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Pharmaceutical properties of two ethenzamide-gentisic acid cocrystal polymorphs: Drug release profiles, spectroscopic studies and theoretical calculations

Agnieszka Sokal[a], Edyta Pindelska[a,*], Lukasz Szeleszczuk[b], Waclaw Kolodziejski[a]

[a] Faculty of Pharmacy with Laboratory Medicine Division, Medical University of Warsaw, Department of Inorganic and Analytical Chemistry, Banacha 1, 02-093, Warsaw, Poland

[b] Faculty of Pharmacy with Laboratory Medicine Division, Medical University of Warsaw, Department of Physical Chemistry, Banacha 1, 02-093, Warsaw, Poland

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ABSTRACT

The aim of this study was to evaluate the stability and solubility of the polymorphic forms of the ethenzamide (ET) – gentisic acid (GA) cocrystals during standard technological processes leading to tablet formation, such as compression and excipient addition. In this work two polymorphic forms of pharmaceutical cocrystals (ETGA) were characterized by ^{13}C and ^{15}N solid-state nuclear magnetic resonance and Fourier transformed infrared spectroscopy. Spectroscopic studies were supported by gauge including projector augmented wave (GIPAW) calculations of chemical shielding constants. Polymorphs of cocrystals were easily identified and characterized on the basis of solid-state spectroscopic studies. ETGA cocrystals behaviour during direct compressionand tabletting with excipient addition were tested. In order to choose the best tablet composition with suitable properties for the pharmaceutical industry dissolution profile studies of tablets containing polymorphic forms of cocrystals with selected excipients were carried out.

1. Introduction

Increased interest in the synthesis and design of new forms of drugs, such as cocrystals, is caused by their ability to change physical and chemical properties of active pharmaceutical ingredients (API) (Shan and Zaworotko, 2008; Qiao et al., 2011). Polymorphs and salts formation of API is almost omnipresent. Polymorphic forms are formed when a substance crystallizes in two or more crystal structures. Cocrystals are structurally homogeneous crystalline materials containing two discrete neutral molecular reactants or more components (solids under ambient temperature) present in definite stoichiometric ratio (Shan and Zaworotko, 2008). In recent years, the number of multicomponent crystals containing an API and coformer which is chosen from the GRAS list (*generally recognized as safe*) is significantly growing (Stahl and Wermuth, 2008). The idea of developing pharmaceutical cocrystals involving more than one drug is becoming more popular due to some advantages (Jones et al., 2006; Porter et al., 2008; Brittain, 2013). The successful development and commercialization of any drug requires adequate manufacturability, stability and bioavailability (Duggirala et al., 2016; Li et al., 2016). Cocrystal engineering has been proposed as a good way of enhancing dissolution rates and solubility (Mittapalli et al., 2015), improving stability of the drug in tablets (Swapna et al., 2014) and developing their mechanical properties (Hiendrawan et al., 2016). However, the number of polymorphic cocrystals is still very limited.

Ethenzamide (2-ethoxybenzamide, **ET**, Fig. 1) is an API from the non-steroidal anti-inflammatory (NSAID) group of drugs which shows analgesic and antipyretic activity (Uehara et al., 1998). It is a poorly-water soluble drug used for treatment of moderate and mild pain. Combinations of **ET** with aspirin, caffeine or paracetamol are widely used e.g. in Japan and Poland. The list of

* Corresponding author.
E-mail addresses: agnieszka.sokal@wu.edu.pl (A. Sokal), edyta.pindelska@wum.edu.pl (E. Pindelska), lukasz.szeleszczuk@wum.edu.pl (L. Szeleszczuk), waclaw.kolodziejski@wum.edu.pl (W. Kolodziejski).

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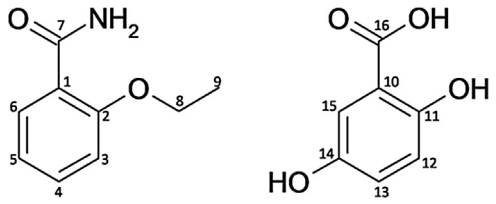

Fig. 1. Chemical structures of **ET** (left) and **GA** (right).

pharmaceutical formulations containing **ET**, taken from the Micromedex base, is included in Supporting information. It is reported that low solubility and bioavailability of **ET** could be improved by using some drug modifications. Dissolution rate can be increased by obtaining solid dispersions of the drug and preparation with low molecular weight sugars or using controlled release of the drug form carries such as Carbopol (Danjo et al., 1997). Another good example of improving the dissolution rate of **ET** is synthesis of amorphous material by mixing **ET** with porous crystalline cellulose using a twin screw extruder (Kazuhiro et al., 1994; Matsumoto et al., 1998). It was proved that cocrystallization of **ET** can be a proper way to obtain better soluble and more stable forms of that drug (Aitipamula et al., 2009, 2012). From the pharmaceutical point of view, cocrystals of ethenzamide with gentisic acid (2,5-dihydroxybenzoic acid, **GA**, Fig. 1) are very interesting due to the fact that they contain more than one API in cocrystal structure and occur in three polymorphic forms with different physical and chemical properties (Aitipamula et al., 2009). **GA** as well as **ET** is NSAID with antioxidant and anti-aging activity (Brand-Williams et al., 1995). This kind of biological activity indicates that combinations of two APIs could be possibly an alternative to standard treatment of cold, joint disorders or musculoskeletal pain.

The structure of **ET** has been published and deposited in CSD (Cambridge Structural Database (Allen, 2002), refcode DUKXAJ (Back et al., 2012)), together with the structures of three polymorphic forms of cocrystals of **EA** with **GA** (refcodes: QULLUF, QULLUFO1, QULLUFO2)(Aitipamula et al., 2009). For all polymorphic forms PXRD (powder X-ray diffraction), DSC (differential scanning calorimetry) and dissolution rate studies were performed. It has been found that the most stable form of the cocrystals is form I (**ETGA1**), the less stable form is form III (**ETGA3**), which can convert to **ETGA1** by solid-state grinding or by heat-cool-heat experiments. The **ETGA1** form can be obtained by either solid-state grinding or slow evaporation from a convenient solvent, whereas **ETGA2** and **ETGA3** forms can be obtained only from slurry experiments. What is more, all of the **ETGA** cocrystals show better dissolution rate than the separate drug. Cocrystallization with 2,5-dihydroxybenzoic acid improves dissolution rate of **ET**, especially of metastable polymorphic forms (**ETGA2** and **ETGA3**) versus stable **ETGA1** form (Aitipamula et al., 2009). Differences in dissolution rate and stability of polymorphs of **ETGA** cocrystals emphasize the significance of selecting a proper polymorphic form for pharmaceutical development.

In this work high-resolution solid-state NMR (ssNMR) studies were performed to characterize and select polymorphic forms of **ETGA** convenient for drug dosage production. The ssNMR studies were supported by FT-IR and theoretical calculations of NMR chemical shielding constants. We have also tested which of the investigated polymorphic forms of **ETGA** cocrystals is stable during the standard tabletting process. Despite the numerous attempts to obtain **ETGA3** polymorphic form, we were not able to obtain proper crystals to perform adequate studies. Therefore, we compared the stability only for two of them: **ETGA1** and **ETGA2** during direct tabletting and tabletting with an addition of different excipients. Additionally, for all prepared tablets dissolution studies in vitro were performed in order to analyse the influence of the excipients on dissolution profiles of the cocrystals.

2. Materials and methods

2.1. Materials

Ethenzamide (purity 97%) and gentisic acid (purity 98%) were purchased from Sigma-Aldrich. Lactose monohydrate (**LA**) and potato starch (**PS**) were purchased from AMARA company (standard substance used for tabletting process). PROSOLV HD 90 (silicified microcrystalline cellulose, **PR**) was obtained from JRS Pharma. Potassium bromide (purity ≥ 99%, FT-IT grade) and simulated gastric fluids without enzyme (SGF) were purchased from Sigma Aldrich. Toluene (purity 99.5%) and acetonitrile (purity 99.5%) for slurry experiments were purchased from POCH S.A. All chemicals and solvents were used without additional purification.

2.2. Methods

2.2.1. Formation of *ETGA* cocrystals

Both polymorphic forms of **ETGA** were prepared by using the previously reported method (Aitipamula et al., 2009). In the case of ethenzamide-gentisic acid cocrystals, polymorphic form **ETGA1** could be obtained via solid state grinding. When an exact amount of substances in stoichiometric ratio (1:1) was taken to reaction, the yield of cocrystal synthesis was 100%. In the case of the **ETGA2**, when slow evaporation from solution (toluene: ethyl acetate (1:1)) was used as a cocrystallization method, the yield of cocrystal synthesis was about 70%. The ssNMR (Fig. S1) was used for quick confirmation which polymorphic form was obtained. The purity of obtained polymorphic forms of cocrystals was determined by means of X-ray Powder Diffraction (Fig. S2).

2.2.2. Preparation of tablets with *ETGA* cocrystals

Cylindrical tablets were prepared by direct compression of the **ET**, **ETGA1** or **ETGA2** with an addition of **LA**, **PS** and **PR** to finally obtained tablets whose total weight was 350 mg. All tablets were prepared using laboratory press fitted with a 14 mm flat-faced punch and die set, applying 10 t force for 30 s. All formulations had **ET** concentration of 100 mg per tablet.

2.2.3. Solid-state nuclear magnetic resonance (ssNMR)

All the measurements shown in this work were made on crystals obtained by slow evaporation from a acetonitryle:toluene (1:1) solution. High-resolution solid-state ^{13}C and ^{15}N NMR spectra were recorded on a Bruker Avance 400 WB spectrometer at 9.4 T. All experiments were performed at 298 K. The 100 and 40.5 MHz resonance frequencies were used, respectively. The ^{13}C and ^{15}N experiments were carried out with cross-polarization (CP), high power decoupling and magic angle spinning (MAS). Samples were prepared by packing an adequate amount of each sample into 4 mm zirconia rotors and driven by dry air. The MAS rate used in ^{13}C and ^{15}N NMR experiments was 7.5 kHz and 5 kHz, respectively. Adamantane and glicyne-^{15}N were used to match the Hartmann-Hahn conditions for ^{13}C and ^{15}N,respectively. The optimized recycle delay for **ET**, **ETGA1**, and **ETGA2** was 35 s. The contact time was varied from 25 μs up to 20 ms. Additionally, for both obtained polymorphic forms of **ETGA** experiments with dipolar dephasing were carried out. The NMR spectra were processed with the ACD/SpecManager NMR program (version 10.0, Advanced Chemistry Development, Inc., Toronto, ON, Canada). The Microsoft Excel program was used to fit CP kinetics functions to experimental points.