DIRECT ADHESION MEASUREMENT OF INDIVIDUAL SOLID PARTICLES TO GELATIN CAPSULE SURFACES

Taleb H. Ibrahim[1], Tonia R. Burk[2], Ronald D. Neuman[3] and Frank M. Etzler[4]

1: Assistant professor, Chemical Engineering Department, American University of Sharjah.
2:Post doctor, Veterinary medicine, Auburn University.
3: Alumni professor, Chemical Engineering, Auburn University.
4:Group leader, Research and Development Center, Boehringer Ingelheim Pharmaceuticals, Inc.

Correspondence address: American University of Sharjah, Chemical Engineering Department, P.O. BOX 26666, Sharjah, UAE. E-mail: italeb@aus.ac.ae

ABSTRACT

A significant amount of research attempting to evaluate the adhesion forces between particles and solid surfaces has been performed over the years. For example, a number of experimental techniques based on the detachment of particles from surfaces have been utilized for measuring adhesion: centrifugal, impact separation, aerodynamic and cantilever beam methods. These methods provide only limited insight into the microscopic details which are needed for an improved understanding of the factors influencing particle adhesion and removal.

Atomic force microscopy (AFM) was used to directly measure the adhesion of individual lactose and drug particles to the surface of gelatin capsule surfaces. In this study, AFM shows that gelatin capsule surfaces with high surface heterogeneity and high-contrast friction exhibit high adhesion, and gelatin capsule surfaces with low surface heterogeneity and low-contrast friction exhibit low adhesion. In addition, the adhesion appears to be proportional to the particle size for homogeneous surfaces. The physicochemical nature of the capsule surface seems to dictate the spatial variation of adhesion across the surface. The AFM results clearly show that the surface physicochemical properties depend on the gelatin and the mold release agent utilized in the manufacture of gelatin capsules.

Keywords: *Atomic force microscopy, adhesion, friction imaging, topography imaging, particle-surface adhesion.*

الملخص

منذ وقت ليست بالقليل جرت عدة محاولات بحثية ودراسية خاصة بالقوى اللاصقة بين السطوح الصلبة والجزيات ويستخدم على سبيل المثال لا الحصر عدد من الطرق لفصل السطوح عن بعضها البعض مثل طريقة الطرد المركزي ؛ التصادم الانفصالي ؛ الديناميكية الهوائية و الكابول الاشعاعي وباستخدام الميكروسكوب تمكن من التوصل الى معلومات تفصيلية تساعد في التعرف على العوامل و القوى المؤثرة في عملية فصل السطوح .

في هذا البحث تم استخدام ميكرسكوب القوة الذرية مباشرة لقياس مقدار القوى الالصقة بين ذرتي اللكتوز و الدواء وسطح الكبسولة(الجلاتين) وقد تم بالفعل التوصل الى اثبات علاقة بين القوى اللاصقة وطبيعة سطح الكبسولة بما في ذلك الاحتكاك وا لحجم البلوري للمواد, وان لنوع المواد المزيتة المبطنة للكبسولة لهى التاثير الاعظم على القوى اللاصقة .

1. INTRODUCTION

Dry powder inhaler (DPI) devices are used to deliver micronized drug and carrier particles from a gelatin capsule to the lung. The carrier is used in the formulation because carrier particles are typically more free flowing, thereby contributing to ease of handling during manufacture and improving emptying from the capsule during inhalation [Buckton, 1995]. In addition, carrier particles can significantly improve the mass of drug particles in the respirable range in some inhaler devices [Broadhead et al., 1995]. The surface properties of both the powder formulation and gelatin capsules and the environmental conditions control the physical properties of the aerosol cloud during inhalation. In lactose inhalation formulations, variability in the respirable fraction has been a development obstacle. Earlier work suggested that the adhesion of lactose particles to capsule surfaces seem to be controlled by the physicochemical nature of both the particles and gelatin capsule surfaces utilized in the dry powder inhalation system [Ibrahim et al., 2000]. In order to understand the adhesion behavior of lactose and drug particles to gelatin capsule surfaces, the surface chemical properties of lactose particles and gelatin capsules need to be determined. Adhesion is an interfacial phenomenon that depends on the nature, dynamic, orientation and contact areas of surfaces of interest. A better understanding of particle adhesion to solid surfaces and to other particles is essential for improving the aerosol properties and, therefore, controlling the respirable fraction.

Many investigators have been attempted to evaluate the adhesion forces between particles and solid surfaces over the years [Visser, 1995 and Mittal, 1999]. For example, a number of methods based on the detachment of particles from surfaces have been employed for measuring adhesion: centrifugal [Corn and Stein, 1965, Both and Newton, 1987, Kulvanich and Stewart, 1988, Iida et al., 1992, Podczeck et al., 1994], impact separation [Otsuka et al., 1983, Otsuka et al., 1988, Iida et al. 1993], aerodynamic [Corn and Stein, 1965, Larsen, 1958, Bhattacharya and Mittal, 1978] and cantilever beam [Corn, 1961] methods. These methods provide some insight into microscopic details which are needed for a better understanding of the factors controlling particle adhesion and removal. Atomic force microscopy (AFM) is a more powerful method since it allows one to characterize surfaces at the atomic scale. AFM is a high resolution imaging technique giving topographical images by scanning a sharp tip at the end of a cantilever over a surface [Binnig et al., 1986]. Most importantly, AFM can image surfaces in air and liquids without special surface treatment. A major advantage of using AFM is that it allows materials to be studied under conditions in which they are used. A further great benefit of AFM is the ability to quantify the force of interaction between surfaces as a function of separation distance [Ducker et al., 1991, Ott and Mizes, 1994, Schaefer et al., 1994, Sindel et al. 1998] by using the colloidal probe technique. In addition to topographic imaging, AFM can be operated in lateral force

microscopy (LFM) mode to yield maps of surfaces that indicate the friction interactions with a scanning probe. If the magnitude of the friction force is only compared with that of the adhesion force (or energy) no information is gathered since friction and adhesion are not generally related, however recent experiments with the surface forces apparatus (SFA) technique have shown that the (kinetic) friction force correlates with the hysteretic or irreversible component of the adhesion energy [Yoshizawa et al., 1993, Israelachvili et al., 1994]. As the humidity of the ambient environment can significantly influence both adhesion and friction forces [Yoshizawa et al., 1993], and therefore the relative humidity (RH) must be controlled in friction and adhesion measurements.

In this paper, we report direct adhesion measurements of individual lactose and drug particles to gelatin capsule surfaces using AFM by employing the colloidal probe technique. Furthermore, the adhesion of lactose particles is correlated with the surface physicochemical variation observed by friction imaging of the capsule surfaces and the dynamics of the lactose particle surfaces.

2. EXPERIMENTAL

2.1 Materials

Pharmaceutical grade lactose (Pharmatose 200M) was obtained from De Melkindustrie Veghel, Netherlands. Hard gelatin capsules of commercial origin were employed in this study. The capsule samples are designated as follows: 72601, 29625 and 29625ext which was the same as 29625 but was subsequently extracted by a proprietary process.

2.2 Scanning Force Microscopy

A Nanoscope III MultiMode^{TM} AFM (Digital Instruments) with an extender electronics module was mounted on a pneumatic vibration isolation table. The sample chamber was sealed with a Humplug (BioForce Laboratory) with accommodation for the cantilever holder handle and an internal humidity/temperature sensor with digital readout. The relative humidity in the AFM sample chamber was controlled to within ±2 % using a humidity generator (Model RH1500, VTI). The AFM was equipped with a "J" vertical scanner with scan size 125 x 125 μm and vertical range 5 μm. Cantilevers (0.58 N/m spring constant) with silicon nitride tip were used for both imaging and adhesion measurements**.** The force-distance measurements were performed at a vertical scan rate of 6.5 μms^{-1} and a loading force of approximately 6 nN**.** All gelatin capsule samples and lactose colloidal probes were equilibrated for at least overnight at 50 % relative humidity in Pyrex containers and in the humidity controlled AFM sample chamber for at least one hour before measurements. The contact force used for imaging was minimized within the allowance that the tip would not lose contact with the surface during scanning due to drift. Different areas on capsule samples prepared from multiple gelatin capsules were examined to verify that the surface and adhesion characteristics presented are representative.

A typical force curve reflecting the forces experienced between the lactose probe and the gelatin samples during approach, contact and separation of the two surfaces is shown in Figure 1. The change in cantilever deflection (Δd) at pull-off may be used with the effective spring constant (k) of the cantilever and Hooke's law ($F = k \times \Delta d$) to calculate the adhesion force between the probe and the sample. However, when a large range of adhesion forces is obtained using a single cantilever, the complete deflection of the cantilever is often not evident. Adhesion force was calculated based on the horizontal distance (Δz) between the point at which the probe crosses the zero deflection line upon retraction and the point at which the probe pulls free of the surface. Essentially a right triangle forms between Δz and the negative portion of the force curve which results upon retraction as can be seen in Figure 1. Since Δz is proportional to Δd, a relative adhesion force is determined in this study rather than an absolute adhesion force.

2.3 Capsule Sample Preparation

The preparation of the gelatin capsule samples was performed in a laminar flow hood using stringent surface-chemical procedures. The gelatin capsules were sectioned using a scalpel to obtain 0.5-cm-square samples. The inside surface of the capsule, which comes into contact with pharmaceutical formulations, was mounted face up on an epoxy adhesive-coated glass slide. While the epoxy adhesive was allowed to set, the capsule sample was maintained essentially flat using a custom-made Teflon clamp which avoided contact of the gelatin sample where imaging and adhesion measurements were to be performed.

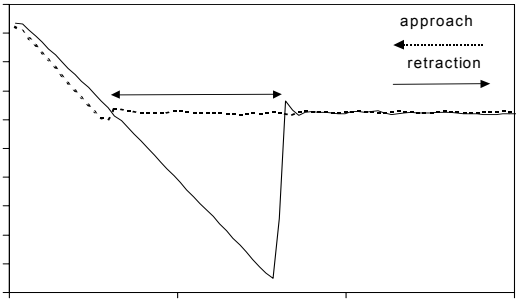

Figure 1. Typical lactose particle-gelatin capsule force curve.

2.4 Colloidal Probe Preparation

A lactose particle was attached to a silicon nitride tip as follows: briefly, two clean ultrafine wires were attached to a XYZ-translation stage for micromanipulation of adhesive and colloidal particle (see Figure 2a). The first wire was used to obtain and deposit a small amount of adhesive onto the end of the cantilever tip where the probe particle was to be attached. The other wire then was used to pick up and attach a selected particle onto the cantilever tip. Figure 2b shows a typical lactose particle mounted on a cantilever.

Top

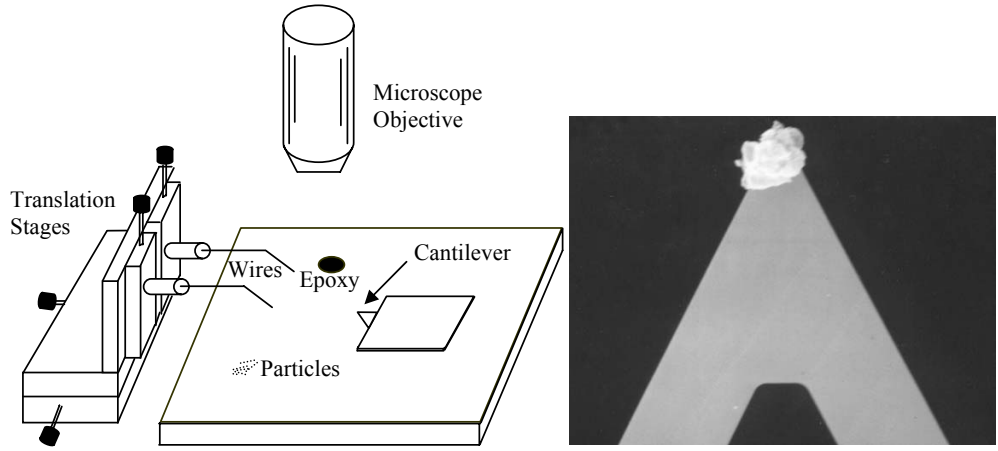

Figure 2. (a) Apparatus for colloidal probe and (b) Lactose probe

3. RESULTS AND DISCUSSION

Direct adhesion measurements of individual lactose and drug particles to gelatin capsule surfaces were performed at 50% RH. This RH was selected for study as being representative of the "water activity" that tends to be in the range of 40-60% RH in packaged (sealed) dry powder inhalation products (unpublished results). The adhesion of a lactose (and drug) particle was measured 50 times at a single location on a capsule surface to examine the reproducibility of the adhesion measurements. Next, the adhesion was measured ten times per location while the lactose (and drug) particle was translated laterally across the surface at 1-μm intervals to provide an indication of the intrinsic site-to-site variability of the adhesion characteristics. The ten adhesion measurements at each location were averaged to yield an adhesion profile over a 50-μm scan length across the capsule surface. Figure 3 shows both the stationary and scanned adhesion of a 6-μm lactose (and 5-μm drug) particle to the surface of gelatin capsules 72601, 29625 and 29625ext plotted as a function of contact number and distance. In addition, the adhesion forces for three different lactose and drug (probe) particles on the three above-referenced capsule surfaces, as well as the overall average adhesion values, are shown in Figure 4.

The adhesion profile can be markedly different depending on the source of commercial gelatin capsules as can be seen in Figure 3. For example, compare the adhesion profiles for gelatin capsules 72601 and 29625 which are illustrated in Figures 3(a and d) and 3 (b and e), respectively. In the case of gelatin capsule 72601 the adhesion of a lactose particle and drug across the capsule surface is relatively uniform as compared with the adhesion profile for capsule 29625. It can be seen that the adhesion force between a lactose particle and the surface of gelatin capsule 72601 is lower than that for capsule 29625. Furthermore, as shown in Figure 3(c), the adhesion characteristics, namely, the adhesion force and its spatial variation, for lactose particles on gelatin capsule 29625ext are very similar to those for lactose particles on capsule 72601. On the basis of Figure 4, the apparent order of adhesion for lactose particles is as follows: 29625ext $\leq$ 72601 < 29625.

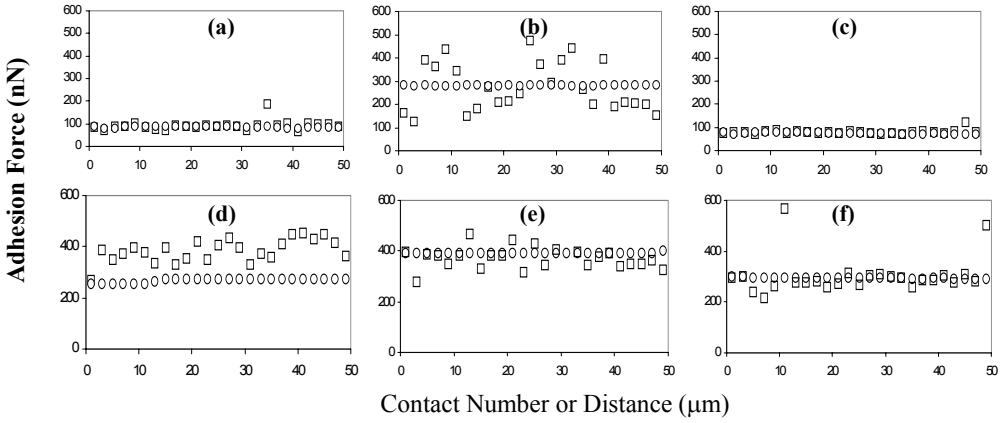

Figure 3. Adhesion of a single lactose particle (6 μm, a, b and c) or drug particle (5 μm, d, e and f) to surfaces gelatin capsules (a and d) 72601, (b and e) 29625, and (c and f) 29625ext. (○) Adhesion at a single location and (□) average adhesion of ten separate measurements at multiple locations.

The adhesion force between a lactose (and drug) particle and a gelatin capsule surface is affected by a number of factors, not the least of which are the surface properties of the two solids, the particle size and the relative humidity of the ambient environment. In practice, van der Waals, electrostatic and capillary forces usually play an important role in the adhesion of particles to surfaces [Hoh and Engel, 1993, Rumpf, 1977]. Upon contact of a particle with a solid surface, deformation of the particle and/or surface occurs due to surface force-induced stresses, such that the contact area and, hence, the particle-surface adhesion force increases [Bowling, 1988, Derjaguin, 1934]. The extent and nature of the adhesion- induced (elastic, viscoelastic and plastic) deformation depends on the strength of the interaction forces and the mechanical properties of the contacting materials [Bradley, 1936, Rimi et al., 1994]. The adhesion and removal of particles to and from solid surfaces is further complicated by the shape and surface asperities of particles [Otsuka et al., 1988], surface roughness of the substrate [Iida et al., 1993, Corn, 1961], as well as the initial applied load [Schaefer et al., 1994], contact time [Rimai et al., 1994], temperature [Rimai and Busnaina, 1995] and cohesive strength of the particle and solid substrate.

The presence of water vapor in the ambient atmosphere can affect the adhesion of particles to solid surfaces in several ways. For example, it is well known that an adsorbed water film can aid in the dissipation of electrical charges on solid surfaces [Lam and Newton, 1992]. In the absence of electrical charge effects, however, there is usually an increase in the adhesion tendency of a particle to a surface with an increase in RH [Binnig et al., 1986, Nguyen and Nieh, 1989, Zimon, 1982]. At high humidity conditions, a liquid film can also form by capillary condensation of water around contacting surfaces [Podczeck et al., 1997], and the resulting capillary force can make a

large contribution to the total force of adhesion [Rumpf, 1977]. The actual RH at which capillary bridges form also depends on the nature of the particle-surface system [Coelho and Harnby, 1978[a]], but rather than considering the overall curvature of the particle in contact with a flat surface, the more relevant curvatures are the local radii of the contacting microasperities [Coelho and Harnby, 1978[b]]. In addition, the presence of moisture may soften the surface of the particle and/or solid substrate due to water sorption, and the surface force-induced deformation, once again, increases the contact area and consequently the adhesion force [Iida et al., 1992].

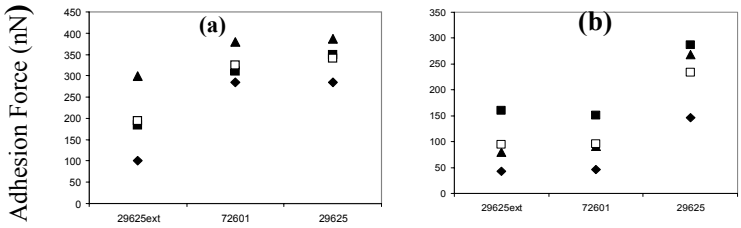

Figure 4. Average adhesion (500 measurements) of a single particle of (a) drug ((♦) 3 μm, (▲) and (■) 5 μm and (□) average adhesion of all measurement (1500) for the three probes) and (b) lactose ((♦) 5 μm, (▲) 6 μm, (■) 15 μm and (□) average adhesion of all measurement (1500) for the three probes) to the surface of gelatin capsules at multiple locations. Ten separate measurements were performed at each location.

In an attempt to identify the nature of the adhesion forces between lactose particles and gelatin capsule surfaces under the conditions of this study, direct adhesion measurements were performed with several lactose particles of different sizes. Figure 4 shows that the adhesion force appears to be directly proportional to the size (nominal diameter) of the lactose particle for gelatin capsule 72601. A linear trend was observed (Figure isn't shown) which is consistent with the view that the dominant component of the total adhesion force, on the basis of theoretical considerations for the interaction between a sphere and flat surface, arises from van der Waals forces [Coelho and Harnby, 1978[b]]. However, when one considers the surface chemistry of the component materials in pharmaceutical products, it seems more appropriate that the principal forces contributing to particle-surface adhesion can be classified as Lifshitz-van der Waals forces [Lam and Newton, 1992, van Oss et al. 1988] and acid-base interactions [van Oss et al. 1988, van Oss, 1994, Fowkes, 1987]. The results of the adhesion force measurements can be explained by an increase in the molecular contact area with increasing particle size since the number of real contacts will usually be proportional to the size of a rough particle [Coelho and Harnby, 1978[b]]. On the other hand, if electrostatic forces of interaction were to predominate in the lactose particle-gelatin capsule system, the measured adhesion force likely would not exhibit a linear variation with particle size [Coelho and Harnby, 1978[b]]. Furthermore, capillary interactions are not believed to play a significant role since the RH was below 65% [Nyguyen and Nieh, 1989].

However, the linear increase in adhesion force with respect to particle size was not observed for gelatin capsule 29625. One interpretation for the nonlinear trend is that the physicochemical nature of this capsule surface is not uniform. Indeed, the adhesion force measurements shown in Figure 3(b) indicate that there is a significant surface heterogeneity associated with capsule 29625. This heterogeneity is probably due, in large part, to the presence of contaminants on the gelatin capsule surface. Therefore, gelatin capsule 29625 was extracted to learn to what extent the removal of (presumed) extraneous surface contaminants would impact the adhesion profile. As might be expected, the adhesion profile for capsule 29625ext, which is illustrated in Figure 3(c), shows that the surface heterogeneity is greatly reduced, and the plot of the adhesion force versus particle size.

The direct adhesion measurements of individual lactose (and drug) particles to gelatin capsule surfaces clearly indicate the need for investigating the physicochemical nature of the capsule surfaces. Thus, the lateral force microscopy (LFM) mode was used to simultaneously obtain images of the gelatin capsules that show the topographic features and the friction interactions with the cantilever tip. LFM is an extension of contact mode imaging, and it identifies and maps relative differences in surface frictional characteristics in response to the torsion or twisting of the cantilever as the tip is scanned perpendicular to the length of the cantilever. LFM can be extremely useful for identifying surface composition differences and/or surface contamination where the materials have different friction characteristics and the topography is relatively invariant.

The representative AFM images which are presented in this paper illustrate the complexity and variability of the surface of gelatin capsules. Figure 5 shows height (constant force mode) and friction images of gelatin capsules 72601, 29625 and 29625ext. The friction image, which results upon subtraction of the re-trace scan image from the trace scan image, portrays the friction contrast more clearly by eliminating a large degree of friction artifacts arising from topographic effects. Both types of images are displayed in shades of gray. In the height images, the highest topographic features are the brightest. In the difference friction images (hereafter referred to as friction images) the areas where the greatest friction forces occur are the brightest.

Figure 5a shows that the surface topography of capsule 72601 consists of a complex network of fibrillar structures and many very small “craters” of approximately 200 nm in diameter. The friction image, shown in Figure 5b, reveals that the majority of the surface of capsule 72601 exhibits essentially uniform friction. The observed friction artifacts, which are identified by comparing areas of abrupt change in surface topography, are associated with the craters. These artifacts are the result of an increase (or decrease) in frictional drag on the cantilever tip upon ascending (or descending) a marked topographic slope. A more detailed investigation is in progress to elucidate the physicochemical nature of the features of the craters. The AFM images shown in Figures 5a and 5b are significant in that topographically smooth areas of the capsule exhibit undifferentiated friction.

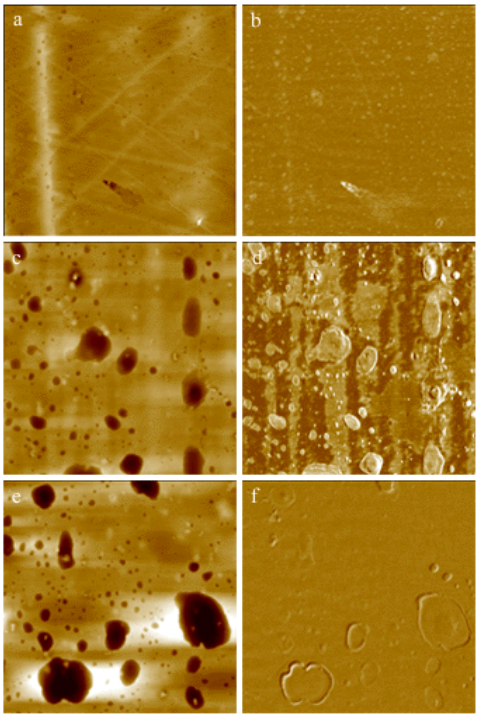

Figure 5. Height images of gelatin capsule (a) 72601, (c) 29625 and (e) 29625ext and friction images of gelatin capsule (b) 72601, (d) 29625 and (f) 29625ext. The scanning region is 25 x 25 μm, and the z contrast range is 400 nm. Higher pixel brightness corresponds to higher elevation or friction force.

Figure 5c shows that the topography of the surface of gelatin capsule 29625 is extremely heterogeneous with respect to the size and occurrence of the craters. The craters range in size from approximately 0.2 μm to 5 μm. However, craters up to about 10 μm in diameter have been observed in other height images of capsule 29625. Furthermore, the fibrillar structures observed in the height images of capsule 72601 are not present. The friction image shown in Figure 5d reveals extremely nonuniform friction. Three relatively distinct levels of friction force can be seen in this image. The majority of the capsule surface exhibits low friction, which is presumably due to the mold release agent used in the capsule manufacturing process. One distinct region of intermediate friction is observed, and high friction areas are also present, many of which appear as streaks on the surface.

The height image of capsule 29625ext is topographically similar to that of capsule 29625 (unextracted) as can be seen in Figure 5e. However, the friction image shown in Figure 5f appears distinctly uniform as compared with that of the unextracted capsule. There is no

discernible friction contrast on the surface of the extracted capsule. This clearly indicates that extraction of the gelatin capsule has resulted in a significant change in the physicochemical nature of the capsule surface.

Capsules 72601 and 29625, as mentioned earlier, were obtained from different commercial sources. It is common practice in the manufacturing process of hard gelatin capsules that a lubricant or release agent is applied to stainless steel pins to enable the gelatin shells, which form after dipping and withdrawal of the pin bar from gelatin solutions, to be stripped from the mold pins [Mittal and Anderson 1991]. ESCA analysis (data not shown) indicates that a small amount of mold release agent remains on the inner surface of the gelatin capsules after their manufacture. As can be seen in Figure 5d, it appears that the mold release agent employed does not wet the entire surface of capsule 29625. The spatial variation in friction force correlates with that of the adhesion force as shown in Figure 3b. In a separate preliminary study, an attempt was made to spread the mold release agent used for capsule 29625 on pure gelatin films. The mold release agent was observed to exhibit similar behavior, namely, it did not wet the gelatin surface and exhibited lower friction relative to the gelatin surface. On the other hand, the mold release agent utilized for capsule 72601 seems to wet the capsule surface, since essentially uniform friction force (Figure 5b) and relatively constant adhesion force between the lactose particle and capsule surface (Figure 3a) are observed. This suggests that the mold release agent used for capsule 72601 is not the same as that employed for capsule 29625. In addition, gelatin capsule 29625ext appears to exhibit uniform friction (Figure 5f) and relatively constant adhesion between the lactose particle and capsule surface (Figure 3c), thereby indicating that the extraction process has removed a significant amount of mold release agent.

The AFM results show that gelatin capsule 29625 which exhibits high-contrast friction tends to have high adhesion, whereas gelatin capsules 72601 and 29625ext which exhibit low-contrast friction have low adhesion. The surfaces of capsules 72601 and 29625ext also appear to be of relatively uniform friction which is in accordance with the observed relatively constant adhesion. On the other hand, the nonuniform friction associated with capsule 29625 correlates with the observed spatial variation in adhesion. The implication is that the physicochemical nature of the capsule surface, which is dependent on the gelatin and mold release agent used in the capsule manufacturing process, is a crucial factor in the adhesion of lactose particles to gelatin capsule surfaces. Further systematic investigations are underway in our laboratory to provide a more complete basic understanding of the adhesion of pharmaceutical particles in dry powder inhalation products.

4. CONCLUSIONS

The AFM results show that scanning probe techniques can provide unique information on the adhesion interactions and surface physicochemical nature of pharmaceutical materials. The direct measurement of adhesion by use of the colloidal probe technique has provided new insights into the mechanisms of particle-surface adhesion in dry powder inhalation products. The microscopic

measurements of the adhesion of individual lactose particles to the surface of gelatin capsules have not only shown the effect of surface chemistry on adhesion, but they also correlate well with the macroscopic performance of a large population of particles such as the retention of lactose particles in gelatin capsules. In addition, AFM shows that the physicochemical nature of the gelatin capsule surface, which depends on the gelatin and mold release agent utilized in the manufacture of commercial capsules, plays a critical role in the adhesion of pharmaceutical particles. By the appropriate choice of gelatin capsules, one can enhance and control the respirable fraction in dry powder inhalation products. Furthermore, one can conclude that the particle-surface adhesion in pharmaceutical systems can be advantageously modified by appropriate surface treatment of the gelatin capsules and/or lactose carrier particles.

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