Effect of Air Jet Micronization on Particle Properties and the Correlation of Interparticle Interactions by Atomic Force Microscopy with Surface Forces by Inverse Gas Chromatography

Vibha Puri, Jagdeep Shur, Robert Price, Andreas Stumpf, & Ajit Narang

Summary

Micronization of pharmaceutical powders can induce structural and surface disorder on the surface of constituent particles, which can impact their aerodynamic performance in dry powder inhaler (DPI) formulations. Furthermore, these materials undergo surface re-construction on storage, which can then impact their physicochemical properties over time. Identifying and mapping the interparticle interactions that can be directly linked to aerodynamic performance is challenging. In this work, we studied the correlation of interparticle interactions measured by atomic force microscopy (AFM) with particle surface forces by inverse gas chromatography (IGC) for a model active pharmaceutical ingredient (API), Compound A.

Micronized API produced by air jet milling was stored under different stress conditions. The drug-drug cohesive interactions and drug-lactose adhesive interactions were measured by AFM. The cohesive-adhesive balance (CAB) ratio was calculated. The freshly micronized API showed an AFM CAB ratio of 0.69 that suggested greater API-lactose adhesive interactions, while its IGC CAB ratio of 1.16 suggested higher API-API cohesive interactions. Nonetheless, both techniques reported reducing CAB ratio upon storage of the micronized API at accelerated conditions of temperature and humidity, suggesting increase in API-lactose adhesive interactions and lowering of API cohesive interactions. The magnitude of change in AFM CAB ratios was greater than the IGC CAB ratios, indicating greater sensitivity of AFM technique. In summary, while the initial CAB may depend on the technique used for measurement, changes in the CAB on storage were consistent across the two analytical tools investigated.

Introduction

The performance of pharmaceutical powders in drug products, such as dry powder inhalations (DPIs) and powder mixtures for granulation, is predominantly governed by the interparticle interactions in the multi-component powder blend. The surface properties of pharmaceutical powders are largely controlled by the processing history of the active pharmaceutical ingredient (API). Air jet micronization processes are commonly used for particle size reduction of synthetic, crystalline APIs. However, this high energy process can induce structural and surface disorder in the micronized API. Furthermore, this mechanically activated API on storage can undergo relaxation or surface stabilization that can alter the material’s surface properties. Hence, there is a requirement for tools that expedite rigorous characterisation of the surface of micronized pharmaceutical solids.

Surface-based techniques such as atomic force microscopy (AFM) and inverse gas chromatography (IGC) have been employed to map interparticle interactions. These techniques are further used as predictive tools to understand product design and performance. The sample preparation and the measurement principles differ significantly for these two techniques. For example, the cohesive-adhesive balance (CAB) approach to colloid-probe AFM, employs use of crystallized substrate on which micronized particles are interacted by over a known area of the dominant crystal face of the API and excipient such as lactose. The force of cohesion and adhesion are then determined from the array of force-distance curves. In contrast, the IGC technique measures surface free energy in bulk powder sample by surface adsorption of gases. Both techniques enable the investigation of the work of cohesion and adhesion of processed pharmaceutical solids.

In this study, we characterized the cohesive and adhesive interactions of micronized Compound A using AFM-CAB and IGC and investigated effect of storage of micronized API at high temperature and humidity conditions on the changes to the CAB.

Materials

Compound A was micronized by air jet micronization (Food Pharma Systems PM2 mill, Italy) with milling conditions of grind pressure of 7 bar and injection pressure of 8 bar. The micronized API was stored at 25°C/60% RH and 40°C/75% RH open conditions for 8 weeks. Lactose monohydrate (Respitose SV003) was obtained from DFE Pharma (NJ, USA).
Methods

Cohesive-adhesive balance (CAB) by colloid probe atomic force microscopy (AFM)

Smooth lactose monohydrate crystalline substrates were prepared by a method described by Begat et al. Unmicronised crystals of compound A had the required rugosity on which the force of cohesion was determined. Five micronised drug particles at the initial time-point and upon storage under different environmental conditions were attached to AFM cantilevers using a custom-built micro-manipulation technique. AFM cantilevers with drug particles attached to them are referred to as drug probes. Cohesion and adhesion force measurements between the drug probes and primary crystals (drug or lactose monohydrate) were conducted using force volume mode (n=5 probes), which records a total of 1098 force-distance curves within a specified area at 25°C and 44 % RH. The force of cohesion and adhesion for each drug probe for each API sample was plotted against each other to produce a CAB plot. The regression analysis was conducted on Minitab, which provided an output of the standard error of the regression and error of the estimate. The AFM-CAB measurements were then performed as described by Begat et al and Kubavat et al.

Cohesive-adhesive balance (CAB) by inverse gas chromatography (IGC)

IGC experiments were conducted on surface energy analyzer (SMS Instruments, Allentown, USA) with flame ionization detector. Powder samples were packed into silanized glass columns (2 mm diameter) in weight range of 50-200 mg, tapped for 4 min, and visually inspected for absence of void spaces. Columns were conditioned for 2 h at 25°C and 0% RH conditions, followed by pulse injection measurements. Methane was used to determine the column dead time. The probe solvents used were nonane, octane, heptane, hexane, ethyl acetate and dichloromethane (purity>99%, HPLC grade). Probe solvent was injected to achieve target surface coverage (n/n_m) in the range of 0.5 to 10% at 25°C and 0% RH conditions with helium carrier gas at flow rate of 10 ml/min. Surface coverage is defined as n/n_m, where n is number of probe moles adsorbed and n_m is the number of moles required for a theoretical monolayer surface coverage. Samples were analyzed in triplicate.

The dispersive work of cohesion and work of adhesion plots were determined using the dispersive surface energy of the API and lactose (mean of n=3). The IGC-based CAB ratios were calculated as the ratio of the average dispersive work of cohesion and adhesion values at infinite surface coverage of 0.04 n/n_m and as slope of the plot of work of cohesion and adhesion for surface coverage range from 0.02 to 0.1 n/n_m.

IGC data analysis

The surface energy components were determined from the retention time of dispersive and polar probes which interact with the solid surface sample. At each surface coverage, the net retention volume (V_n) was calculated for each probe.

When a series of liquid n-alkane are used as probes, the adsorption dispersive free energy of the methylene group \( \Delta G^{CH_2} \) can be calculated from the slope of the plot of adsorption free energy of the probes versus the carbon number n using the Dorris-Gray method:

\[
\Delta G^{CH_2} = -RT \ln \left( \frac{V_{N,n+1}}{V_{N,n}} \right)
\]

where R is the universal gas constant (J/mol K), T is the temperature (K), \( V_{N,n} \) is the net retention volume of the n-alkane probe with the carbon number n.

The dispersive surface energy of solid sample \( \gamma_s^d \) can be obtained by:

\[
\gamma_s^d = \frac{1}{4\gamma CH_2} \left( \frac{\Delta G^{CH_2}}{N_{CH_2}} \right)^2
\]

Surface energy is directly related to the thermodynamic work of adhesion between two materials. According Fowkes the total Work of cohesion/adhesion can be described as the sum of the dispersive contribution and the specific (or acid-base) contribution to the work. The dispersive work of cohesion (\( W_{coh}^d \)) and adhesion (\( W_{adh}^d \)) can be calculated with the following equations:

\[
W_{coh}^d = 2 (\gamma_s^d)
\]

\[
W_{adh}^d = 2 (\gamma_s^d - \gamma_f^d)^{1/2}
\]
Results and Discussion

The AFM based CAB plots (Fig 1) were obtained using the force of cohesion and adhesion for the micronized API with lactose, for samples stored under different conditions. The AFM CAB ratios are provided in Table 1. The AFM CAB ratio of micronized API batch was 0.69, which suggested that the adhesive interactions of the API to lactose were 1.45 times greater than the cohesive interactions of the API particles. After 8-weeks of storage at 25°C/60% RH and 40°C/75% RH conditions the AFM CAB ratio reduced to 0.35 and 0.30, respectively. This suggested about 2-fold increase in the API affinity to the lactose compared to the API cohesive interactions.

![Figure 1. AFM based force of cohesion and force of adhesion plots of freshly micronized API and after storage at different conditions. The force of adhesion is determined between API and lactose](image)

Table 1. Comparison of CAB ratios of different samples derived from AFM and IGC techniques.

<table>
<thead>
<tr>
<th>Micronized API</th>
<th>AFM based CAB ratio</th>
<th>IGC based CAB ratio at surface coverage 0.04 n/n,</th>
<th>IGC based CAB ratio for surface coverage range of 0.02-0.1 n/n,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freshly micronized</td>
<td>0.69</td>
<td>1.15</td>
<td>1.16</td>
</tr>
<tr>
<td>Stored at 25°C/60%RH_8Week</td>
<td>0.35</td>
<td>1.08</td>
<td>1.08</td>
</tr>
<tr>
<td>Stored at 40°C/75%RH_8Week</td>
<td>0.30</td>
<td>1.05</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Fig 2. shows the dispersive surface free energy plots for the freshly micronized API, and micronized API after storage under different environmental conditions. As the plots show, the SFE reduced significantly when stored at 40°C/75% RH condition and to a smaller extent for samples stored at 20°C/65% RH condition. The polar SFE showed less significant changes (data not shown). Thus, changes in the surface interactions of the API could primarily be related to reduction in the dispersive surface energy.

IGC-based CAB ratios indicated that the micronized API cohesive interactions lowered on exposure to the stress conditions (Table 1 and Fig 3). During storage under high humidity conditions, water can develop strong interactions (e.g., hydrogen bonding) with the high energy sites (surface disorder/surface amorphous regions) of the micronized API and cause plasticization of these regions. This phenomenon of surface relaxation can then lower the surface energy of the particles. In case of micronized Compound A, both, the dispersive and specific (polar) surface energy lowered, with overall increase in the contribution of specific surface energy to the total surface free energy.

The AFM and IGC based CAB ratios for the freshly micronized API were significantly different. The AFM CAB ratio of 0.69 suggested greater drug-lactose adhesive interactions, while the IGC CAB ratio of 1.16 suggested higher drug-drug cohesive interactions.

As described by Bunker et al., the AFM technique measures direct forces that are sum of the Van der Waals forces, electrostatic forces, and capillary forces under the testing conditions. However, surface energy measurements by IGC are a measure of the Van der Waal forces only. AFM was performed at 44% RH conditions, which could promote adhesive interactions between API and lactose, through the capillary forces. Additionally, the freshly micronized Compound A is likely to have electrostatic forces contributing to the surface interactions. In contrast, the IGC analysis was conducted in 0% RH environment, where there would be absence of surface water, and the surface energy of API and lactose could be different when exposed to 44% RH.
Nonetheless, for the stressed API samples both techniques showed similar trend of reducing CAB ratio suggesting that the treated API particles had greater affinity for API-lactose interactions, than the cohesive interactions. Although for the stressed samples, the extent of change in the AFM derived CAB ratios was higher than for the IGC derived CAB ratios. Interestingly, the IGC CAB ratios trends measured using the infinite regimen and a wider finite dilution regimen differed, with the later showing more differences between the samples.

The compound A was found to be non hygroscopic in nature, with moisture uptake about 0.3% wt at 25°C-90% RH. Therefore, the change in the force balance was less likely due to capillary forces but more likely due to physical annealing of the material. From the formulation performance, the data suggests that the micronized Compound A is likely to exhibit less self-agglomeration and might achieve homogenous blend. Over time the adhesive interactions were observed to increase, which could lead to changes in performance, for example reduce powder dispersibility or aerosolization performance of DPIs.
Conclusions

Ait jet micronization of the Compound A significantly changed its surface properties. Further, on storage, the micronized API underwent surface relaxation that changed its surface interactions. This study highlights that apart from the need to fully understand the effect of micronization process variables, the storage history of the micronized API can also impact the overall product performance. These factors can be critical to the drug product performance, for example, by impacting the API distribution homogeneity at low drug loading and the aerodynamic performance of dry powder inhalation formulations.

For the drug-lactose system studied, the interparticle interactions determined from AFM and IGC matched only in qualitative trends. The AFM and IGC CAB ratios were significantly different for the freshly micronized API, however both techniques showed similar trend of increased API-lactose adhesivity under stress conditions. As discussed the two techniques differ in the sample preparation, experimental conditions, and the kind of measurement made and this could contribute to the different interpretations the two techniques provided.

References

2. Rasenack N. Particle Engineering for Pulmonary Dosage Forms, American Pharmaceutical Review 2010; April 01, 2010.