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Cocrystal screening of hydroxybenzamides with benzoic acid derivatives: A comparative study of thermal and solution-based methods

Alex N. Manin [a], Alexander P. Voronin [a], Ksenia V. Drozd [b], Nikolay G. Manin [a], Annette Bauer-Brandl [c], German L. Perlovich [a,*]

[a] G.A. Krestov Institute of Solution Chemistry of the Russian academy of Sciences, 1, Akademicheskaya, 153045 Ivanovo, Russian Federation
[b] Ivanovo State University, 39, Ermaka, 153025 Ivanovo, Russian Federation
[c] Department of Physics, Chemistry and Pharmacy, University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark

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ABSTRACT

The main problem occurring at the early stages of cocrystal search is the choice of an effective screening technique. Among the most popular techniques of obtaining cocrystals are crystallization from solution, crystallization from melt and solvent-drop grinding. This paper represents a comparative analysis of the following screening techniques: DSC cocrystal screening method, thermal microscopy and saturation temperature method. The efficiency of different techniques of cocrystal screening was checked in 18 systems. Benzamide and benzoic acid derivatives were chosen as model systems due to their ability to form acid-amide supramolecular heterosynthon. The screening has confirmed the formation of 6 new cocrystals. The screening by the saturation temperature method has the highest screen-out rate but the smallest range of application. DSC screening has a satisfactory accuracy and allows screening over a short time. Thermal microscopy is most efficient as an additional technique used to interpret ambiguous DSC screening results. The study also included an analysis of the influence of solvent type and component solubility on cocrystal formation.

1. Introduction

In the last few decades, pharmaceutical industry has achieved a great progress in its search for new drug compounds by applying combinatorial approaches and high throughput in vivo screening. However, compounds obtained by such methods typically have a number of defects, the main one being their low solubility in aqueous media and, consequently, their low bioavailability. 70% of the compounds under development and 40% of the drugs on the market have poor water solubility (Thayer, 2010). Therefore, creating soluble drug compounds by using innovative techniques is now becoming one of the most urgent tasks.

Cocrystallization is a promising approach increasing the bioavailability of active pharmaceutical ingredients (API) (Schultheiss and Newman, 2009), their thermodynamic stability (Vishweshwar et al., 2006) and a wide range of mechanical properties (Sun and Hou, 2008; Karki et al., 2009). Besides, using coformers of different nature (as a second component of cocrystals) allows us to change physicochemical and pharmacokinetic properties of the system, thus making it possible to "fine-tune" products under development to market requirements (Shan and Zaworotko, 2008). Cocrystals are also interesting as potential intellectual property items which can bring back into the market generic drugs with improved characteristics as a unique brand (Trask, 2007).

The literature describes a lot of approaches to obtaining cocrystals (Karki et al., 2007; Rodríguez-Hornedo et al., 2006; Padrela et al., 2009; Daurio et al., 2011; Eddleston et al., 2013; Alhalaweh and Velaga, 2010; Morrison et al., 2013; Oswald and Pulham, 2008), as well as analytical methods suitable for their identification (Trask et al., 2005; Allesø et al., 2008; Elbagerma et al., 2010; Maruyoshi et al., 2012). Unfortunately, there are still no universal rules for selection of more suitable algorithms for cocrystal screening of preassigned system. The choice of a screening method depends on the problem to be solved, the nature of the object of research (such as the difference in solubility of API and coformers in the used solvents, thermal stability or aptness to form stable solvates) and availability of sufficient amount of the substance. The strengths and weaknesses of many screening

* Corresponding author. Tel.: +7 4932 533784; fax: +7 4932 336237.
E-mail address: glp@isc-ras.ru (G.L. Perlovich).

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methods have not been objectively analyzed yet, though they determine the methods real application range. As new approaches appear, it becomes more and more difficult to choose among them the most suitable one for certain research objects. Therefore, it is necessary to develop a number of criteria of comparing the efficiency of different cocrystal screening techniques.

Using powder X-ray diffraction analysis (PXRD) can be suitable for quick identification of the substance and its cell parameters (Trask et al., 2005). However, this technique is not suitable for full-scale high throughput screening if it is used as the only identification technique (Allesø et al., 2008) because in this case samples should be additionally treated by neat grinding, solvent-drop grinding or other cocrystal preparation techniques. Therefore, our study was aimed at conducting comparative analysis of the practical efficiency of a number of alternative methods currently used in pharmaceutical cocrystal screening.

The screening procedure of selecting pharmaceutical cocrystals with preset properties includes two consecutive stages: (a) cocrystal formation and (b) identification of its properties (solubility, thermodynamic stability, dissolution kinetics, etc.). In turn, the methods of obtaining cocrystals can be divided into kinetic and thermodynamic types (Newman, 2013).

Thermodynamic methods are used to obtain a stable crystal form under the given conditions (usually this process goes under conditions close to equilibrium and requires a lot of time) (Newman, 2013). Thermodynamic methods include crystallization through slow evaporation of solvent, crystallization from melt and solution-mediated phase transformation.

Kinetic methods are most suitable for searching metastable crystal forms with higher Gibbs energy values compared to stable crystals. Experiment conditions for these methods are non-equilibrium. In some cases additional energy is supplied to overcome energy barriers and the process usually takes minutes or even seconds. Kinetic methods include grinding, slurry sonication and fast solvent evaporation (such as spray-drying, crystallization from supercritical states). Such division was used by Anderton (2007) to classify the methods of obtaining polymorph modifications.

There is a number of screening techniques that combine cocrystal formation and its analysis. They include DSC screening (Lu et al., 2008), thermal microscopy (TM) (Berry et al., 2008) and saturation temperature method (STM) (ter Horst et al., 2009). When these methods are used, a cocrystal is formed from a physical mixture right during the experiment and has strictly determined characteristics (solubility, fusion temperature and enthalpy, crystal habit, etc.). As such methods can increase screening applicability, in this work we analyze and compare their efficiency in a number of model binary systems.

Benzoic acid and benzamide derivatives capable of forming a stable acid-amide supramolecular heterosynthon (Shan and Zaworotko, 2008) (Fig. 1) were chosen as the research objects. 2-hydroxybenzamide (2-OHBZA, salicylamide) and its meta- and para-isomers (3-/4-OHBZA) were used as model compounds with an amide group, with benzoic (BA), salicylic (SA), acetylsalicylic (ASA), 2-,3- and 4-acetamidobenzoic ((2-/3-/4-AcAmBA) acids as coformers (Table 1).

Salicylic, acetylsalicylic acids and 2-hydroxybenzamide are nonsteroidal anti-inflammatory drug compounds of the salicyl series, the biological action of which is based on selective inhibition of cyclooxygenase enzyme (COX-1 and COX-2) catalyzing prostaglandin synthesis (Rainsford, 2004). The literature shows that benzoic acid and its derivatives form cocrystals with many drug compounds and widely used coformers (Seaton and Parkin, 2011), such as carbamazepine (Childs et al., 2008), fluconazole (Kastelic et al., 2011) and anti-HIV compound didanosine (Alatas et al., 2013). Acetylsalicylic acid is proved to form a soluble drug-drug cocrystal with meloxicam (Cheney et al., 2011). Salicylamide isomers are also used as model coformers in pharmaceutical cocrystal screening (Tothadi and Desiraju, 2012).

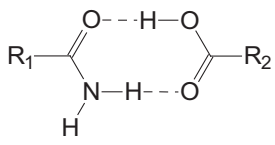

Fig. 1. Acid–amide heterosynthon.

2. Materials and methods

2.1. Materials

2- and 3-hydroxybenzamide (assay 98%) were purchased from Fluka. 4-hydroxybenzamide, 3- and 4-AcAmBA (98%), BA, SA and 2-AcAmBA ($\geqslant$99%) were purchased from Sigma–Aldrich. Acetylsalicylic acid with minimal purity of 98% was purchased from Norsk Medisinal Depot. Ethanol, methanol and acetone (assay 99 + %) by CHEMMED company were used as solvents in STM screening experiments.

All substances were used as received without additional purification. The purity of substances was controlled by DSC.

2.2. Methods

2.2.1. Differential scanning calorimetry

DSC screening was carried out using the DSC 204 F1 Phoenix differential scanning heat flux calorimeter (NETZSCH, Germany) with a high sensitivity μ-sensor (sensitivity 0.0025 μW (65 μV/mW), time constant 2.3 s). The sample was heated from 25 to up to 270 °C depending on melting point of less fusible component at the rate of 10 K $\times$ min^{-1} in an argon atmosphere and cooled with gaseous nitrogen. Temperature calibration of the DSC was performed against six high-purity substances, cyclohexane (99.96%), mercury (99.99 + %), biphenyl (99.5%), indium (99.999%), tin (99.999%), and bismuth (99.9995%). Through calibration experiments the temperature error was established as ±0.5 K, error in phase transition enthalpy – ±1%. The sample quantity in all experiments was between 1.80 and 2.50 mg, while the accuracy of weighting procedure was ±0.01 mg.

2.2.2. Solvent-drop grinding

The grinding procedures were performed as follows: a stoichiometric mixture of components was placed into the agate milling jar of Pulverisette 7 planetary micromill and a corresponding quantity (approx. 1 μl per 1 mg of mixture) of ethanol was added. Then the mixture was ground for 30 min at 600 rpm with 10 5-mm agate balls and the jar was left for 5–10 min at a room temperature to let the solvent evaporate. The purity of produced cocrystal was controlled by observing the endotherms on the DSC curve.

2.2.3. Saturation temperature method

STM screening was carried out according to the method described in the article by ter Horst (ter Horst et al. (2009)) with ethanol, methanol and acetone used as solvents. First, saturated solutions of pure components were prepared by isothermal saturation method by stirring them in an air thermostat for 20–24 h at a starting temperature t_0 of 20 °C and the equilibrium concentrations were measured using the UV–Vis Varian Cary 50 spectrophotometer. Then, the sample mixtures corresponding to 1 ml of saturated solution of both components at t_0 were prepared and the said volume of solvent was added to each of them. The temperature, at which the mixtures have completely dissolved, was determined