Investigation of Surface Characteristics of Micronized Salbutamol Sulphate Particles Formulated in Different Propellants Using Integrated Scanning Electron Microscopy & Atomic Force Microscopy

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Key Message

The integration of AFM (Atomic Force Microscopy) and SEM (Scanning Electron Microscopy) via the LiteScope module provides comprehensive insights into particle topography, although further optimization is needed to address technical challenges in energy dissipation measurements.

Introduction

Micronized materials, often used in pharmaceuticals and material science, possess significant surface amorphous content and dislocations, resulting in high surface free energy [1]. When these materials are exposed to different propellants, the surface may undergo annealing, impacting both surface free energy and surface morphology. This study leverages the combination of Atomic Force Microscopy (AFM) and Scanning Electron Microscopy (SEM) to provide a comprehensive analysis of these changes. The LiteScope AFM module for SEM, through Correlative Probe and Electron Microscopy (CPEM), allows simultaneous acquisition of AFM and SEM data [2] [3]. This integration enables a multidimensional analysis of various samples, including salbutamol sulphate (SS) samples: SS HFA-152a, SS HFO-1234ze, SS HFA 134a, and SS raw active ingredient/powder. This study aims to investigate the surface characteristics and behaviour of micronized SS upon exposure to different propellant systems including HFA-134a, HFA-152a and HFO-1234ze.

Materials and Methods

MATERIALS

SAMPLE PREPARATION

- Manufactured pMDIs were primed before the collection of the particles for SEM/AFM testing.
- Samples were prepared on a purified SiO2 wafer glued to the SEM stub (wafer surface was cleaned with iso-propyl alcohol and compressed nitrogen to eliminate contamination).
- For pMDI analysis, the content from canister was sprayed from ≈ 3 cm (after shaking).
- For SS raw sample analysis, the pure powder was applied directly onto the wafer.
- Prepared samples were purged with nitrogen to prevent particles from moving in SEM when pumping or touching with the tip.

SEM/AFM TESTING

- The LiteScope module is designed for integration into SEM instruments
- This study employed the LiteScope for in-situ 3D correlative imaging, focusing on surface structure, roughness, and energy loss during interactions between the probe and the sample surface. Measurements included secondary electron (SE) imaging, topography, energy dissipation, phase imaging, and roughness calculations (Ra and Rq).

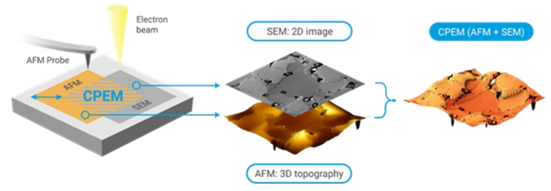

Figure 1. Representation of the CPEM method.

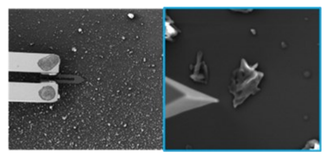

Figure 2. SEM overview and navigation to the particle using AFM probe in situ.

Results and Discussion

For the SS raw active ingredient/powder, AFM images displayed surface morphology consistent with the habit of salbutamol sulphate. The micronized material appeared to be impacted by the testing environmental conditions, suggesting dynamic changes in the surface behaviour of the material. This has been reported by Begat et al. [1]. The Root Mean Square (RMS) roughness of the micronized material was 5.7 nm, while Ra was around 4.2 nm.

For the SS HFA-152a sample, detailed AFM images revealed surface structures with roughness values of Ra 3.2 nm and RMS around 4.3 nm. Energy dissipation measurements indicated significant interactions at specific regions, highlighting areas of energy loss. These data suggest that the surface of the micronized SS particles had annealed resulting in the surface of the material to smoothen when exposed to HFA152a. These findings support the use of surface characterization in understanding the material's interaction dynamics (Figure 3). In contrast, SS HFO-1234ze, AFM images showcased surface details, with roughness values of RMS 6.3 nm, Ra 4.4 nm. These data suggested no change to the surface topography of micronized SS when formulated with HFO-1234ze.

The SS HFA 134a sample exhibited a higher concentration of smaller particles, as visible in the large SEM overview. The roughness values varied, with Ra 4.1 nm and RMS approximately 5.6 nm. Energy dissipation for this sample displayed evident edge effects with distinct energy loss patterns around the particles. Another method to analyse mechanical properties is phase imaging (Figure 4), where lower phase in the image conveys higher adhesion or lower local stiffness (inverse to Energy dissipation). Based on additional micromechanical tests using F-z spectroscopy, the particle shows lower adhesion compared to the propellant on the wafer (typically leading to an increase in phase), but also significantly lower stiffness than the wafer, resulting in an overall phase decrease. Such a variability in roughness and mechanical properties highlights the complex nature of particle surfaces and their interactions.

The integration of AFM and SEM via the LiteScope module provides comprehensive insights into the topography of particles. Energy dissipation measurements, though affected by edge effects, offer valuable data on the interaction dynamics at the nanoscale. The study highlights the necessity for precise tuning of energy dissipation measurements to mitigate edge effects and improve accuracy. These findings underscore the potential of CPEM for detailed correlative analysis.

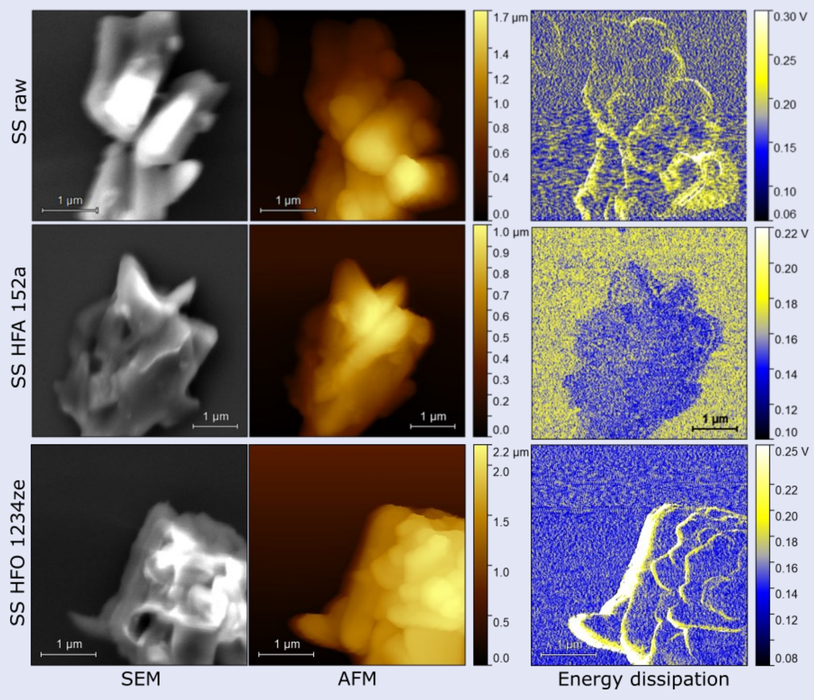

Figure 3. SEM (left), AFM (centre), and Energy dissipation signals (right) of SS samples without (raw material), and with different propellant types reveal strong differences. Upper row shows raw SS particles, middle SS particles with HFA 152a propellant, bottom row corresponds to SS particles with HFO 1234ze propellant. Lighter areas in energy dissipation correspond to higher energy losses. Large energy losses at the edges may have made small differences between particles and substrate indistinguishable.

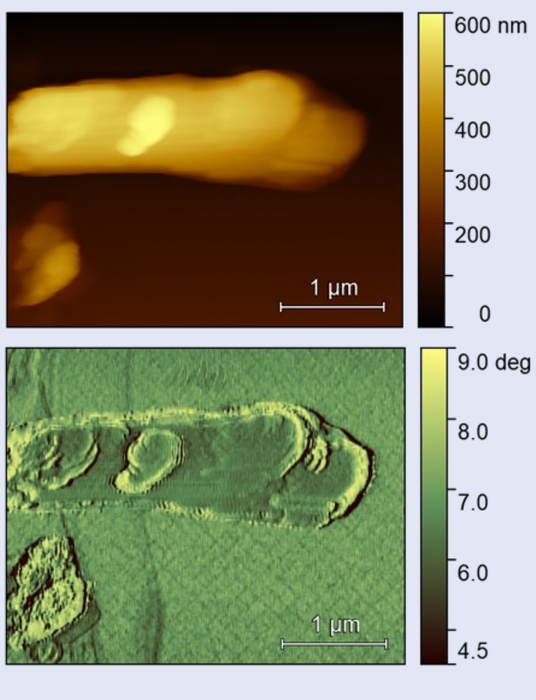

Figure 4. SS particle with HFA 134a propellant (top) AFM topography and (bottom) phase imaging, where lower phase corresponds to higher adhesion or lower local stiffness.

Conclusions

This research successfully demonstrated the capabilities of CPEM using the LiteScope AFM module for SEM in analysing particle topography, energy dissipation, and calculating surface roughness. While the findings provide significant insights, further optimization of the measurement techniques is required to address technical challenges and enhance the reliability of the results. The successful integration of AFM and SEM allows for a more detailed and multidimensional analysis, which may be useful in detecting microstructural differences in drug particles from different propellant systems.

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