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Utilization of oriented crystal growth for screening of aromatic carboxylic acids cocrystallization with urea

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ABSTRACT

The possibility of molecular complex formation in the solid state of urea with benzoic acid analogues was measured directly on the crystallite films deposited on the glass surface using powder X-ray diffractometry (PXRD). Obtained solid mixtures were also analyzed using Fourier transform infrared spectroscopy (FTIR). The simple droplet evaporation method was found to be efficient, robust, fast and cost-preserving approach for first stage cocrystal screening. Additionally, the application of orientation effect to cocrystal screening simplifies the analysis due to damping of majority of diffraction signals coming from coformers. During validation phase the proposed approach successfully reproduced both positive cases of cocrystallization (urea:salicylic acid and urea:4-hydroxy benzoic acid) as well as pairs of co-formers immiscible in the solid state (urea:benzoic acid and urea:acetylsalicylic acids). Based on validated approach new cocrystals of urea were identified in complexes with 3-hydroxybenzoic acid, 2,4-dihydroxybenzoic acid, 2,5-dihydroxybenzoic acid, 2,6-dihydroxybenzoic acid and 3,5-dihydroxybenzoic acid. In all cases formation of multicomponent crystal phase was confirmed by the appearance of new reflexes on the diffraction patterns and FTIR absorption band shifts of O–H and N–H groups.

1. Introduction

According to widely accepted definition [1] a cocrystal is a homogeneous crystalline solid that contains stoichiometric amounts of discrete neutral molecular species, which are solids under ambient conditions. These kind of solution differ from other dispersions as eutectic or monotectic systems by congruent melting and a molecular complex formation of a definite proportions of interaction components [2–4]. The practical application of organic solid alloys encompassing variety industries as pharmaceutical, textile, paper, chemical processing, photographic, propellants or electronics [5] stimulated growth of accumulated knowledge and diversity of obtained materials. This explosion of interests resulted in 7688 structures of binary cocrystals solved so far [6] not counting hydrates, solvates, clathrates nor organometallic species. The change of physicochemical properties of cocrystals with respect of the coformers is especially useful and important in the case of active pharmaceutical ingredients (API). There are many examples of significant improving of API behaviors both in vivo and in vitro [7–12]. The advantages of cocrystallization for pharmaceutical industry are not only related to bioavailability enhancement but also to the increase of stability [13], hygroscopicity decrease [14], mechanical properties improvement [15] and also due to intellectual property issues [16].

Urea is a quite common former of cocrystals and in the Cambridge Structural Database (CSD) [6]. One can find more than 100 records documenting its involvement in multicomponent compounds. One of the reason of so common occurrence of urea is the diversity of possible interactions offered by two amino groups. Although, the pure urea crystal is deposited 18-times in the CSD corresponding to measurements at different temperatures but only one polymorphic form is reported, which adopts tetragonal system of P421m symmetry. Urea molecule can form strong intermolecular hydrogen bonds and can act both as acceptor and donor. Indeed, the carbonyl group is very strong acceptor center interacting with three neighboring urea molecules via four hydrogen bonds. The bi-center interactions with amino groups lead to formation of 1D columns each surrounded by four identical chains. The stabilization of

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resulting perpendicular 2D sheets is gained via hydrogen bonds formed with amino groups [17–24]. This ability of divers hydrogen bonding is the source of observed variety of cocrystals structures of urea since it can cocrystalize with polar coformers as for example with salicylic acid (SLCADC) but also with non-polar species as for instance with 1,10-phenanthroline (AMILUD). The other interesting feature of the cocrystals formed by urea is significant diversity of stoichiometry of complexes found in the solid phase. Although the 1:1 ratio predominates in cocrystals but one can find as high as 10:1 proportion in the case of urea-2,12-tridecanedione (MISNOR). Also many drugs can cocrystalize with urea as for example barbital (BARBUR) – a hypnotic and sedative agent also used in veterinary practice for central nervous system depression, febuxostat (HIQQUV) – inhibiting xanthine oxidase, nitrofurantoin (ORUXUV) – an antibiotic usually used for treatment of urinary tract infections or betonicin (REGKUK) – a psychoactive agent. On the other hand there are many drugs that have not been cocrystalized with urea as for example aspirin (acetylsalicylic acid) – a common prototypical analgesic having anti-inflammatory and antipyretic properties. However, structurally very similar salicylic acid used as analgesics was successfully cocrystalized with urea (SLCADC). Besides, urea in some case can form eutectic or monotectic mixtures with organic compounds for example with 4-chloronitrobenzene [25]. There is remarkably small data about cocrystallization of urea with other aromatic carboxylic acids. Apart from salicylic acid also 3,5-dinitrosalicylic acid (NUHYAQ), 1,1-binaphthyl-2,2′-dicarboxylic acid (ROGKOO), trimesic acid (benzene-1,3,5-tricarboxylic acid) (CEKSIU) and 4-hydroxycarboxylic acid (JOZZIH) cocrystalize with urea in the monoclinic system. The orthorhombic crystal system is typical for 4-aminobenzoic acid:urea cocrystal (NUHYEU). Finally the triclinic system is observed in the case of o-phthalic acid (NUHYIY, NUHYIY01) and 5-nitrosalicylic acid (NUHXUJ) cocrystals with urea. It is slightly surprising that no more structures of urea cocrystals with other aromatic carboxylic acid were determined, despite the fact that stabilization of such potential systems might be gained from quite common $\text{R-COOH}\cdots\text{H}_2\text{NCO-R}$ heterosynthon of $C_2^2(8)$ type. These observations suggest that predicting of the ability of cocrystal formation of urea with other coformers is not straightforward and non-trivial task. This is the starting point of our investigations. There are many ways of cocrystal preparation and among them the mechanochemical approach [26] is commonly used. In fact, this method was applied for obtaining the very first cocrystal of quinone and hydroquinone [27]. Besides, many alternative methods were adopted for cocrystallization purposes [28] as for example sonication [29], melting [30] including direct phase transition observations under thermal microscopy [31] and many other techniques. Generally speaking, two basic categories of cocrystals screening methods can be distinguished: thermodynamic (slow crystal growth) and kinetic (fast crystallization) [32–34]. Particularly noteworthy are the latter methods relying on the fast solution evaporation like spray drying [35], spin coating [36], microwave-accelerated evaporative crystallization [37–39] and droplet evaporation [40–46]. Hence, they are routinely utilized for cocrystals synthesis [47–49]. One of the form of such crystallization are preparation of oriented samples. As we reported previously [45,46] the crystallization on the polar surfaces leads to interesting effect of reducing number of peaks on PXRD spectra if measurements are performed directly on thin layer deposits. The origin of this phenomena is the orientation effect of exposed faces toward solution which exhibits both the highest adhesive and cohesive properties [45,46]. It is worth noting that, PXRD measurements of so-called oriented samples is commonly used in geology and soil science [50–53]. Noteworthy, preparation of oriented phenzaine–chloranilic acid cocrystal thin films using sublimation method was reported by Thompson et al. [54]. The main advantage of oriented samples measurements is enhancing the intensity of certain diffraction signals and diminishing majority of the rest. Therefore, it is interesting to see if oriented samples measurements can be useful in identification of cocrystal formation what stands for the purpose of this paper. Below, the verification of proposed methodology of identification of known cocrystals of urea with aromatic carboxylic acids is followed by screening of urea cocrystallization landscape for finding new homogeneous bi-component solids that were not-reported in the literature so far.

2. Materials and methods

2.1. Chemicals

All analytical grade chemicals were purchased from commercial suppliers and used without further purification. Urea (U, CAS: 57-13-6), benzoic acid (BA, CAS: 65-85-0), salicylic acid (SA, CAS: 69-72-7), acetylsalicylic acid (ASA, CAS: 50-78-2), 3-hydroxybenzoic acid (3HBA, CAS: 99-06-9), 2,5-dihydroxybenzoic acid (2,5DHBA, gentisic acid, CAS: 490-79-9), 2,6-dihydroxybenzoic acid (2,6DHBA, γ-resorcylic acid, CAS: 303-07-1) and methanol (CAS: 67-56-1) were obtained from POCH (Poland). Other compounds namely, 4-hydroxybenzoic acid (4HBA, CAS: 99-96-7), 2,4-dihydroxybenzoic acid (2,4DHBA, β-resorcylic acid, CAS: 89-86-1), 3,5-dihydroxybenzoic acid (3,5DHBA, CAS: 99-10-5) were purchased from Sigma-Aldrich (USA). Structures of used dicarboxylic acids were presented on Scheme 1.

2.2. Crystallization and samples preparation procedures

First, 0.724 M methanolic solutions of coformers were prepared and mixed together to obtain urea/carboxylic acid solutions at unimolar composition. Then, such mixtures and the pure components solutions were used for preparing of crystallite layers according to previously described procedure [45,46]. This method involves placing of 20 μl of the solution on glass microscope slide and letting for fast evaporation at 43 °C under atmospheric pressure.

Additional cocrystallization experiments were performed for all new cocrystals (2,4DHBA, 2,5DHBA, 2,6DHBA, 3,5DHBA and 3HBA) for alternative verifications. The PXRD patterns recorded for oriented crystallites were compared with diffractograms of powder samples obtained using mechanochemical method and bulk evaporation approach. In the case of the mechanochemical method, coformers crystals were mixed in the 1:1 M proportion and ground in the mortar for an hour. The bulk evaporation cocrystallization 30 ml of methanolic solutions were evaporated in a glass beaker at 43 °C under atmospheric pressure.

2.3. Measurements

The Fourier transform infrared (FTIR) spectra were recorded on a Bruker Alpha-PFT-IR spectrometer (Bruker, Germany) with a diamond attenuated total reflection (ATR) crystal. Powder X-ray diffraction (PXRD) patterns were recorded with the use of Goniometer PW3050/60 armed with Empyrean XRD tube Cu LFF DK303072. Diffraction data were collected in the range of 2θ between 5° and 40° with 0.001° step width. The patterns were processed in Reflex module of Accelrys Material Studio 8.0 [55] by Kα2 stripping, background computation and subtraction followed by curve smoothing and normalization.

3. Results and discussion

In this study, the possibilities of binary homogeneous mixture formation of urea in solid state with nine aromatic carboxylic acids