Purpose

Hygroscopicity of an API, leading to changes in surface and bulk properties can affect subsequent drug product manufacturability and final drug product performance. This work describes the use of environmental atomic force microscopy (AFM) and environmental scanning electron microscopy (ESEM) coupled with solid state characterization techniques to investigate how BMS-663068 free acid (API) responded to changes in relative humidity.

Methods

Solid state characterization was carried out using dynamic vapour sorption (DVS), solid-state nuclear magnetic resonance (ssNMR) and powder X-Ray Diffraction (PXRD). ESEM images were collected using a Phillips XL-30 ESEM-FEG. The relative humidity (RH) of the ESEM chamber was modified by changing the temperature of the specimen stage and vacuum pressure of the chamber. AFM images were collected using an Enviroscope Atomic Force Microscope with a controlled humidity chamber.

Results

DVS revealed a reversible moisture sorption event in the 42 - 46% RH range. This effect was reproducible on repeated cycles suggesting that the structural integrity of the material was not compromised due to the inter-conversion process. PXRD differentiated two distinct forms. ssNMR observed small, reversible and predictable changes in the atomic structure which were consistent with an interaction with water between form II (anhydrous) and III (hydrate) coupled with some intra/inter bond changes. AFM and ESEM could discern changes in the surface topography of the API as a function of RH. Surface cracks were visible at 25% RH (Figure 1, left), most of which disappeared at 60% RH (Figure 1, right). This change was reversible on reducing RH, with cracks reappearing in the same locations (Figure 2, right). The phenomenological, material observations by AFM/ESEM were consistent with the atomic alterations seen with ssNMR.

Conclusion

The combined use of microscopy and bulk scale methods enabled the relationships between the environmental, material and crystalline properties to be better understood. Changes in unit cell dimensions are not uncommon with channel hydrates; however concomitant, reversible surface morphology property changes have not been widely reported.