

monohydrate is significantly smaller than the adhesion forces measured in particle-on-particle experiments. This is due to differences in the surface structure and in particular in the surface roughness of the compacted and particulate surfaces. Thus, it is recommended to base adhesion studies which aim to investigate the possibility of forming interactive mixtures between a drug and an excipient on particle-on-particle experiments. The difference in adhesion of the drug to the plastic and aluminium surfaces is much more pronounced. Strong adhesion exists between drug and aluminium or polyvinylchloride, whereas extremely low adhesion occurs between drug and polyhydroxymethylene. However, this difference might not be of importance if the drug can be detached from the surface materials without small amounts being left on the surfaces (preferred mode of adherence: brittle, F_{b}).

Table 3 lists the model values calculated on basis of Eqs. (8)–(11) and (13). The first observation that can be made is that in general the micronized particles have been deformed fully plastic during the press-on phase. The press-on forces applied led to adhesion forces similar to those which occur after mixing of the drug with the excipient. This has been confirmed using a drug-excipient mixture, prepared in a turbula mixer, and measuring the adhesion force in a particle-on-particle experiment without application of an additional press-on force. Thus the deformation mechanisms and modes of adherence found reflect practical situations.

Due to the fact that fully plastic deformation always has occurred, the values for $|F_{\mathrm{d}}^*|$ need only to be compared with $|F_{\mathrm{m}}^*|$ and $|F_{\mathrm{b}}^*|$ calculated for this type of deformation (Table 3, right column). If $|F_{\mathrm{d}}^*| > |F_{\mathrm{m}}^*|$ and $|F_{\mathrm{m}}^*| < |F_{\mathrm{b}}^*|$, the criterion ϕ needs to be less than one for the F_{m}-mode to be valid. Otherwise, i.e. $\phi > 1$, the F_{b}-mode is valid, even if $|F_{\mathrm{m}}^*| < |F_{\mathrm{b}}^*|$.

The mode of adherence proposed for the autoadhesion of the drug and the excipient is brittle separation (F_{b}-mode) for all press-on forces. This implies that a maximum extent of plastic deformation was reached already at the lowest press-on force applied. The related ϕ values obtained for the autoadhesion of the drug are, however, very close to one, especially for the two lowest press-on forces. This implies, that the press-on force applied was just large enough to allow sufficient elastic recovery to change the mode of adherence from a ductile to a brittle separation. Thus, the two autoadhesion systems (drug-drug and excipient-excipient) are not similar in their properties. In the case of adhesion between drug and excipient, ductile rupture always occurs. Thus the particles are plastically deformed during the press-on stage, but not to their maximum extent. Comparing the physical properties of the contiguous bodies in contact, the most obvious difference between the autoadhesion of lactose monohydrate and the adhesion is the yield strength Y, which is nearly eight times larger for the autoadhesion contact (see Table 1). Furthermore, the reduced Young's modulus E ($E = 13.35$ GPa for autoadhesion of lactose monohydrate, $E = 8.14$ GPa for adhesion, $E = 5.85$ GPa for autoadhesion of drug) indicates that stiffer materials are already deformed to their maximum extent at lower press-on forces when compared with more elastic materials. Obviously, the most difficult situation occurs when a comparatively stiff material comes into adhesion contact with a soft elastic material. The mode of adherence for the adhesion contact between drug and excipient implies that a detachment of the drug is complimented with small loss of drug on the excipient surface (ductile rupture), and that higher forces should be applied to increase the amount of elastic recovery and thus to transform the mode of adherence into a brittle one. In this respect, particle-on-surface and particle-on-particle experiments led to the same conclusions.

Comparing the mode of adherence evaluated for the drug adhered to the plastic and aluminium surfaces, it occurs either a ductile rupture (F_{d}-mode, polyhydroxymethylene, aluminium) or a brittle separation at a smaller radius of contact than achieved during the application of the press-on force (F_{b}-mode, polyvinylchloride, polyethylene). Furthermore, a ductile-brittle transition exists for the highest press-on force using aluminium as surface. Polyvinylchloride and polyethylene have the smallest Young's moduli. The higher elasticity might be the reason for the

Table 3
Modes of adherence for micronized particles adhered to surfaces

Number	Elastic deformation		Elasto–plastic deformation			Fully plastic deformation			Mode
	$\|F_d^*\|$	$\|F_b^*\|$	ϕ	$\|F_m^*\|$	$\|F_b^*\|$	ϕ	$\|F_m^*\|$	$\|F_b^*\|$	
1	1.20	0.42	0.78	1.40	1.46	1.05	1.09	1.10	FP, B
	1.45	0.42	0.84	1.53	1.57	1.10	1.19	1.20	FP, B
	1.89	0.42	0.93	1.73	1.73	1.17	1.33	1.37	FP, B
	2.54	0.42	1.04	1.94	1.94	1.26	1.48	1.59	FP, B
	2.77	0.42	1.07	2.00	2.01	1.29	1.52	1.66	FP, B
2	4.35×10^4	29.71	13.54	3.48×10^4	2.22×10^2	14.44	3.75×10^4	2.09×10^2	FP, B
	6.43×10^4	29.71	15.53	5.46×10^4	2.60×10^2	15.92	5.62×10^4	2.54×10^2	FP, B
	8.88×10^4	29.71	17.38	7.91×10^4	2.96×10^2	17.26	7.85×10^4	2.98×10^2	FP, B
	1.26×10^5	29.71	19.63	1.18×10^5	3.42×10^2	18.86	1.13×10^5	3.56×10^2	FP, B
	1.53×10^5	29.71	20.96	1.47×10^5	3.69×10^2	19.79	1.38×10^5	3.91×10^2	FP, B
3	0.08	0.18	0.34	0.24	0.43	0.53	0.21	0.28	FP, D
	0.12	0.18	0.40	0.32	0.50	0.59	0.28	0.34	FP, D
	0.22	0.18	0.51	0.48	0.63	0.68	0.42	0.47	FP, D
	0.23	0.18	0.52	0.49	0.64	0.69	0.43	0.48	FP, D
	0.28	0.18	0.56	0.55	0.69	0.72	0.49	0.53	FP, D
4	0.17	0.21	0.44	0.41	0.60	0.64	0.36	0.41	FP, D
	0.26	0.21	0.52	0.53	0.70	0.71	0.46	0.51	FP, D
	0.37	0.21	0.60	0.67	0.80	0.78	0.58	0.61	FP, D
	0.45	0.21	0.64	0.75	0.86	0.82	0.65	0.67	FP, D
	0.48	0.21	0.66	0.78	0.88	0.83	0.68	0.70	FP, D
5	0.22	0.21	0.49	0.49	0.66	0.69	0.42	0.47	FP, D
	0.32	0.21	0.56	0.61	0.76	0.75	0.53	0.57	FP, D
	0.55	0.21	0.69	0.83	0.92	0.86	0.73	0.74	FP, D
	0.73	0.21	0.77	0.97	1.03	0.92	0.85	0.85	FP, D
	0.77	0.21	0.78	1.00	1.05	0.94	0.87	0.88	FP, D
6	1.18×10^{-4}	0.01	0.05	2.20×10^{-3}	0.02	0.10	2.14×10^{-3}	0.01	FP, D
	1.62×10^{-4}	0.01	0.06	2.78×10^{-3}	0.02	0.11	2.70×10^{-3}	0.01	FP, D
	2.73×10^{-4}	0.01	0.08	4.09×10^{-3}	0.03	0.13	3.98×10^{-3}	0.02	FP, D
	2.78×10^{-4}	0.01	0.08	4.14×10^{-3}	0.03	0.13	4.03×10^{-3}	0.02	FP, D
	2.96×10^{-4}	0.01	0.08	4.34×10^{-3}	0.03	0.13	4.22×10^{-3}	0.02	FP, D
7	4.46×10^5	54.25	27.04	4.32×10^5	6.38×10^2	25.85	4.12×10^5	6.68×10^2	FP, B
	1.93×10^6	54.25	44.31	2.20×10^6	1.17×10^3	37.30	1.83×10^6	1.39×10^3	FP, B
	2.80×10^6	54.25	50.07	3.29×10^6	1.37×10^3	40.91	2.66×10^6	1.67×10^3	FP, B
	4.19×10^6	54.25	57.12	5.10×10^6	1.62×10^3	45.24	4.00×10^6	2.05×10^3	FP, B
	3.52×10^6	54.25	53.95	4.22×10^6	1.50×10^3	43.30	3.35×10^6	1.88×10^3	FP, B
8	1.88×10^3	6.60	6.09	1.17×10^3	46.88	6.58	1.31×10^3	43.36	FP, B
	6.38×10^3	6.60	9.32	5.23×10^3	76.62	8.94	4.96×10^3	79.91	FP, B
	1.20×10^3	6.60	11.55	1.09×10^4	99.14	10.46	9.68×10^3	1.09×10^2	FP, B
	1.23×10^3	6.60	11.65	1.12×10^4	1.00×10^2	10.53	9.95×10^3	1.11×10^2	FP, B
	1.36×10^3	6.60	12.05	1.27×10^4	1.04×10^2	10.80	1.11×10^4	1.17×10^2	FP, B
9	0.41	0.16	0.66	0.69	0.78	0.80	0.62	0.64	FP, D
	0.67	0.16	0.79	0.90	0.94	0.90	0.81	0.82	FP, D
	0.71	0.16	0.80	0.92	0.96	0.92	0.84	0.84	FP, D
	0.71	0.16	0.80	0.92	0.96	0.92	0.84	0.84	FP, D
	1.02	0.16	0.92	1.10	1.11	1.00	1.01	1.01	FP, B

FP, fully plastic deformation; D, ductile rupture (F_d-mode); B, brittle separation (F_b-mode).

F_b-mode to occur, because higher elasticity results in more pronounced elastic recovery, which favours a brittle separation (Maugis and Pollock, 1984). The results also imply that the use of surfaces with lower surface free energy (aluminium, polyhydroxymethylene) is complemented by ductile rupture as the apparent mode of adherence, whereas a higher surface free energy of the surface material (polyvinylchloride, polyethylene) will result in brittle separation. Thus by varying the surface materials for containers, hoppers or other equipment used for powder handling and processing, it is possible to prevent drug loss or product contamination by choosing the appropriate surface material.

It can be concluded that the use of theoretical calculations of the mode of adherence for an adhesion contact between particles and surfaces offers the possibility to choose appropriate working materials for the handling and processing of powders. The adhesion force measurements necessary can be performed using the centrifuge technique, which is an effective, low cost procedure that works with minimal amounts of powder and thus can be used in the early stage of dosage form development.

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