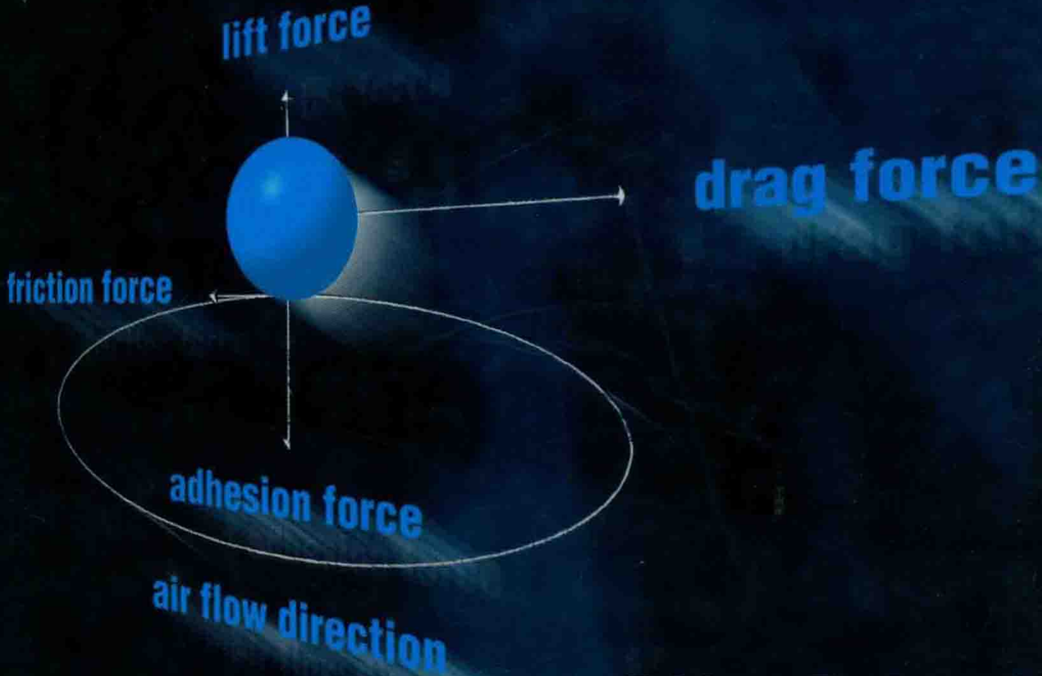
Particle-particle Adhesion in Pharmaceutical Powder Handling



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PREFACE

This monograph describes the physical principles of adhesion between particles and surfaces. These principles are then applied to some situations, where there are interactions between powders and surfaces and also powders and powders when pharmaceutical processes are involved and dosage forms are produced. These issues are generally important at some stage of the preparation of the majority of pharmaceutical products. In particular, the text involves powder flow, powder mixing, dry powder inhalations, agglomeration and agglomerate strength, and the mechanical strength of tablets.

The field covered is somewhat wider than the title might indicate. To aid a wider appreciation of the problems, the monograph also deals with physical properties of solid surfaces as far as these are relevant to the understanding of particle adhesion. The theory of friction is also introduced and the differences between friction of macroscopic bodies and particle friction are highlighted. Finally, techniques to measure particle adhesion and particle friction are described, as are techniques to determine fracture mechanical properties of powders, whose knowledge is required if the application of principles described in this monograph are sought.

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CHAPTER 1

FUNDAMENTALS OF ADHESION OF PARTICLES TO SURFACES

1.1 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 particles and between particles and surfaces determines the properties of the powder bulk, e. g. during mixing, powder flow, granulation, compaction or drug delivery to the lungs.

The major mechanisms of interaction between particles and particles or surfaces to be considered during powder handling are (1) adhesion and (2) friction.

(1) Adhesion

Particle adhesion is the result of forces which exist between particles and a solid surface in contact, where the solid surface can be a particle surface itself. *Dry* adhesion can be observed for surfaces in contact under vacuum or any other environment that completely excludes adsorption or capillary condensation in the contact zone. *Boundary* adhesion occurs, if the gap between the surfaces in contact is so narrow that the properties of the contact spot differ from the properties of the separated surfaces. *Static* adhesion is measured applying a minimum force required for detachment at an infinitely slow rate, while *dynamic* ("kinetic") adhesion is determined applying a detachment force at a finite rate. In the latter case the force measured is detachment rate dependent and also changes with increasing distance between the contiguous surfaces (Deryaguin et al. 1978a, pp. 279–280). Not only can an adhesion contact occur between particles and surfaces of different chemical nature, but also between particles and surfaces of the same material. This is often referred to as *cohesion* in the pharmaceutical literature and has its origin in soil mechanics, where powders or wet powder masses are treated as a continuum, from which gross measures are taken. However, with respect to single particle interactions, the term cohesion is the correct terminology only for those cases where the particles come as close as an atomic distance between each other i. e. in tabletting or granulation. In contrast, this phenomenon is correctly called *autoadhesion* with respect to single particle interactions in powder mixtures or only loosely densified powder beds, for example in capsules, because the particles are not at an atomic distance from each other, nor do they form a single solid body (Zimon 1982, p. 1).

(2) Friction

Friction is the force preventing the tangential displacement of two solid surfaces in contact, where again the solid surfaces can be particle surfaces (see Chapter 2).

The presence of adhesion and friction between powder particles and solid surfaces may be deliberate and advantageous, for example when preparing an interactive powder mixture from an inert excipient as carrier and micronized drug particles for dry powder inhalations (see Chapter 3, section 3. 2). 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. Friction between powder particles and a solid surface is usually regarded as an unwanted effect, and indeed often requires the addition of lubricants to formulations to overcome or at least reduce its influence.

In processes such as powder flow from hoppers during tabletting or nozzle retention during capsule filling, the contact with the powder leads eventually 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 1990a). However, substances with large adhesion tendency such as lactose gave unsatisfactory filling results, especially when the surface of the nozzles was worn (Joliffe and Newton 1983). The adhesion force of tablets to the lower punch of a rotary tablet machine was measured by Mitrevej and Augsburger (1980) following the cantilever–strain gauge principle first described by Fuller and Tabor (1975). The former authors connected the cantilever beam to the feed frame in front of the sweep-off blade of the tabletting machine. When the tablet struck this blade to be pushed off the lower punch, the net adhesion force, i. e. the total force measured less the force due to the momentum of the tablet, was determined. To study such 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. Their findings suggest, that the effect a lubricant exerts on a particle to surface contact depends on the material and surface properties as well as the force with which they are pressed together during powder handling. Hence, one specific lubricant concentration, which is optimal in reducing particle to surface interactions, that can be used for any powder and surface in contact will not exist. Podczeck (1997a,b) has shown that the measurement of adhesion forces between drug and carrier particles in interactive powder mixtures can be used for quality control purposes in the industrial manufacture of dry powder inhalations, and to predict the in vitro–properties of dry powder aerosols during the development phase of this dosage form.

While the above examples from the pharmaceutical literature involved the experimental determination of adhesion forces and the investigation of the relationship between the measured adhesion forces and the performance of a dosage form, the majority of pharmaceutical references lacks a proper understanding and assessment of particle adhesion. For example, Steckel and Müller (1997a) found that an increase in carrier particle size was complimented by a reduction of the amount of re-suspended drug in in vitro–tests of dry powder inhalations. They felt that this was contradictory to the theory of adhesion, because '. . . decreasing free surface and surface free energy due to increasing carrier particle size should result in lower adhesive forces between drug and carrier' (neither the adhesion force nor the surface free energy had been measured). However, as will be shown in Chapter 3, section 3. 2, the force of adhesion between drug and carrier particles is not the only entity to modulate the re-suspension of the drug in an air stream. First, various re-suspension models (see section 1. 7) have shown that an increase in carrier particle size will result in more pronounced hinderance of re-suspension. Secondly, not only the surface free energy of the coarser particles will have changed, but also the surface roughness, which influences both adhesion and friction. Usually, the surfaces of coarser particles are less rough, thus the adhesion force might have increased rather than decreased. A scientific evaluation of the observations made by Steckel and Müller (1997a) would therefore require the measurement of adhesion forces plus the factors influencing this physical property.

The few examples mentioned above already show, how important the understanding of adhesion and friction phenomena in pharmaceutical powder handling is. The great variety of such phenomena will be discussed in Chapter 3 in more detail. At this point, however, it appears necessary to introduce the main concepts and models of adhesion and their physical background.

1.2 Forces Causing Adhesion of Particles To Particles or Surfaces

1.2.1 Lifshitz–van der Waals Forces

The long-range interaction between molecules, collectively known as the "van der Waals force" consists of 3 main types of forces, which are the "Debye–induction force", the "Keesom–orientation force" and the "dispersion force" (Israelachvili 1992, pp. 93–94). Induction and orientation forces are the characteristic forces for dipole molecules. If two dipole molecules are in contact, they orientate themselves so that the negative pole of one molecule is directed towards the positive pole of the other molecule (orientation force). Molecules comprising a permanent dipole can induce an electrical dipole in apolar but polarizable molecules (induction force). To explain the adhesion between macroscopic bodies, for example particles onto surfaces, in terms of van der Waals forces, often only dispersion forces are taken into account (Rumpf 1977), because the dispersion forces generally exceed the induction and orientation forces. The existence of dispersion forces can be explained as follows: for an apolar atom, the time average dipole moment is zero. However, due to the instantaneous position of the electrons with respect to the nuclear protons, finite dipole moments arise at any instant. These in return generate an electrical field, which polarizes any neutral atom nearby inducing a dipole moment in them. These dipoles interact, which results in a finite attractive force between the atoms. These attraction forces between apolar molecules are generally present. After the discovery of the basic structure of atoms (nucleus and electron shell) and the resulting theory of quantum mechanics, London (1930, 1937) applied these principles to describe the force acting between two molecules. He proposed that the force varies inversely with the sixth power of the distance between the centres of the molecules. However, London's theory is not valid if the distance between the molecules is very close, i. e. not more than one or two times the diameter of the molecules (Deryaguin 1960), or if the distance between the molecules is very large, i. e. more than 1 nm (Rumpf 1977). Casimir and Polder (1948) proposed, that for large distances of more than 100 nm between the molecules London's 6th power law changes into a 7th power law. The problem with both theories is that one cannot measure these forces directly, because the attraction force between two solid bodies separated by a narrow gap is influenced by many molecules, closely packed together, at the same time.

The development of a macroscopic theory of van der Waals interactions of condensed bodies by Lifshitz (1955, 1956) explains attractive forces in the range between 1 and 100 nm, the range not covered by London's and Casimir and Polder's theories. The latter two theories can be regarded as the limiting cases of Lifshitz's theory (Deryaguin 1960), which hence describes a general attraction force between solid contiguous bodies ("Lifshitz–van der Waals force"). To explain Lifshitz–van der Waals forces, first the natural fluctuations in density of the electron cloud surrounding the nucleus of an atom should be considered. These fluctuations lead to consistent fluctuations of the appearance of dipole moments and hence to fluctuations of an electromagnetic field surrounding the atom. The electromagnetic field acts over a comparatively wide distance, which allows interactions with other electromagnetic fields and hence attractive forces between solid bodies beyond the London distance. Secondly, Lifshitz's theory refrains from the explanation of attractive forces based on a pair-wise additivity of inter-atomic contacts completely and treats large bodies as continuous media. The magnitude of the forces arising are derived from bulk properties such as dielectric constants or refractive indices. The application of Lifshitz's theory to experimental data, where the gap between the solid contiguous bodies was about 20 to 40 nm due to surface roughness, was able to match theoretical and experimental force values for the first time (Deryaguin 1960). The magnitude of the Lifshitz–van der Waals forces depends on the properties of the materials and their surfaces in contact (e. g. surface roughness, surface free energy, hardness, elasticity), and also on particle size and true area of contact. A change of any of these factors can change the magnitude of the Lifshitz–van der Waals force and hence the adhesion strength (Zimon 1982, p. 125).

Idealizing the shape of particles to be spherical, the Lifshitz–van der Waals forces can be calculated for the 3 different cases of contact, which are (a) sphere–on–sphere, (b) sphere–on–plane surface, and (c) contact between two plane surfaces—as follows (Rumpf 1977):

(a):

$$F_{vdW} = \frac{\hbar\bar{\omega}}{16\pi z_o^2} R \tag{1.1}$$

(b):

$$F_{vdW} = \frac{\hbar\bar{\omega}}{8\pi z_o^2} R \tag{1.2}$$

(c):

$$F_{vdW} = \frac{\hbar\bar{\omega}}{8\pi^2 z_o^3} \tag{1.3}$$

where F_{vdW} is the Lifshitz–van der Waals force [N], $\hbar\bar{\omega}$ is the Lifshitz–van der Waals constant [J], R is the particle radius [m], and z_o is the distance of separation between the contiguous bodies [m].

The Lifshitz–van der Waals constant is a measure of the energy of the van der Waals interaction between two bodies of similar or different geometry. Its magnitude ranges between 10^{-18} to 10^{-20} J. For example, for lactose monohydrate $\hbar\bar{\omega}$ was found to be 3.5×10^{-18} J (Podczeck et al. 1994).

The Lifshitz–van der Waals constant can be obtained using dielectric spectroscopy (Krupp 1967; Gregory 1969; Osborne–Lee 1988; Anandarajah and Chen 1995), and depends on the properties of the materials in contact. For contacting bodies of identical material separated by a medium other than air, the Lifshitz–van der Waals constant is always positive ("attractive"), whereas for bodies of different materials in contact attractive or repulsive ("negative") Lifshitz–van der Waals constants can be found. If the separating medium is air or vacuum, the Lifshitz–van der Waals constant between any two contacting bodies is positive. For interactions between surfaces of identical material through a separating medium, the Lifshitz–van der Waals constant remains unchanged if the separating medium is exchanged (Israelachvili 1992, p. 185).

1.2.2 Capillary Forces

Capillary forces arise from moisture in the gap between contiguous bodies. Hydrophillic, porous materials often contain moisture trapped in the pores. Such liquid is able to build up liquid bridges to adhered surfaces (Schubert 1974). A second source of capillary forces is moisture which condenses in the gap between the contiguous bodies. 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). Liquids which wet a surface (small contact angle) spontaneously condense from vapour into cracks and pores and thus build the so-called "bulk liquid" (Israelachvili 1992, p. 330). During adhesion contact, the liquid pressure is less than the air pressure, which results in a concave meniscus and a state of tension (Colbeck 1996).

Several theories are reported in the literature to calculate capillary forces acting between a particle and a 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 can provide a rough estimate of the order of magnitude and magnitude of change of capillary forces. Most of the equations cited below can be used both to estimate adhesion or autoadhesion capillary forces. In this respect it should be noted that powder particles and surfaces made from identical materials can have different surface properties i. e. different contact angles (Buckton and Newton 1986).

When a liquid condenses between for example a sphere of radius R and a plane surface, the Laplace pressure developed due to the curved liquid surface pulls sphere and plane surface together. McFarlane and Tabor (1950) could show that the resulting capillary force F_c equals:

$$F_c = 4\pi R \gamma_L \cos\theta \tag{1.4}$$

where F_c is the capillary force [N], R is the radius of the adhered sphere [m], γ_L is the surface tension of the condensed liquid [mNm^{-1}], and θ is the contact angle of the liquid. Eq. (1.4) describes the Laplace pressure contribution to the total adhesion force measured. Eq. (1.4) was found to predict F_c correctly within a few percentage points using glass spheres adhered to plane glass surfaces in saturated vapour of water, glycerol, decane, octane, ethanol, benzene and aniline (McFarlane and Tabor 1950). However, real particles usually comprise a rough surface, and their adhesion is thus not always correctly predicted using Eq. (1.4). As long as the condensed moisture connects the surfaces via small asperities only, the adhesion force will be much lower than theoretically predicted. However, if the amount of condensed moisture exceeds the asperity size, Eq. (1.4) becomes valid (Israelachvili 1992, p. 333).

Eq. (1.4) has caused dispute in the literature, and is probably only valid if very small amounts of moisture are present in the gap between the contiguous bodies. Also, it accounts only for autoadhesion contacts. Thus a variety of other equations have been developed over the years, all comprising their own advantages, disadvantages and limitations.

A very simple calculation method of capillary forces has been developed by O'Brien and Hermann (1973) for spherical particles adhered to a plane surface:

$$F_c = 2\pi R \gamma_L (\cos\theta_1 + \cos\theta_2) \tag{1.5}$$

where θ_1 and θ_2 are the contact angles between the two bodies in contact and a liquid. In the case that the influence of the relative humidity of the air is to be studied, the contact angles between the two powder materials and water are needed. The model does not allow the possible adjustment of 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 ("surface tension force"). The surface tension force ($F_{c,1}$ [N]) can be calculated from:

$$F_{c,1} = 2\pi a_o \gamma_L \tag{1.6}$$

where a_o is the radius of the meniscus [m]. The meniscus formed along the surfaces will also reduce the so-called "liquid pressure". The liquid pressure ($F_{c,2}$ [N]) can be expressed as:

$$F_{c,2} = \pi a_o^2 P_c \tag{1.7}$$

where P_c is the capillary pressure [Pa]. Therefore, the capillary force (F_c) can be calculated as (Zimon 1982, p. 109):

$$F_c = F_{c,1} - F_{c,2} = 2\pi a_o \gamma_L - \pi a_o^2 P_c \tag{1.8}$$

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

$$a_o = R \sin\alpha + \frac{R(1-\cos\alpha)\cos(\theta+\alpha)}{1+\sin(\theta+\alpha)} \tag{1.9}$$

where θ is the contact angle between the adhered particle and the liquid, and 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 (see Fig. 1.1).

The capillary pressure (P_c [N]) is an index for the difference in pressure, which exists between two bulk phases that are separated by a curved surface and are in a state of equilibrium (Zimon 1982, p. 109). 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 refers to 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 the contact between a particle and a plane surface, which have different wetting properties:

$$P_c = \frac{\gamma_L}{R}\left(\frac{\cos(2+\theta_1)+\cos\theta_2}{1-\cos\alpha}\right) \tag{1.10}$$

where θ_1 is the contact angle for the particle, and θ_2 is the contact angle for the substrate surface. Zimon (1982 p. 111) quotes the following equation for the case that $\theta_1 = \theta_2$:

$$P_c = \frac{\gamma_L}{R}\left(\frac{R}{a_o} - \frac{\cos(\theta+\alpha)}{1-\cos\alpha}\right) \tag{1.11}$$

For autoadhesion contacts, where the contact angle θ between the condensed water and the surface is small, and the radius of the meniscus a_o [m]

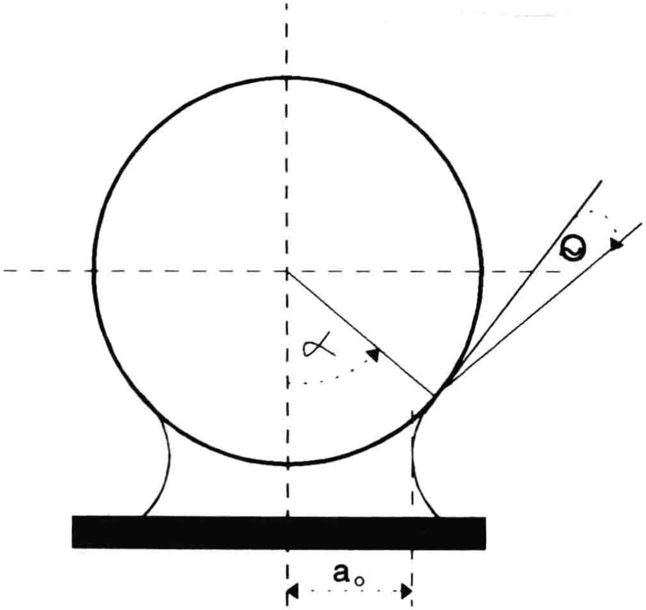

Figure 1.1. Determination of the radius of the liquid meniscus (a_o) formed in the contact zone between a spherical particle and a flat surface under the influence of condensed moisture (Eq. (1.9))
α, angle between the perpendicular from the centre of gravity of the particle and the connecting line between the centre of gravity of the particle and the outer surface of the meniscus; θ, contact angle between the adhered particle and the liquid.