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The construction, prediction and measurement of co-crystal ternary phase diagrams as a tool for solvent selection

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ABSTRACT

Many active pharmaceutical ingredients (APIs) are poorly soluble and therefore poorly bioavailable. In recent years, the advances in crystal engineering have motivated the research in the design of pharmaceutical co-crystals. This study examines the combination of solvent selection and co-crystal ternary phase diagram prediction on the basis of solubility measurements into a single methodology that can be integrated into the pharmaceutical process development workflow. Ternary diagrams constructed from agomelatine citric acid co-crystal solubility data were compared with those obtained by modern calorimetric method called discontinuous isoperibolic thermal analysis (DITA). A suitable solvent for the co-crystallization process has been chosen on the basis of agomelatine citric acid co-crystal solubility, which is connected to the yield of the crystallization process. Furthermore, the quality of final crystals from crystallization experiments was evaluated.

1. Introduction

Enhancing the solubility of active pharmaceutical ingredients (APIs) is currently one of the main challenges for the pharmaceutical industry (Good and Rodríguez-Hornedo, 2009). Many new molecules discovered by high-throughput screening and combinatorial chemistry are increasingly larger and more lipophilic. These molecules are usually characterized by poor water solubility, which is a key issue for commercial production and introduction to the market (Aakeroy et al., 2009). Over the last decade, there has been a growing interest in the design of co-crystals, which emerges as a potential method for improving bioavailability of drugs with low aqueous solubility (Qiao et al., 2011). Co-crystals are defined as homogenous crystalline materials containing two or more components as neutral molecules in the crystal lattice with defined stoichiometry at room temperature (Mohammad et al., 2011). According to this definition, the pharmaceutical co-crystals consist of API(s) and other components called co-formers (Qiao et al., 2011). Co-crystals can enhance other essential properties such as physical and chemical stability, powder flowability, compressibility and hygroscopicity (Lu and Rohani, 2009) and can be useful for discovering new co-crystal forms (Chadwick et al., 2009).

There are various approaches to obtaining a co-crystal. Solution crystallization (Chiarella et al., 2007), mechanical grinding (Delori et al., 2012) or melt crystallization (Berry et al., 2008) are some of the general techniques used for preparing co-crystals in the pharmaceutical industry. Solution crystallization is the most preferred process in terms of high volume production. However, this procedure bears a risk of crystallizing the single component phases (Thakuria et al., 2013). Hence, solvent selection and ternary phase diagram construction is crucial for the crystallization process design. Several methods for obtaining ternary phase diagrams are known. Earlier methods involved analyzing both the liquid and the solid phase for each composition. These analyses are extremely time consuming and generally incomplete (Ainouz et al., 2009). Other quantitative techniques have been used on the basis of concentration measurement (spectroscopic methods, density, vapor pressure, conductivity) (Hamedi et al., 2006; Grossjohann et al., 2012).

Regarding the specific determination of co-crystals ternary phase diagrams, Chiarella et al. (2007) described a ternary phase diagram of *trans*-cinnamic acid/nicotinamide co-crystal where the solid phase composition was analyzed by X-ray diffraction and the liquid phase by HPLC (high-performance liquid chromatography). Grossjohann et al. (2012) presented a phase diagram of benzamide/dibenzyl sulfoxide in water and investigated the solid-state characteristics, solubility and dissolution behavior by X-ray diffraction, DSC

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(differential scanning calorimetry), TGA (thermogravimetric analysis), and ATR-FTIR (attenuated total reflection Fourier transform infra-red spectroscopy). Ainouz et al. (2009) developed a calorimetric method called discontinuous isoperibolic thermal analysis (DITA) for the construction of the co-crystal phase diagram based on the solubility of API and a co-former (glutaric acid).

The crystallization and co-crystallization process requires a careful selection of solvent. The solvent can have an influence on the purity of the API, the size and shape of crystals, polymorphism and co-crystal formation itself. The most important factors for solvent selection are the yield and the physical quality of the crystallizing drug. Organic solvents are largely used in the synthetic pathway and crystallization (Mullin, 2001). For toxicological reasons, manufactures are increasingly required to minimize the number of solvents used in drug production. According to the Q3C guideline, solvents are divided into four classes (Grogowska and Parzcewski, 2010). Class 1 contains human carcinogens and environmental hazards. Class 2 represents non-genotoxic animal carcinogens or possible causative agents of irreversible toxicity, such as neurotoxicity or teratogenicity. Solvents in class 3 are commonly used in the chemical and pharmaceutical industry and have a permissible daily exposure of up to 50 mg. For the fourth group, there are no adequate toxicological data enabling the formulation of an acceptable limit. Solvents used in this work were chosen from third class and are presented in the experimental section.

The aim of the present work was to combine solvent selection and co-crystal ternary phase diagram prediction on the basis of solubility measurements into a single methodology that can be integrated into the pharmaceutical process development workflow. Ternary diagrams constructed from solubility data, which is a simple but not so accurate method, were compared with those obtained by a modern calorimetric method (DITA) (Ainouz et al., 2009) for the specific case of agomelatine/citric acid co-crystal (Zentiva, 2012). A suitable solvent for the co-crystallization process was chosen on the basis of the co-crystal solubility, which is connected to the yield and solubility of agomelatine and citric acid. Furthermore, crystallization experiments were performed and the quality of the final crystals were evaluated.

2. Methodology

2.1. Chemicals

An active pharmaceutical ingredient (agomelatine) was prepared in Zentiva. Agomelatine is produced industrially in large quantities and it is used for the treatment of major depressive disorder (Du et al., 2013). Citric acid was purchased from Alfa Aesar GmbH & Co KG (Karlsruhe, Germany). The solvents methylethyl ketone (MEK), acetone, methanol, ethanol, isopropanol and tetrahydrofuran (THF) were provided by Penta (Chrudim, Czech Republic). Co-crystal (agomelatine/citric acid 1:1) was obtained from solution by cooling crystallization. 100 g (0.411 mol) of agomelatine and 79 g (0.411 mol) of citric acid were dissolved in 200 mL of MEK at 80 °C in an agitated 1 L glass vessel. The solution was cooled down to 60 °C and seeded by co-crystal (3 g) prepared in a previous synthesis. The mixture was cooled to 0 °C during 3 h and stirred for a further half an hour at the final temperature. The resulting crystals were filtered, washed and dried overnight. The prepared co-crystal was confirmed by X-ray and NMR analysis.

2.2. Solubility measurement

The solubility of a crystallizing material (defined as the amount of a substance that dissolves in a given volume of solvent at a specific temperature) is an indispensable requirement for the successful development of a crystallization process (Grogowska and Parzcewski, 2010). There are two basic types of solubility: kinetic and thermodynamic solubility. Kinetic solubility values are strongly time dependent and are not expected to be reproducible between different kinetic methods. Kinetic solubility also depends on the physical properties of the dissolving material (polymorphism, particle size). On the other hand, thermodynamic solubility represents the saturation solubility of a compound in equilibrium with an undissolved substance in the solvent at the end of the dissolution process. Thermodynamic solubility (equilibrium solubility) is usually determined by a single measurement, generally after 24–48 h (Alsenz and Kansy, 2007).

In the present work, the kinetic solubility measurements of all compounds were performed by Crystal 16 (Avantium, Netherlands). Crystal 16 measures solubility on the basis of turbidity measurement in vials. The range of sample weight for agomelatine, citric acid and co-crystal solubility measurement by Crystal 16 was approximately 0.030–0.630 g per 1 ml of solvent depending on the type of solid and solvent. Several solvents common for crystallization in the pharmaceutical industry were used (acetone, ethanol, methanol, isopropanol, THF and MEK). The temperature was increased from 0 to the boiling point of each solvent at the rate 0.2 °C/min. When the transmission of light through the vial reached 100% of transmission corresponding to a pure solvent, all solid material was considered dissolved. From the solubility curves, solubility data were used for ternary phase diagrams construction at two temperatures, namely 26 and 40 °C.

2.3. Construction of phase diagrams

2.3.1. Theory

Ternary phase diagrams can be represented using a right triangle or an equilateral triangle diagram. The equilateral triangle diagram is preferred due to its clarity. Each corner in the triangle represents a pure compound A, B and C. The triangle's sides represent the binary systems A + B, A + C and B + C. Triangular phase diagrams are usually presented as isothermal. In the specific case of co-crystal phase diagrams, the three components are the solvent, the API and the co-former.

The presence of a solvent in the crystallization process causes a lowering the activation energy barrier for the rearrangement of the solute molecules into a crystalline structure. Thus, the solvent has a function of a "catalyst" with an influence on the kinetics but not the thermodynamics of the transformation. The solvent as a third component in the mixture minimizes the overall Gibbs free energy of the ternary system (Wouters, 2012). According to the Gibbs rule of phases (Smirnov, 2006), the number of degrees of freedom (F) specifies how many parameters may be changed without changing the phases and can be defined as:

$$F = C - P + 2 \quad (1)$$

where C is the number of independent components, P means the number of phases in thermodynamic equilibrium and 2 refers to the external parameters pressure and temperature. To maintain two-dimensional representation in a ternary system, temperature or pressure must be constant (Nývlt, 1975). In the case of ternary phase diagram of co-crystal measured at constant temperature and pressure, the number of degrees of freedom can be reduce by two:

$$F' = C - P \quad (2)$$

where F' is the number of degrees of freedom with isobaric and isothermal conditions. A typical phase diagram for high a thermodynamic stability co-crystal 1:1 is presented in Fig. 1.

The diagram is divided into several areas with different composition and phases as summarized in Fig. 1. The points I