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Salt or cocrystal of salt? Probing the nature of multicomponent crystal forms with infrared spectroscopy

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ABSTRACT

The recognition of the nature of a multicomponent crystal form (solvate, salt, cocrystal or cocrystal of salt) is of great importance for pharmaceutical industry because it is directly related to the performance of a pharmaceutical ingredient, since there is interdependence between the structure, its energy and its physical properties. In this context, here we have identified the nature of multicomponent crystal forms of the anti-HIV drug lamivudine with mandelic acid through infrared spectroscopy. These investigated crystal forms were the known *S*-mandelic acid cocrystal of lamivudine *R*-mandelate trihydrate (**1**), a cocrystal of salt, and lamivudine *R*-mandelate (**2**), a salt. This approach also supports the identification and distinction of both ionized and unionized forms of mandelic acid in the infrared spectrum of **1**. In this way, infrared spectroscopy can be useful to distinguish a cocrystal of salt from either salt or cocrystal forms. In the course of this study, for the first time we have also characterized and determined the crystal structure of *R*-mandelic acid cocrystal of sodium *R*-mandelate (**3**).

1. Introduction

Crystal engineering is an approach that has been of great use nowadays to yield new solid forms with better properties [1–2]. In this line of work, researchers have studied multicomponent systems of pharmaceutical interest such as salts, cocrystals and more recently, cocrystals of salts of drugs [3–7]. The definition of the terms "salt, cocrystal and cocrystal of salt" are still debatable, however, the major difference between cocrystal and salt is that the proton transfer occurs in the latter, while no molecules are charged in the cocrystal phase [7–8]. The cocrystal of salt form contains both charged and neutral molecules of the same compound within the same crystalline structure [8]. Usually X-ray diffraction technique is employed in the characterization and elucidation of the crystal structure of these solid forms, however, obtaining suitable crystals for single crystal X-ray analysis can be challenging as well as expert dataset processing and handling is needed by a crystallographer, which demands on long-time X-ray diffraction intensity collects.

Identifying the nature of a multicomponent solid form is of great importance for the pharmaceutical industry because even a small difference, as the position of a proton in one of the species forming the multicomponent system (cocrystal, salt or cocrystal of salt) can directly influence the physical properties such as solubility, stability and dissolution rate. Therefore, even if this difference may seem minor in the multicomponent solid form of a drug, it can have a considerable effect on the lattice energy of a structure which may change the performance of the solid form [2,7]. The identification of the nature of the multicomponent system can also be difficult, especially because it is not easy to isolate a single crystal and because poor quality crystals may be obtained. Also, suspicions about the proton transfer between the two species present in the crystalline solid may arise as a result of uncertainties in the bond length of the species involved in hydrogen bonding pattern. In this way the pKa rule have been applied in many studies lately to help understand whether the solid form is a salt or a cocrystal [7,9,10]. Sometimes, when this rule cannot be used accurately, for example, when the ΔpKa ($pKa_{base} - pKa_{acid}$) is in the range of 0 to 3, the decision about the nature of the complex depends on the C—O distances. However, the C—O bond distance can only assist in the distinction between a salt or a cocrystal when carboxylic acids are utilized as a crystallization agent [7,9]. Besides all these aspects, the use of low temperature and copper radiation to obtain more accurate bond lengths is generally recommended in single crystal X-ray diffraction analysis. Therefore, many difficulties may be faced during the study of a new multicomponent system through single crystal X-ray diffraction.

In this context, infrared (IR) vibrational spectroscopy method can be used as an alternative approach to explore the disparity at molecular level by checking the variation in the spectral signatures of the spectra belonging to the solid phases under study [5–6,9–13]. This technique provides a faster and simpler analysis when compared to X-ray diffraction and uses small amount of material and does not require the material to be a larger single crystal. There are reports of infrared

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spectroscopy offering conditions to evaluate if the proton transfer has occurred or not between the pharmaceutical ingredient and the counterion, in salt phases, or coformer in cocrystals, respectively [5,7,12]. Mukherjee et al. and Chakraborty and co-workers performed vibrational spectroscopy experiments to identify the hydrogen pattern present in multicomponent molecular crystal structures [5,13]. Hinsmann et al., studied the capability of infrared spectroscopy in combination with capillary electrophoresis to separate enantiomeric complexes. They could also distinguish between the diastereomers in such system [14]. Furthermore, IR spectroscopy along with complementary techniques, such as differential scanning calorimetry (DSC), thermogravimetry (TG) and powder X-ray diffraction (PXRD), can be enough to characterize pharmaceutical multicomponent systems.

In this study, it is described the application of IR technique to distinguish between the nature of a cocrystal of salt and a salt. The present paper also shows that is possible to identify different ionization states in a same multicomponent crystal form simultaneously and directly from the signatures of the spectra. To accomplish these goals here, two multicomponent crystal systems of lamivudine and mandelic acid recently reported [4] were chosen as template and characterized by infrared vibrational spectroscopy together with thermal analysis (DSC and TG) and powder X-ray diffraction methods. The known *S*-mandelic acid cocrystal of lamivudine *R*-mandelate trihydrate (**1**, a cocrystal of salt) and lamivudine *R*-mandelate (**2**, a salt) were these templates (Fig. 1). To the best of our knowledge, lamivudine is an active pharmaceutical ingredient (API) with high therapeutic relevance marketed under the name EPIVIR by GlaxoSmithKline® and is used in the treatment of AIDS and hepatitis B [15–16]. In general, lamivudine solid forms are only featured by single crystal X-ray diffraction and there are few of them being characterized by IR spectroscopy. In addition, density functional theory (DFT) calculations were performed in order to support our bands assignments. In the course of the rational approach used in the IR characterization of **1** and **2**, the crystal structure of *R*-mandelic acid cocrystal of sodium *R*-mandelate (**3**) was determined and therefore is also reported for the first time here.

2. Experimental

2.1. Preparation of multicomponent crystal forms

Crystals of **1** and **2** were obtained after complete evaporation of the solvent matrix at room temperature (298 K), according to the literature protocol [4]. This solvent matrix from which the salt form **2** was isolated has been set by dissolving an amount of lamivudine form II (0.04 mmol, 10 mg) in 5 mL of isopropyl alcohol under stirring at 308 K. After the solution has cooled until room temperature, an amount of 6.5 mg (0.04 mmol) of *R*-mandelic acid was added and dissolved directly. Crystals were obtained after slow evaporation at room temperature (5 days). The procedure carried out to obtain the cocrystal of salt **1** consisted of dissolving 10 mg of lamivudine form II in a mixture of ethyl alcohol (2.5 mL) and water (2.5 mL) under stirring at 308 K. Then, an amount of 13 mg (0.08 mmol) of racemic mandelic acid was directly dissolved into the solution containing lamivudine under stirring at 298 K. The resulting solution was allowed to evaporate slowly and crystals were obtained after 10 days. More details about the preparation and crystal structure determination of these solid forms can be found in reference 4.

Crystals of **3** were produced by slow evaporation (4 days) of the solvent matrix at room temperature. This crystal phase was prepared by dissolving 10 mg of *R*-mandelic acid in isopropyl alcohol followed by the addition of NaOH solution 0.1 mol L^{-1} (0.5 mL).

2.2. Single crystal X-ray diffraction

A single crystal of **3** was selected for the X-ray diffraction experiment. The data were collected on a Bruker-AXS Kappa Duo diffractometer with an APEX II CCD detector using Mo Kα radiation. Bruker programs SAINT and SADABS [17] were used for cell refinement and data reduction. Multi-scan absorption correction was performed with the ration between the minimum and maximum apparent transmission of 0.760. The structure solution and refinements were carried out using SHELX97 [18] within the WinGX [19]. Non-hydrogen atoms were refined anisotropically. Some hydrogen atoms were located on the difference Fourier map but they next were constrained following a riding model. For hydrogens bonded to carbons and oxygen atoms, their isotropic thermal parameters were set to $1.2U_{iso}$ or $1.5U_{iso}$, respectively. The X-ray diffraction dataset for this structure is available under CCDC number 1449139.

2.3. Powder X-ray diffraction (PXRD)

In order to know if crystallization procedure of **1** and **2** has yielded pure samples, without starting materials or undesirable products, the produced crystalline materials were analyzed by PXRD using an X-ray beam (Cu–Kα radiation, l = 1.5418A°) generated at 40 kV and 30 mA on a Shimadzu XRD-6000 diffractometer. The powder X-ray diffraction pattern was acquired at room temperature under a continuous scan mode (scan axis θ–2θ) with a scan speed of 1.000° min^{-1}. Intensity data were measured at each 0.020° in a 2θ range between 5° and 40°. Experimental and calculated PXRD patterns were compared in order to confirm if the composition of each sample was consistent with that expected from single crystal X-ray diffraction analysis.

2.4. IR spectroscopy analysis

All IR spectra were collected on a Spectrum 400FT-IR/FT-FIR spectrometer (PerkinElmer®). Samples were examined by IR transmission technique as KBr pellets prepared using a hydraulic press. An amount of 200 mg of KBr and 1 mg of each sample were used to prepare the pellets. The FT-IR spectra were obtained after a number of 16 acquisitions at a spectral resolution of 4 cm^{-1}.

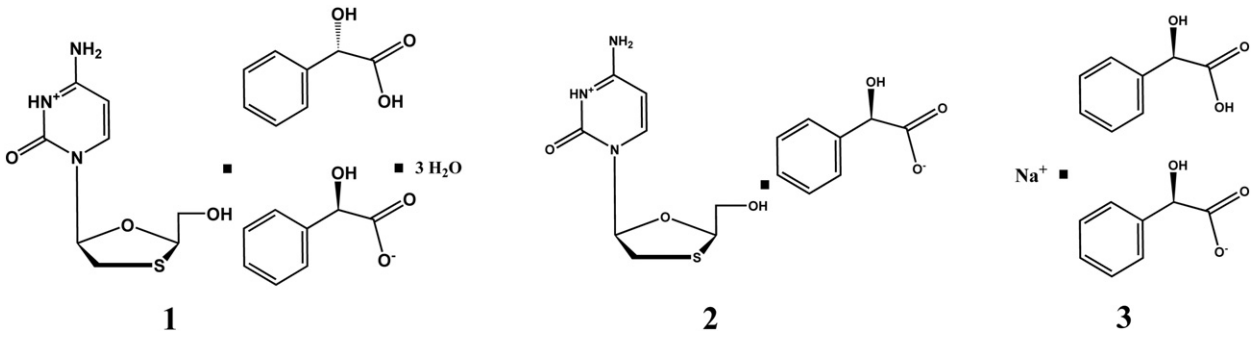

Fig. 1. Chemical structures of *S*-mandelic acid cocrystal of lamivudine *R*-mandelate trihydrate (**1**), lamivudine *R*-mandelate (**2**) and *R*-mandelic acid cocrystal of sodium *R*-mandelate (**3**).