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Quantification of Lubricant Activity of Magnesium Stearate by Atomic Force Microscopy

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Magnesium stearate (MgSt) is commonly used in pharmaceutical formulations as a lubricant to facilitate tablet release from the die after compression. In this study, we quantify the effect of MgSt on the interaction forces between microcrystalline cellulose (MCC) and steel surfaces. A quantitative approach to better understand the mechanism by which MgSt affects powder performance will assist in improved control and formulation design. We find that the forces between MgSt and steel surface are stronger than the interactions between MgSt itself, between MgSt and an MCC particle, and an MCC particle and a steel surface. These quantitative findings offer an explanation how MgSt facilitates lubrication during tablet ejection.

Keywords atomic force microscopy; magnesium stearate; microcrystalline cellulose; cohesion force

INTRODUCTION

Tablets are the most popular solid dosage form in the pharmaceutical industry due to their relative ease of manufacturing and self-administration by the patient. Typically in a tablet formulation, lubricants are used to reduce the friction between the tablet and the die wall during tablet ejection following compression and to prevent powders from sticking to the surfaces of the tablet punch. Magnesium stearate (MgSt) is a prevalent choice of lubricant. Its chemical and physical properties are well described as well as its effect on tablet hardness and drug dissolution kinetics (Barra and Somma, 1996; Ertel & Carstensen, 1988; Otsuka, Yamane, & Matsuda, 2004, Wada & Matsubara, 1994). However, little work has been done to elaborate the mechanism of MgSt as an antiadherent in the tablet compaction process, as in the work done by Lee on the adhesion force of lubricants to a steel sphere (Lee, 2004).

In recent years, atomic force microscopy (AFM) has been widely exploited as a powerful tool to measure the interaction forces between pharmaceutical materials, such as the cohesion forces between a single particle of crystalline lactose and a tablet of lactose (Sindel & Zimmermann, 2001), the adhesion forces between a lactose (carrier) particle and an active drug particle (Begat, Morton, Staniforth, & Price, 2004; Berard et al., 2002), and the surface energy of an excipient or drug particle against a substrate of polytetrafluoroethylene (PTFE) or graphite (Eve, Patel, Luk, Ebbens & Roberts, 2002; Hooton et al., 2003).

This study aims to investigate the effect of MgSt on particle interactions with other particles and surfaces at a microscale. Different combinations of interaction forces between microcrystalline cellulose (MCC), MgSt, and a steel surface are assessed by AFM.

EXPERIMENTAL PROCEDURE

Materials

MgSt (CAS no.: 557-04-0) was used as provided (Mays Chemical Company, Indianapolis, IN, USA). MCC (CAS no.: 9004-34-6) used in the experiments was Celphere® (Asahi Kasei Corporation, Tokyo, Japan). A polished stainless-steel plate was fixed on a sample plate for adhesion measurements.

Sample Preparation

MgSt compacts were made in a manual lab-scale tablet press to obtain MgSt agglomerates of similar size to the Celphere® MCC particles. For that, a manually pressed tablet size MgSt agglomerate was broken down into smaller pieces using tweezers. All materials were stored in a desiccator for at least 24 h at ~30% relative humidity before experiments.

Individual particles were attached to the tip of an AFM cantilever (Shape A, Silicon Nitride DNP-20, Veeco, Santa Barbara, CA, USA) with a 5-min epoxy resin adhesive (Devcon, Illinois Tool Works Inc, Glenview, IL, USA). The spring constant of each cantilever was determined using a Molecular Force Probe MFP-1D (Asylum Research Inc., Santa Barbara, CA, USA). A typical value was 0.450 ± 0.008 N/m.

Micrographs of particles were taken with an XL30 FEG environmental scanning electron microscope (ESEM) (FEI Company,

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Hillsboro, OR, USA). Before each measurement, the steel plate was rinsed thoroughly with ethanol to avoid contamination.

AFM Force Measurements

Forces between particles were measured with a MultiMode scanning probe microscope (MM-SPM; Digital Instruments, Santa Barbara, CA, USA) in force volume mode. In this mode, force measurements were performed at regular intervals across the surface of the sample. An array of 128 × 128 data points was collected during each measurement, corresponding to a scanning area of $5 \times 5\ \mu m^2$. For each pair of particles, three repeated measurements were conducted. The interparticle force reported here is the average of these 128 × 128 × 3 = 49, 152 data points. Reported standard deviations refer to the three repeated measurements, if not stated otherwise. The relative humidity during AFM measurements was kept at 30 ± 4%.

To measure forces between two single particles, one particle was attached to the tip (see Figure 1) and brought into contact with another particle fixed with a double-sided adhesive tape on a sample plate. When the tip was bent by attractive or repulsive forces acting on the tip, the deflection was detected by a laser aligned on the top of the tip. The deviation of the laser spot on a photodiode was recorded and the corresponding distance calculated. The deflection difference between the maximum separation point and the noncontact regime is proportional to the cohesion force. The actual force values were calculated from the raw AFM data by a MATLAB®code written in our lab.

To compare the cohesion energy between different material particle interactions, the force values were normalized by the reduced radius R_r to eliminate the bias of differing particle sizes. R_r was calculated by

$$R_r = \frac{R_1 R_2}{R_1 + R_2},$$

where R_1 and R_2 are the particle radii of the two particles in contact, respectively.

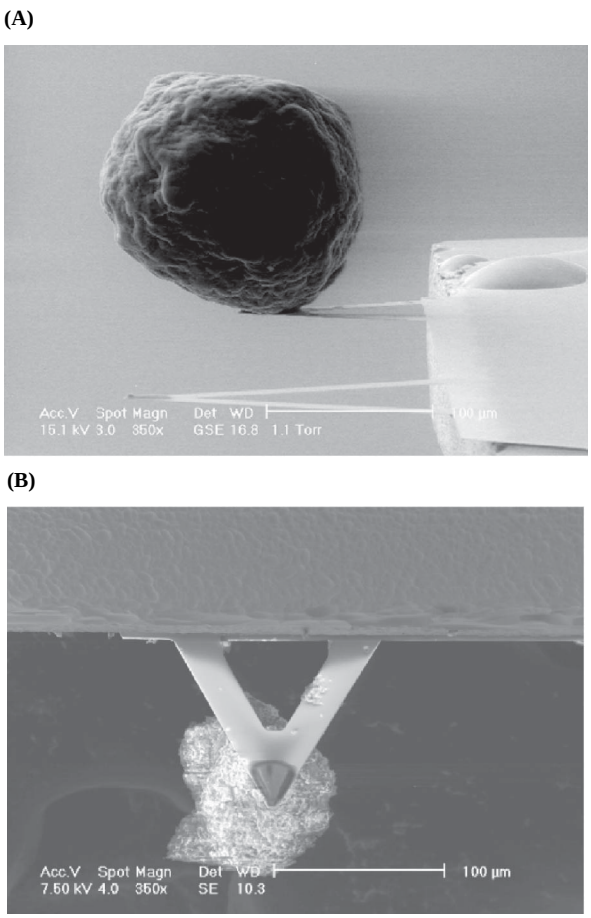

FIGURE 1. Environmental scanning electron microscope (ESEM) pictures of (A) a microcrystalline cellulose (MCC) particle on a cantilever (side view) and (B) a magnesium stearate compact on a cantilever (top view).

RESULTS AND DISCUSSION

The different material combinations and their sample sizes in AFM measurement are given in Table 1. They represent the different possibilities of particle interactions with other than the active pharmaceutical ingredient.

As illustrated in Figures 2 and 3, the interaction force of MgSt with itself is weak (0.25 nN/µm). There is no difference between MgSt–MgSt and MgSt–MCC particle interactions and only a slight difference between these two and MCC–steel. In contrast, adhesion of MgSt to the steel surface is notably higher (0.70 nN/µm). Table 2 summarizes the key parameters of each force distribution.

In unlubricated tablets, the excipient would solely be in contact with itself or with the steel surface. When the tablet is ejected, the excipient will have to slide over the steel surface and may stick to it, causing defects in the tablet. However, in lubricated tablets, the presence of MgSt flakes dispersed on MCC particle surfaces prevents the excipient from direct contact with the steel surface. Due to its higher interaction force with steel,

TABLE 1
Sample Size of AFM Force Measurements for Different Combinations of Interaction Among MCC, MgSt, and Steel

	Cantilever	
Substrate	MCC	MgSt
MCC	15	10
MgSt	–	10
Steel	10	10

AFM, atomic force microscopy; MCC, microcrystalline cellulose; MgSt, magnesium stearate.

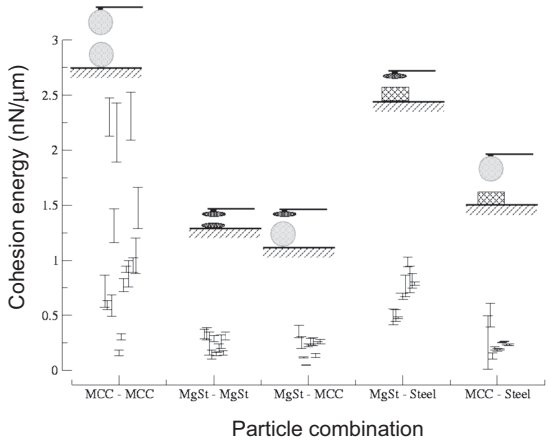

FIGURE 2. Illustration of cohesion energy distribution of different types of particle interactions.

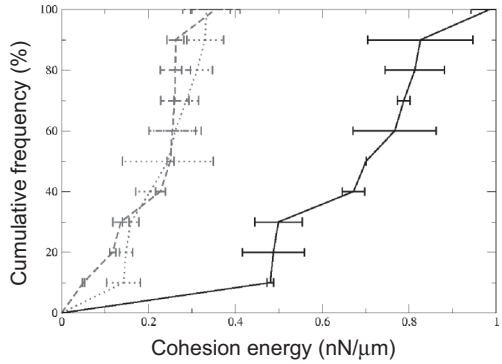

FIGURE 3. Cumulative frequency distribution of cohesion energy for magnesium stearate (MgSt) particle interactions (solid line, MgSt–steel; dashed line, MgSt–MCC (microcrystalline cellulose); dotted line, MgSt–MgSt).

when the tablet is ejected, MgSt will reduce the friction between the tablet and the die wall, resulting in lower ejection energies.

CONCLUSIONS

AFM has been applied in our study to investigate the impact of MgSt on particle interactions. It was found that MgSt has a higher affinity to a steel surface than MCC. Also, its affinity to steel is higher than its affinity to MCC. This lubrication function prevents the excipient (e.g., MCC) from sticking to the steel surface and consequently reduces ejection energies. Quantifying cohesion energies between particles of a pharmaceutical formulation using AFM offers a rational approach to formulation design and thus contributes to replacing the trial and error approach commonly used in the pharmaceutical industry.

TABLE 2
Cohesion Energy Values for Different Combinations of Interaction Among MCC, MgSt, and Steel

Material	Median Cohesion Energy (nN/μm)	Average Cohesion Energy (nN/μm)	Standard Deviation (nN/μm)
MCC–MCC	0.91	1.09	0.68
MCC–steel	0.23	0.24	0.09
MgSt–MgSt	0.25	0.24	0.07
MgSt–steel	0.73	0.70	0.16
MgSt–MCC	0.25	0.22	0.09

MCC, microcrystalline cellulose; MgSt, magnesium stearate.

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