Imaging Dehydration Kinetics of a Channel Hydrate Form of the HIV-1 Attachment Inhibitor Prodrug BMS-663068

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ABSTRACT: An analysis of the free acid form of the HIV-1 attachment inhibitor prodrug BMS-663068-01 revealed a reversible moisture sorption event in the 42%–46% relative humidity (RH) range. An existing single-crystal analysis indicated that these observations were due to the formation of a nonstoichiometric channel hydrate. This effect was reproducible on repeated cycles, suggesting that the material's structural integrity was not compromised because of the interconversion process. Small, reversible, and predictable changes in the atomic structure were observed by solid-state nuclear magnetic resonance (ssNMR). Atomic force microscopy (AFM) and environmental scanning electron microscopy (ESEM) could discern changes in surface topography as a function of RH. Surface cracks were visible at 25% RH, most of which disappeared at 60% RH. This change was reversible on reducing the RH, with cracks reappearing in the same locations. A reduction in surface roughness was seen at high humidity, which was consistent with the uptake of moisture causing surface swelling. The observations by AFM/ESEM were consistent with the atomic alterations seen with ssNMR. Changes in unit cell dimensions are not uncommon with channel hydrates as the crystal lattice expands or contracts when the crystal structure absorbs/desorbs water, but concomitant, reversible surface morphology property changes have not been widely reported. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:4375–4383, 2013

Keywords: hydrates; surface roughness; atomic force microscopy; dynamic vapor sorption; solid-state NMR; ESEM

INTRODUCTION

This paper describes the characterization of different hydrated states of the HIV-1 attachment inhibitor prodrug BMS-663068, a novel compound intended for the treatment of HIV. BMS-663068 is a phosphonooxymethyl ester prodrug of the active moiety BMS-626529, which works by blocking the attachment of HIV-1 to the CD-4 receptor on CD4+ T cells.[1] The free acid of BMS-663068 (BMS-663068-01) was explored during the development of the drug. Characterization of this form found that it readily absorbed water at elevated humidities converting from the anhydrous form II to the hydrate form III.

Hygroscopicity, the uptake of water leading to changes in surface and bulk properties, can occur by different mechanisms.[2] The first mechanism is simple surface adsorption with no penetration into the bulk, which can affect surface properties such as flow and agglomeration. Another mechanism is where there is liquefaction on the surface, either by deliquescence or capillary condensation. This can lead to dissolution of water-soluble components and penetration of water into the bulk of the solid, which in turn may cause solid–solid transformation where water molecules are incorporated into the crystal lattice while remaining in the solid state.[3] Such incorporation of water into the lattice leads to the formation of hydrates that can change the shape, capacity, symmetry, and dimensions of the unit cell, with density, refractive index, and melting point also being affected.[4] Hydration can be highly variable as the properties of the drug substance such as molecular structure, hydrogen bonding patterns, and crystal packing all influence the water interaction.[5] In addition, small amounts of amorphous phase can markedly increased the water uptake. Complex phase transitions dependent on temperature and humidity are common.[6] These properties mean that processing steps during secondary manufacture such as drying, micronization, granulation, compression, and coating have to be carefully controlled to ensure that unwanted forms are not generated.[7] Some secondary processing steps such as wet granulation are the ideal setting for the creation of hydrates as they introduce excess water to the system, often followed by mixing, which leads to intimate association between the Active Pharmaceutical Ingredient (API) and water.[3]

Different hydrate forms can have an effect on the manufacturability and quality of the final drug product.[8] In general, anhydrous forms are more soluble and have a faster dissolution rate than the corresponding hydrate that crystallized from water at the same temperature.[4] This is because the latter has already associated intimately with water and the free energy released on further interaction with water is reduced. Different forms can have different crystal habits with the example of niclosamide, where the anhydrate had a different morphology (plates) compared with the hydrate (acicular).[9] Hydration can affect compaction properties with one study showing that crushing strength of tablets increased with increased dehydration, most likely because of the changes in the

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texture of the particles.[4] In addition, excipients can have an effect on the kinetics of API hydration, which is unpredictable and is probably dependent on both the API and excipient properties.[10]

Hydrates can be broadly divided into two groups.[11,12] Stoichiometric hydrates have a crystalline packing structure, which differs from that of the anhydrate accompanied by well-defined water content. Nonstoichiometric hydrates differ from the former as the amount of water can be variable over a certain range without the crystal structure showing significant changes. However, the picture can be more complex. For example, an SGLT1 inhibitor has been reported to display a combination of stoichiometric and nonstoichiometric hydrates.[13] An alternative classification system for different types of hydrates has been described based on the general structural differences of the water networks.[14]

In the case of BMS-663068-01 free acid, single-crystal data with associated X-ray diffraction (XRD) indicated that there were changes in unit cell dimensions on conversion from the anhydrous form II to the hydrate form III, with the water being located in distinct channels within the crystal lattice.[15] Such channel hydrates have been defined as those exhibiting reversible changes with changes in temperature and humidity while keeping their crystalline structure.[16] The change in unit cell dimensions between forms II and III indicates that this is a particular subtype of a channel hydrate known as an expanded channel hydrate. These occur when, on exposure to high humidity, the crystal hydrate lattice is forced to expand as additional water molecules are incorporated, with the opposite occurring at low humidity. Another example of an expanded channel hydrate is disodium chromoglycate wherein channels in the lattice expand by as much as 0.8 A° causing changes to the powder X-ray diffraction (PXRD) pattern, density, and other physical properties. In this case, the water absorption was also reversible with no collapse of the lattice seen.[17]

This study aimed to determine whether conversion between the different channel hydrates led to changes in the surface morphology of the crystals. This is an area that has not been widely described but has shown the potential to have a disproportionate effect on material-handling properties in drug-product processing and performance parameters such as compaction,[18] flow,[19] granulation behavior,[20] segregation,[21] and powder dispersion.[22] Solid-state nuclear magnetic resonance (ssNMR) characterization was carried out to give qualitative and quantitative information on solid-state interactions.[23–30] In particular, this would encompass whether the uptake of water was reversible and whether repeated cycling from low to high humidity affected the conformation and the crystal lattice.

Microscopy techniques were chosen to carry out particle property evaluation with atomic force microscopy (AFM) and environmental scanning electron microscopy (ESEM) selected based on their ability to monitor the physical appearance of the surface over an entire humidity cycle at a much greater sensitivity than bulk-scale quantitative methods. In particular, AFM has been well utilized to study surface mobility because of adsorbed water on crystalline solids,[31] the effect of humidity on particle–particle interactions in inhalation formulations,[32] morphology and adhesion changes dependent on specific crystalline face due to humidity[33], and many other humidity-induced phase changes.[34]

EXPERIMENTAL

Materials

The crystalline free acid form of the drug substance, BMS-663068-01, was synthesized at Bristol–Myers Squibb (New Brunswick, New Jersey).

Dynamic Vapor Sorption (DVS)

The samples were analyzed using DVS-1, a DVS system (Surface Measurement Systems, Alperton, UK). The sample was equilibrated at 0% relative humidity (RH) 25°C prior to the analysis. The sample was then taken through an isothermal step method from 25% to 60% RH (and back) using 1% RH steps with mass stability at each step indicated by a dm/dt of less than 0.002% over a period of 5 min, following which the sample was stepped from 0% to 60% RH three consecutive times to assess the rate of sorption/desorption (and if a change over the repeated cycles was observed). The method was also run at an elevated temperature of 35°C to assess the impact of temperature.

Solid-State Nuclear Magnetic Resonance

Carbon cross-polarization magic angle spinning (CPMAS) ssNMR experiments were conducted on a Bruker AV III instrument (Bruker BioSpin, Billerica, Massachusetts) operating at a proton frequency of 500.01 MHz. Solid samples were spun at 13 KHz in a 4-mm ZrO_2 rotor. The contact time was 3 ms, and was ramped on the proton channel from 50% to 100%.[35,36] The relaxation delay was maintained at 20 s. Proton decoupling was applied using a two-pulse phase modulation (TPPM) sequence with a 4-μs pulse (62.5 KHz nominal band width). The spectral sweep width was 300 ppm centered at 100 ppm. 4096 data points were acquired and zero-filled to 8192 prior to apodization with 20 Hz line broadening. Typically, 2096 free induction decays were coadded. The spectra were referenced indirectly to TMS using 3-methylglutaric acid.[37] Approximately 70 mg of sample was used for each experiment. Temperature control of the sample during data acquisition was achieved passing cooled nitrogen gas over the rotor supplied by a BCU05 (Bruker BioSpin). The temperature stability was approximately 1°C.

Samples for ssNMR were prepared under constant RH conditions by equilibrating the material and rotor at the specific RH (25% or 90%) for at least 24 h. The sample was then packed into the rotor and sealed with a Kel-F cap. Data acquisition was promptly initiated. Studies have demonstrated that the RH inside the NMR rotor does not change significantly during data acquisition.

Powder X-ray Diffraction

The API for this study was prepared by recrystallization from an aqueous acetone solution with temperature cycling between 50°C and RT to afford plate-like single crystals suitable for crystallographic studies. The API was filtered and then dried in a vacuum oven at 50°C to prepare the anhydrous form (II), whereas the hydrate form (III) was prepared by placing the anhydrous crystals in a humidity chamber under 65% RH and room temperature for 1 week. PXRD data were collected on both bulk materials with capillary specimens using a Bruker-Axs D8 Discover-GADDS X-ray diffractometer (Bruker AXS Inc., Madison, Wisconsin).

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