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Real-time monitoring of cocrystallization processes by solvent evaporation: A near infrared study

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ABSTRACT

This work aims at pinpointing some of the events that can be detected during a solvent evaporation cocrystallization process by near infrared spectroscopy, highlighting the importance of the real-time monitoring strategy of these processes. Small differences in process parameters such as temperature or composition can lead to substantial differences in the polymorphic form or in the purity of the cocrystal. To demonstrate this, a solvent evaporation type cocrystallization process involving furosemide and *p*-aminobenzoic acid was selected. Initial components were dissolved in a mixture of methanol and water (8:1 v/v) and the cocrystallization process was monitored in-line by near infrared spectroscopy using a diffuse reflectance probe set 1 cm above the cocrystallization medium. All batches were run at room temperature under agitation until complete solvent evaporation (approximately 16 h). Acquired near infrared spectra were analyzed by principal component analysis. The final cocrystallization product was characterized using near infrared spectroscopy, differential scanning calorimetry and X-ray powder diffraction. Results show that small variations on the temperature (±3 °C) lead to the appearance of a mixture of the initial components and the cocrystal in varying proportions emphasising the importance of a careful control of the cocrystallization parameters as well the importance of the real-time monitoring.

1. Introduction

Development of cocrystals increased dramatically during the last decade as they show several advantages over crystals such as enhanced API solubility, bioavailability and stability, among others (Ervasti et al., 2015; Wang et al., 2013). Another reason is linked with the enormous intellectual property potential of cocrystals (Manin et al., 2014).

In cocrystal design, crystal engineering principles are normally employed to select a suitable cocrystal coformer. Other factors, such as the composition, solvent, temperature and components solubility are important for a successful cocrystallization process and product with the expected specifications (Aitipamula et al., 2014).

The choice of a screening method to produce cocrystals is also vital and depends on factors such as the difference in solubility of API and coformers in the selected solvents, thermal stability, tendency to form stable polymorphs or solvates and availability of a sufficient amount of the substance (Manin et al., 2014). There are several process approaches to obtain cocrystals. The most widely reported with pharmaceutical industry application are solution cocrystallization (Sarkar and Rohani, 2015; Shayanfar et al., 2014), mechanical grinding (Shimono et al., 2015) or melt cocrystallization (Manin et al., 2014).

Solution cocrystallization is the most preferred due to its simplicity, high volume production and scalability potential. According to the diagram presented in Fig. 1 (typical three component phase diagram involving an API, a coformer and a solvent), a pure cocrystal is only obtained when a limited set of compositions is established. Outside the boundaries of suitable conditions, a mixture of the cocrystal with the API or coformer may be obtained (Aitipamula et al., 2014). Therefore, an appropriate solvent selection and ternary phase diagram construction are essential to design a successful cocrystallization process. However, the methods for their construction are time consuming (Holan et al., 2014) and the unsymmetrical nature of phase diagrams involving cocrystals explain some of the difficulties encountered when developing a robust process (Leyssens et al., 2012). Even with the knowledge of phase solubility behaviour, the generation of pure crystalline materials requires careful control of thermodynamic and kinetic factors (Alhalaweh and Velaga, 2010).

A way to ensure that cocrystals are within the required specifications range in terms of purity and polymorphic form is to monitor the cocrystallization in-line and in real-time to allow process conditions adjustments whenever required. This can be done using spectroscopic

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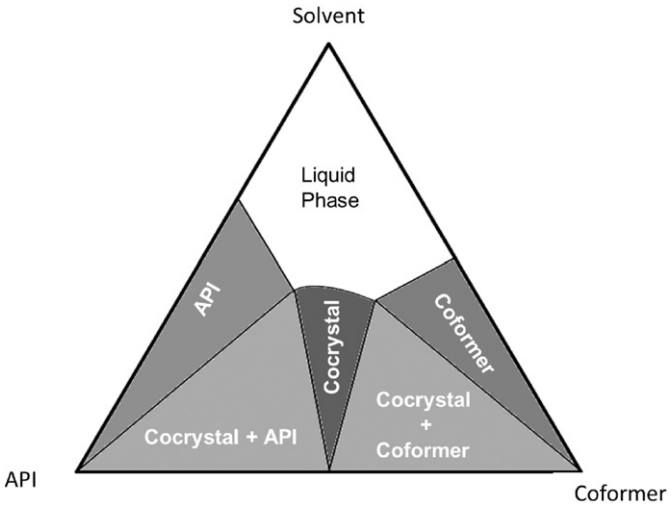

Fig. 1. Example of a three component diagram involving an API a coformer and a solvent. Adapted from Aitipamula et al. (2014).

techniques such as near infrared spectroscopy (NIRS) (Sarraguca et al., 2014) or Raman spectroscopy (Soares and Carneiro, 2013). Alleso et al. (2008) compared NIRS and Raman spectroscopy as methods for screening cocrystals and concluded that the applicability of NIRS is restricted by the availability of reference mixtures but as a monitoring method, it has great potential. NIRS is a fast technique capable of measuring a spectrum in a few milliseconds and due to its low sensibility there is no need of sample pre-processing. It is also possible to fit the near infrared (NIR) equipment with a probe and in this way enabling measurements in-line. Another important advantage is the possibility of extracting not only chemical information but also physical information. NIRS has been used in the pharmaceutical industry for quality and process control in last decades and its implementation is still growing nowadays (Jamrogiewicz, 2012; Sarraguça and Lopes, 2009).

Furosemide (FUR) (Fig. 2) is an anthranilic acid derivative with the chemical name 4-chloro-2[(2-furanylmethyl)-amino]-5-sulfamoybenzoic acid (Babu et al., 2010). FUR is a widely potent loop diuretic applied in several syndromes such as hypertension, heart and renal failure (Agarwal et al., 2008; Garnero et al., 2013). FUR is included in class IV (low solubility and low permeability) of the biopharmaceutical classification system (BCS) with solubility of 6 mg l^{-1} and permeability of log $P_{OW} = 1.4$ (Ambrogi et al., 2012a, b; Maggio et al., 2009; Meka et al., 2009). The cocrystallization between FUR and *p*-aminobenzoic acid (PABA) (Fig. 2) was studied by two different research groups. Goud et al. (2012) used liquid assisted grinding with acetone to produce a 1:1 M ratio cocrystal. The same authors used the slurry cocrystallization method using a mixture of methanol and water to produce the same cocrystal. Harriss et al. (2014), dissolved FUR and PABA in a small amount of ethanol, refluxed the mixture for 10 min and left to evaporate at room temperature. The same procedure was done with methanol. A liquid assisted grinding using acetone was also attempted. In the three situations the same cocrystal was obtained.

The system of FUR and PABA was chosen to this work mainly due to two reasons, first the system was already studied and a single phase cocrystal was obtained and second none of the cocrystallization methods used were by solvent evaporation.

The objective of this work is therefore to show the importance of monitoring a cocrystallization process by solvent evaporation in order to ensure that the cocrystal has the intended quality. This was performed resourcing to NIRS and to a cocrystallization process involving FUR and PABA in a mixture of methanol and water. Results demonstrated that even when all batches are made considering the same process conditions, some problems may occur during the cocrystallization process leading to differences in the cocrystal purity. This work explores a technique that is able to detect these problems in real-time.

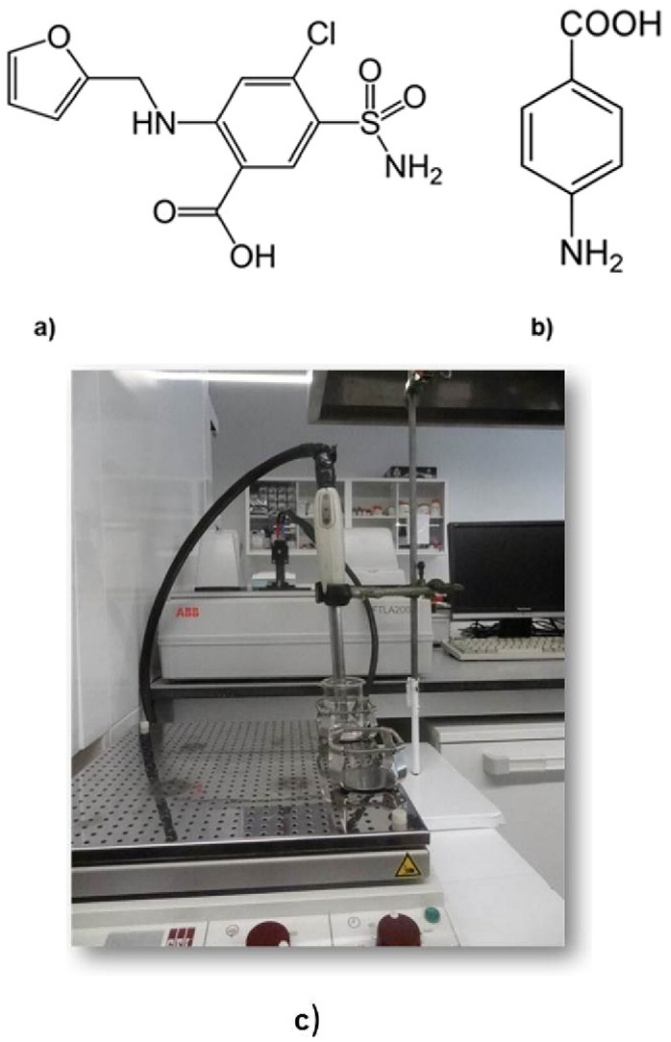

Fig. 2. Molecular structure schemes for (a) FUR and (b) PABA and experimental setup (c).

2. Experimental

2.1. Materials and methods

Furosemide (FUR) (>98% purity), *p*-aminobenzoic acid (PABA) (>99% purity) and methanol (>99.5% purity) were acquired from Sigma-Aldrich (St. Louis, MO, USA). The water used was MilliQ ultrapure.

Cocrystallization of FUR and PABA was done by solvent evaporation method using a mixture of methanol and water (8:1 v:v). Equimolar quantities of furosemide (200 mg, 0.6 mmol) and PABA (82.2 mg, 0.6 mmol) were weighed and completely dissolved in the solvents mixture. The total volume and surface area of the cocrystallization were 9 ml and 3.14 cm^2, respectively.

The solution was then stirred at 150 rpm in an orbital stirring table during 16 h until complete solvent evaporation. In total six batches (B1 to B6) were produced in the same experimental conditions.

2.2. In-line monitoring

2.2.1. Near infrared spectroscopy

A Fourier transform near infrared analyzer (FTLA2000, ABB, Québec, Canada) was used to monitor in-line the cocrystallization process. The spectrophotometer is equipped with an indium–gallium–arsenide