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Improving the solubility of dexlansoprazole by cocrystallization with isonicotinamide

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ABSTRACT

Cocrystallization of an active pharmaceutical ingredient (API) with a cocrystal former (co-former) is widely used to tailor the physicochemical properties of parent APIs. For proton-pump inhibitors (PPIs), the isolation of cocrystals has not been widely investigated. Here, a 1:1 cocrystal of a PPI molecule, dexlansoprazole (DLS), was obtained by solvent crystallization with isonicotinamide (INM). The product was characterized by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), solid-state and liquid NMR, as well as Fourier transform infrared spectroscopy (FTIR) techniques. A two-point $R_2^2(9)$ hetero-synthon was proposed to exist in the cocrystal, where intermolecular hydrogen bonding occurs between NH, SO groups of DLS and amide of INM. The dissolution profiles of DLS and DLS–INM in water were also collected, and the results demonstrate the cocrystal exhibits superior apparent maximum solubility relative to the pure drug.

1. Introduction

Dexlansoprazole (DLS, Scheme 1a) is a proton pump inhibitor (PPI) used to heal and maintain healing of erosive esophagitis and to treat heartburn associated with gastro-esophageal reflux disease. DLS is the *R*-enantiomer of the racemic lansoprazole (LAN), which has same mechanism of action and similar medical use. Compared to the racemic mixture, DLS lasts longer and therefore, requires less dosing frequency to control gastric acid (Behm and Peura, 2011). Although DLS was approved by the U.S. Food and Drug Administration (FDA) in 2009 and is being used as a first line option in gastric acid inhibition (Behm and Peura, 2011), its solubility is not satisfying enough (Shi and Zhang, 2013a; Shi and Zhang, 2015). It is well known that physicochemical properties of a solid active pharmaceutical ingredient (API), including solubility, can be modified by changing the solid form (Elder et al., 2015; Sarma et al., 2011; Tilborg et al., 2014). The solid form changes include, but are not limited to, polymorphs, amorphous form, hydrates, solvates, salts, and cocrystals. To overcome solubility limitations, some effort in altering solid form in the DLS system has been attempted. For example, patent EP2487173A1 demonstrated a novel low temperature process for the preparation of amorphous DLS with high purity. The amorphous form is believed to be more soluble in water than the crystalline form, and consequently results in greater bioavailability (Vladiskovic and Razzetti, 2015). Pharmaceutical salts of DLS have also been reported, which can also overcome the solubility limitations (Shi and Zhang, 2013a; Shi and Zhang, 2015; Wang et al., 2015).

Pharmaceutical cocrystals are another promising approach to improve the API solubility (Schultheiss and Newman, 2009; Qiao et al., 2011). A cocrystal is a multi-component crystalline complex which consists of two or more solid components (at ambient conditions) in a definite stoichiometric ratio held together via noncovalent interactions (Shan and Zaworotko, 2008; Vishweshwar et al., 2006). Nowadays, pharmaceutical cocrystals have received increasing attention in the pharmaceutical industry and been wildly reported in scientific literatures. However, cocrystal reports for PPIs (Scheme 1c), such as omeprazole, rabeprazole, lansoprazole, and pantoprazole, are still very scarce. To the best of our knowledge, only DLS–sorbitol cocrystals have been obtained up to now (Sun and Watson, 2012). For DLS–sorbitol cocrystals, neither crystal structures nor the intermolecular interactions (supramolecular synthons) have been resolved.

It is critical to obtain the structural information (at least intermolecular interactions) for cocrystals to begin identifying structure–property relationships (Karki et al., 2009; Sun, 2013; Chadha et al., 2012; Friščić and Jones, 2007) or for the design of new cocrystals using the known supramolecular synthons (Friščić and Jones, 2010; Mukherjee, 2015; Qiao et al., 2011). In our opinion, there are two main reasons why cocrystal investigation of PPIs is lacking. Primarily, PPIs are not stable in many solutions, including an acidic environment (DellaGreca et al., 2006; Shin et al., 2004), some commonly used sovlents (Shi and Zhang, 2013b), and at elevated temperatures (DiGiacinto et al., 2000; Fang et al., 2014). Because of this inherent instability, acidic co-formers are not

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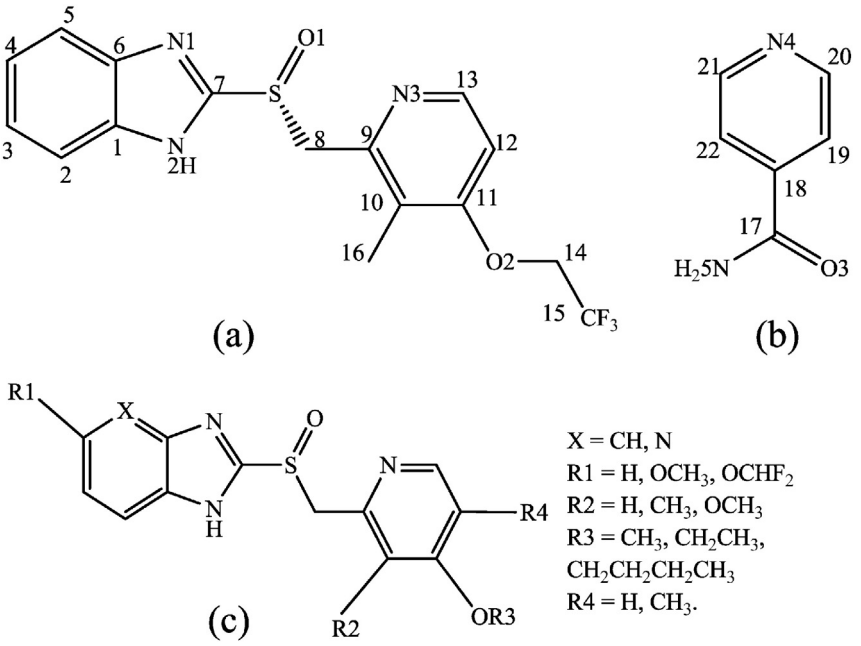

Scheme 1. Molecular structure of dexlansoprazole (a), isonicotinamide (b), and general structure of PPIs (c).

suitable and cocrystal screening condition is very limited. Additionally, though several proton donor/acceptor sites exist in PPI molecules (Scheme 1c), there are no suitable synthons among those well demonstrated ones (Qiao et al., 2011; Thakuria et al., 2013) can be used to design cocrystals of PPIs, such as carboxylic acid···carboxylic acid, carboxylic acid···aromatic nitrogen, and carboxylic acid···amide, amide···amide, etc. In our screening experiments, several organic coformers which contain amide group are used and a crystalline complex of DLS with isonicotinamide (INM, Scheme 1b) was identified. In this contribution, detailed physiochemical analyses were conducted for the DLS–INM sample, including solubilization and understanding intermolecular interactions in the complex.

2. Materials and methods

2.1. Materials

DLS (99.5%) was purchased from Shanghai Huilun Life Science & Technology Co., Ltd. (Shanghai, China). INM and acetonitrile of chromatographic grade were purchased from Sigma-Aldrich (Shanghai, China) and Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China), respectively. Ultrapure water (18.2 MΩ cm) was used throughout the experiments. Other chemicals used were of analytical grade and used as received without any further purification.

2.2. Preparation of DLS–INM

Equimolar amounts of DLS (0.4 mmol, 148 mg) and INM (0.4 mmol, 49 mg) were dissolved in 2 mL and 4 mL of acetonitrile at 50 °C, respectively. The integrity of DLS can be remained after the heating dissolution. The solutions were filtered through 0.22 μm PTFE syringe filters and mixed together in a glass sample bottle under mild magnetic stirring at room temperature. A white precipitate slowly came out of solution. After one day, the precipitate was filtered, dried under vacuum at room temperature and stored in airtight vials. No satisfied single crystal sample was obtained by slow evaporation experiments.

2.3. Physicochemical characterization of DLS–INM

2.3.1. X-ray powder diffraction (XRPD)

The XRPD patterns of all samples were measured on a Bruker D8 ADVANCE X-ray powder diffractometer (Bruker AXS, Germany) equipped with a LynxEye detector. A Cu Kα radiation was used at 45 kV and 40 mA. Samples were scanned in the reflection mode from 3 to 40° 2θ with a scanning step size of 0.0128° and a counting time per step of 16 s.

2.3.2. Differential scanning calorimetry (DSC)

DSC was performed with a TA Q2000 differential scanning calorimeter (TA Instruments, New Castle, DE). Approximately 3 mg of sample was loaded in a hermetically sealed aluminum pan and heated from 25 to 200 °C with scan rate of 10.0 °C/min under nitrogen atmosphere (50 mL/min).

2.3.3. Solid state nuclear magnetic resonance (solid-state NMR)

Solid state ^{13}C and ^{15}N cross-polarization/magic angle spinning (CP/MAS) spectra were performed with a 4 mm double-resonance MAS probe on a Bruker AVANCE III-500 spectrometer (Bruker BioSpin, Karlsruhe, Germany) operating at a magnetic field strength of 11.7 T. The Hartmann–Hahn conditions of the CP experiment for acquiring ^{13}C and ^{15}N spectra were optimized by using adamantane and L-glycine, respectively. For ^{13}C experiments, a total sideband suppression (TOSS) frame was embedded into the conventional CP pulse sequence. ^{13}C NMR spectra were obtained at an 8 kHz MAS spinning speed with a 2.0 ms contact time. ^{15}N NMR spectra were obtained at an 8 kHz MAS spinning speed with a 7.0 ms contact time. ^{13}C and ^{15}N chemical shifts were externally referenced to tetramethylsilane ($\delta = 0.0$ ppm) and L-glycine ($\delta = -347.0$ ppm), respectively.

INM has a very long ^{1}H longitudinal relaxation time. The ^{15}N spectrum of INM was acquired by using CP/MAS flip-back pulse sequence (Saito et al., 2011) with a 3.2 mm double-resonance MAS probe on a JEOL ECZR400 spectrometer (JEOL Ltd., Tokyo, Japan). The pulse delay was set to 200 s and 500 transients were collected.