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Propensity of salicylamide and ethenzamide cocrystallization with aromatic carboxylic acids

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ABSTRACT

The cocrystallization of salicylamide (2-hydroxybenzamide, SMD) and ethenzamide (2-ethoxybenzamide, EMD) with aromatic carboxylic acids was examined both experimentally and theoretically. The supramolecular synthesis taking advantage of the droplet evaporative crystallization (DEC) technique was combined with powder diffraction and vibrational spectroscopy as the analytical tools. This led to identification of eleven new cocrystals including pharmaceutically relevant coformers such as mono- and dihydroxybenzoic acids. The cocrystallization abilities of SMD and EMD with aromatic carboxylic acids were found to be unexpectedly divers despite high formal similarities of these two benzamides and ability of the R2,2(8) heterosynthon formation. The source of diversities of the cocrystallization landscapes is the difference in the stabilization of possible conformers by adopting alternative intramolecular hydrogen boding patterns. The stronger intramolecular hydrogen bonding the weaker affinity toward intermolecular complexation potential. The substituent effects on R2,2(8) heterosynthon properties are also discussed.

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1. Introduction

Many pharmaceutical applications of multicomponent solids such as cocrystals, salts, solvates and clathrates have been explored recently (Fernandes et al., 2003; Grifasi et al., 2015; Jug and Bećirević-Laćan, 2004; Salameh and Taylor, 2006; Shan and Zaworotko, 2008; Steed, 2013; Vishweshwar et al., 2006; Xu et al., 2014). Particularly, the cocrystallization is a useful approach of solubility enhancement (Childs et al., 2013; Good and Rodríguez-Hornedo, 2009; Grifasi et al., 2015; McNamara et al., 2006) and other property improvements (Hiendrawan et al., 2015a; Karki et al., 2009; Sanphui et al., 2015; Sun and Hou, 2008). However, not all multicomponent solids are classified as cocrystals (Thakuria et al., 2013) and according to the most often accepted definition (Aakeröy and Salmon, 2005; Aitipamula et al., 2012a; Bhogala and Nangia, 2008; Jones et al., 2011; Thakuria et al., 2013) two conditions must be met. First of all, coformers should be solid under ambient settings. Besides, after cocrystallization the formed homogeneous phase should comprise stoichiometric proportions of the components. Especial attention has been paid to pharmaceutical cocrystals comprising active pharmaceutical ingredient (API) cocrystalized with molecular complex of some excipients. These pharmaceutically accepted coformers are to be non-toxic and naturally occurring substances (Aitipamula et al., 2012a; Musumeci et al., 2011; Thakuria et al., 2013; Zhang et al., 2014). Substantial effort has been made in the exploration of supramolecular systems leading to rapid development of cocrystals screening both experimentally and theoretically. There are many methods of multicomponent crystals preparation classified into two

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broad categories depending on the cocrystal growth rate (Manin et al., 2014a), namely fast kinetic methods and slow thermodynamic approaches. Both can be implemented on variety manners including solvent evaporation (Hattori et al., 2015; Hiendrawan et al., 2015a; Lin et al., 2013; Przybyłek et al., 2016; Rahman et al., 2011), spray drying (Alhalaweh and Velaga, 2010; Alhalaweh et al., 2013; Patil et al., 2014), neat and liquid assistant grinding (Hiendrawan et al., 2015a; Karki et al., 2007; Sanphui et al., 2015; Sun and Hou, 2008), slurry cocrystallization (Bučar et al., 2010; Kojima et al., 2010; Takata et al., 2008), melting methods (Rahman et al., 2011; Repka et al., 2013; Yan et al., 2015) and supercritical fluids techniques (Cuadra et al., 2016; Hiendrawan et al., 2015b; Padrela et al., 2010, 2009). It is worth mentioning that many pharmaceutical cocrystals containing amides acting either as API or excipients have been studied recently (Aitipamula et al., 2015, 2012b, 2009; Cuadra et al., 2016; Furuta et al., 2015; Gryl et al., 2008; Manin et al., 2014a, 2014b; Wang et al., 2013). The compounds containing amino-carbonyl group including aromatic amides, play many important roles in the medical applications. For examples nicotinamide (vitamin B3), pyrazinamide (antitubercular agent), vindesine (phytogenic and antineoplastic agent, tubulin modulator), L-glutamine (nutritional supplement), cerulenin (antifungal antibiotic), carbamazepine (anticonvulsant), nepafenac and the title compounds (non-steroidal anti-inflammatory drugs) can be found within DrugBank and WHO Collaborating Centre for Drug Statistics Methodology (WHOCC) databases. On the other hand many drugs acting as cyclooxygenase-2 (COX-2) inhibitors belong to the class of carboxylic acids. For example salicylic acid, aspirin and ibuprofen exhibit such activity. However, it was observed (Kalgutkar et al., 2000; Qandil, 2012) that amide and ester derivatives of anti-inflammatory agents have less gastric side effects. Another application of carboxylic acids is pharmaceutical excipients (Rowe, 2009). Noteworthy, benzoic acid and its derivatives have been often used as pharmaceutical cocrystal formers (Berry et al., 2008; Caira et al., 1995; Lin et al., 2015; Manin et al., 2014a, 2014b; Schultheiss and Newman, 2009; Varughese et al., 2010). From pharmaceutical viewpoint particularly important is the class of phenolic acids obtained after hydroxyl substituents attachment to aromatic ring of benzoic acid. According to many reports, these compounds reveal antioxidant activity (Piazzon et al., 2012; Rice-Evans et al., 1996; Sroka and Cisowski, 2003) and possess antimicrobial properties (Baskaran et al., 2013). Furthermore, the phenolic acids are added to food, cosmetics and pharmaceutical formulations to improve their stability (Ash and Ash, 2004; Jones et al., 2006; Vangala et al., 2011).

The aim of this study is to examine the cocrystallization landscape of two active pharmaceutical ingredients (API) namely salicylamide and ethenzamide with aromatic carboxylic acids, including pharmaceutically relevant compounds such as acetylsalicylic acid, 4-acetamidobenzoic acid (acedoben) as well as mono- and dihydroxybenzoic acids. For this purpose a droplet evaporative crystallization (DEC) technique has been applied. This fast and efficient method has been previously developed (Cysewski et al., 2014; Przybyłek et al., 2015) and successfully applied for cocrystal screening (Przybyłek et al., 2016). The experimental data characterizing salicylamide and ethenzamide cocrystallization propensities are also enriched by theoretical screening and detailed analysis of $R_2^2(8)$ heterosynthon properties.

2. Materials and methods

2.1. Materials

All chemicals were applied without purification, as received from commercial suppliers. APIs considered in this study namely, salicylamide (2-hydroxybenzamide, SMD) and ethenzamide (2-ethoxybenzamide, EMD) were obtained from Avantor Performance Materials Poland S.A. (Gliwice, Poland). Also the following compounds were taken from this provider, namely methanol, benzoic acid (BA), 2-fluorobenzoic acid (2FBA), 2-chlorobenzoic acid (2CBA), salicylic acid (SA), acetylsalicylic acid (aspirin, ASA), 4-acetamidobenzoic acid (acedoben, 4ABA) 3-hydroxybenzoic acid (3HBA), 2,6-dihydroxybenzoic acid (2,6DHBA), 2,5-dihydroxybenzoic acid (2,5DHBA) and 3,4-dihydroxybenzoic acid (3,4DHBA). From Sigma-Aldrich (USA) there were purchased the following chemicals 2,4-dihydroxybenzoic acid (2,4DHBA), 3,5-dihydroxybenzoic acid (3,5DHBA), 4-hydroxybenzoic acid (4HBA), 2-bromobenzoic acid (2BBA) and 2-iodobenzoic acid (2IBA).

2.2. Samples preparation procedure and measurements

The cocrystals screening was performed taking advantage of the droplet evaporative crystallization (DEC) technique (Cysewski et al., 2014; Przybyłek et al., 2016, 2015). This very simple, time and chemical preserving approach, yet very efficient, was already validated and successfully applied for new cocrystals preparation (Przybyłek et al., 2016). In this technique the crystallite deposited on the glass surface is analyzed based on the powder X-ray diffraction (PXRD) and Fourier transform infrared-total attenuated reflectance techniques. The DEC procedure consists of mixing methanolic solutions of SMD (0.7 M), EMD (0.1 M) and potential cocrystal formers in 1:1 proportions and allowing the fast drying of the 20 μL-droplets of these mixtures after dropping on the glass surface. The cocrystal occurrence was confirmed by comparison of PXRD and FTIR-ATR spectra of bi-component crystallites with ones recorded for pure components under the same conditions. In the case of low solubility of API the crystallite layers were obtained after repeating of evaporation up to 5 times for obtaining the PXRD diffraction patterns of sufficient quality.

The FTIR-ATR spectra reported in this study were recorded using Bruker Alpha-PFT-IR spectrometer with diamond attenuated total reflection (ATR) equipment. The PXRD patterns were performed using PW3050/60 goniometer with Empyrean XRD tube Cu LFF DK303072 (5°–40° 2θ range, 0.02° step with). All diffraction patterns were preprocessed in Reflex module of Accelrys Material Studio 8.0 (Accelrys, San Diego, 2015) including Kα2 stripping, background subtraction, curve smoothing and normalization.

2.3. Calculation details

2.3.1. Mixing enthalpy estimation

The excess thermodynamic functions characterizing components affinities in liquid state under super cooled conditions are often used as a measure of cocrystallization propensities (Eckert and Klamt, 2014; Loschen and Klamt, 2015). This post-quantum mechanical thermodynamic analysis takes advantage of the Conductor like Screening Model for Real Solvents model (COSMO-RS) (Klamt and Schüürmann, 1993; Klamt, 2011) for sigma profiles generation at semiempirical AM1 (Dewar et al., 1985) level. Based on the statistical analysis offered by COSMOtherm software (Eckert and Klamt, 2014) (parametrization BP_SVP_AM1_C30_1501.ctd) it is possible to obtain the mixing enthalpy. The negative enough values of mixing enthalpy are supposed to indicate that the mixture is thermodynamically favored over the pure component liquids. The miscibility under super cooled liquid is often associated with miscibility in the solid state, hence documenting the ability of cocrystallization (Loschen and Klamt, 2015). The geometries of all amides and coformers were optimized using MOPAC2012 (Maia et al., 2012; Stewart, 2016) both in the gas phase and in the condensed phase modeled with and aid of the COSMO-RS approach.

2.3.2. Computations of the substituent effects on the heterosynthon properties

The full gradient optimization was performed for 180 pairs of para-substituted benzoic acid analogues with salicylamide or enthenzamide using ΩB97XD density functional with 311++G** basis set as implemented in GAUSSIAN package (Frisch et al., 2009). The contributions to the pair stabilization energy were performed

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